Monday 4 June 2012

PL-01. Course, causes and developments in drug treatment of schizophrenia

H.-J. Möller, Ludwig-Maximilians-University, Department of Psychiatry, Munich, Germany

According to recent long-term studies is schizophrenia a chronic disorder with a high risk of poor outcome in terms of symptoms and social functioning and possibly also progressive brain alterations. The relapse rate is high and each relapse can induce further aggravations, both in psychosocial as well as in neurobiological terms. Thus acute and long-term treatment with the highest degree of effectiveness should be provided to the patients in acute and long-term treatment. It is of special interest that some schizophrenia susceptibility genes and chromosomal abnormalities, particularly examined for early onset populations, are associated with premorbid neurodevelopmental abnormalities. Recent MRI imaging studies on patients at risk for schizophrenia showed a specific pattern of brain alterations which is predictive for the development of a full-blown psychosis. In addition to neurodevelopmental disorder, a neuroprogressive brain disorder is increasingly being hypothesized to explain a further decline especially in the poor outcome subgroup of schizophrenic patients. Results from genetic research, especially recently from the genome-wide association studies hint at disturbances of neurodevelopment/neuroplasticity as well as immunological and glutamatergic processes as part of the complex aetiopathogenesis. The relevance of immunological processes is especially supported by results indicating immunological parameter alterations in patients suffering from schizophrenia and especially by the positive outcome of double-blind, randomised add-on studies using the COX-2 inhibitor Celecoxib as add-on to neuroleptic treatment (risperidone, amisulpride). Support for the glutamatergic hypothesis comes primarily from animal models and recently also from the positive outcome of double-blind, randomised trials on new dopaminergic compounds. This glutamatergic approach in the drug treatment seems to be a very promising one, although it currently seems that these compounds are more effective in the treatment of negative symptoms/cognitive symptoms and not so much in positive symptoms.

PL-02. Addiction: From molecules to neuronal circuits

N. Volkow, National Inst. on Drug Abuse, National Institutes of Health, Bethesda, USA

Addiction is a disorder that involves complex interactions between genes, development and the social environment. Studies employing neuroimaging technology paired with behavioral measurements, and more recently genetics, have led to remarkable progress in elucidating neurochemical and functional changes that occur in the brains of addicted subjects. Although large and rapid increases in dopamine have been linked with the rewarding properties of drugs, the addicted state, in striking contrast, is marked by significant decreases in brain dopamine D2 receptor mediated signaling. Such decreases are associated with dysfunction of prefrontal regions including orbitofrontal cortex, cingulate gyrus and dorsolateral prefrontal cortex and impaired striato-frontal connectivity. In addiction, disturbances in salience attribution result in enhanced value given to drugs and drug-related stimuli at the expense of other reinforcers and promote inflexible behaviors. Dysfunction in inhibitory control systems, by decreasing the addict’s ability to refrain from seeking and consuming drugs, ultimately results in the compulsive drug intake that characterizes the disease. Discovery of such disruptions in the fine balance that normally exists between brain circuits underlying reward, motivation, memory and self-control have important implications for designing multi-pronged interventions for the prevention and treatment of addictive disorders.

Tuesday 5 June 2012

PL-03. Depressing tales of adult neurogenesis: A hard look at the evidence

P. Rakic, Yale University School of Medicine, Department of Neurobiology, New Haven, USA

The idea that the beneficial effect of antidepressants in humans acts by enhancing neurogenesis of granule cells in dentate gyrus of the hippocampus was based on the work in young adult mice, where neurogenesis is robust and is increased by antidepressant treatment. However, it is not clear if this correlation in mice can be extrapolated to humans. I will present evidence, from our and many other laboratories, that the effect of various drugs including antidepressants on the turnover (e.g. genesis and death) of granule cells in control mice and in models of depression such as “forced helplessness” is a side effect that is unlikely related to the depression and its treatment in humans. Our strategy has been to compare neurogenesis in developing, young, adult and aged rodents, non-human primates and humans, to learn not only from their similarities, but also from their differences. These differences include how changes in the timing and sequence of gene expression affect molecular and cellular events to produce both quantitative and qualitative changes. Use of various proliferation markers, indicates that the magnitude and timing of neurogenesis in non-human primates is very different from the high neuronal turnover in various vertebrates including rodents. More specifically, division of neural stem cells in primates last almost two days and maturation of the newborn granule cells requires a minimum of 6 months, which is incompatible with the pharmacodynamics of antidepressants in humans, some of which can act within hours or days after exposure. I will also discuss possible molecular pathways implicated in limiting neurogenesis in adult primates and discuss the advantages of this limitation. It is hoped that a better understanding of the evolutionary differences, such as genetically controlled decrease in adult neurogenesis, will allow for insight into its role on brain homeostasis, as well as potential of neural stem cells in replacement therapy of human-specific neuropsychiatric disorders.

PL-04. Psychopharmacology and Cognition

B.L. Sahakian, University of Cambridge, School of Clinical Medicine, United Kingdom

Psychiatric disorders are disorders of neurocognition. Many psychiatric disorders, such as schizophrenia and attention deficit hyperactivity disorder, are of neurodevelopmental origin with an onset or prodromal stage in childhood or adolescence. Cognitive manifestations include: attentional biases; aberrant learning; dysfunctional reward systems; and lack of top down cognitive control by prefrontal circuits.
PL-06. Rational pharmacotherapies of major depressive disorder

S. Kasper, Medical University of Vienna, Department of Psychiatry and P. Austria

Depression is one of the most thoroughly evaluated diseases in psychiatry with regard to diagnosis and treatment possibilities. Early treatment should be achieved and watchful waiting, which is for instance not done in the treatment of high blood pressure or diabetes, has not demonstrated to be a rational approach based on neurobiological considerations. Like in other diseases, it is apparent that an untreated illness may result in biological damage i.e. in depression in a reduced volume size of the hippocampus. Interestingly, the course of illness shows that life events are less important in the later stages of the illness, which can be interpreted that the disease has approached a specific neurobiologically determined course. The introduction of the group of selective serotonin reuptake inhibitors (SSRIs) marked a revolution in the treatment of depression, since it was possible to treat patients effectively with a considerably lower side effect profile than compared to tricyclic antidepressants. More patients could be reached with this approach and a possible association between usage of SSRIs and the reduction of the suicide rates in countries like Sweden, Austria and Hungary have been discussed. Dual reuptake inhibitors effecting both the serotonergic and the noradrenergic pathways and the dopaminergic noradrenergic medication bupropion have been introduced in the field with specific characteristics of treatment goals like pain, somatic symptoms or drive. The recently introduced antidepressant agomelatin demonstrates a novel and unique mechanism of action with a combination of melanotergic agonistic and serotonergic antagonistic activity exhibiting a more distinct influence on the circadian rhythm compared to other currently available antidepressants. Deep brain stimulation and vagus nerve stimulation for treatment refractory depressed patients yield promising first results, although need further substantiation. More thorough characterisation of the underlying pathophysiology of depression including molecular biological variables and brain imaging characterizations will hopefully result in further insight.
into the understanding of the illness and yield rational decisions for the treatment of depression.

**Policy of full disclosure:** Siegfried Kasper received grants/research support, consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers Squibb, CSC, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pierre Fabre, Pfizer, Schwabe, Sepracor, Servier, Wyeth.

**PL-07. Drugs for Alzheimer’s disease**

**B. Winblad. Stockholm, Sweden**

Alzheimer disease (AD) is the most common cause of dementia in advanced age. Currently available medications improve AD symptoms, and development of disease-modifying drugs is a very active area of research, which includes cholinergic, glutamate inhibitor (NMDA receptor antagonist), anti-amyloid compounds, drugs targeting tau-protein or mitochondria, neurotrophins, and other therapeutic approaches. The amyloid cascade hypothesis dominates current drug development strategies. Identification of effective disease-modifying drugs will benefit from understanding the interplay between mechanisms causing neurodegeneration in AD. Combined therapy could me a more effective strategy to halt AD progression. Solving methodological problems in clinical trials on AD – including use of standardized diagnostic criteria able to identify homogeneous group of patients, appropriate treatment duration and measures of disease-modifying effects – will help finding a cure for AD. The lecture will summarize current treatment possibilities for AD, as well as the main findings for new, and less new drugs with novel therapeutic use in AD, focusing mainly on compounds in the human testing phase.

**Thursday 7 June 2012**

**PL-08. The crisis in drug discovery. What can we do to get it right?**

**PL-08-001 Drugs for Alzheimer’s disease**

**A. Carlsson. Göteborg, Sweden**

In Sweden we have recently been reminded of the serious waning of the drug R&D by the closing down of one of the main research units of AstraZeneca in Södertälje, only a few years following upon the closing down of its subsidiary Draco in Lund, Sweden. Less than a decade ago Pharmacia, the other Swedish Big Pharma, was devoured by Pfizer. Thus the drug R&D debacle has hit Sweden probably more than any other country. Nevertheless, the global aspect needs to be considered in the first place, and work to identify its causes is underway. Perhaps especially illuminating is an article by Swimney and Anthony (Nature Reviews, Drug Discovery, Vol. 10, July 2011, p. 507), who examined the discovery process behind all drugs approved by FDA during 1999 through 2008. It is concluded that the pharmaceutical industry has unfortunately concentrated its resources on in-vitro strategies full of pitfalls, i.e. High-Throughput Screening and the like, resulting in a fatally high attrition rate. This shocking outcome needs to be examined further. Should we place most of the blame on the pharmaceutical industry? This is by no means certain. If we look back on the golden half-century of drug R&D starting in the 1940s, preclinical academic research as well as important clinical feedback seem to have been the main driving forces. How come that they apparently have stopped working? The present wave-the way in drug R&D is most unfortunate for millions of sick people as well as for biomedical research as a whole. Moreover, it is paradoxical, given the enormous technical and other scientific advances made during the past century. There is an urgent need for the identification of its causes and for further action. Presumably reversal to a balanced and well integrated use of in-vivo and in-vitro techniques will be required.
Monday 4 June 2012

S-01. Dopamine receptors, noradrenergic mechanisms and D2 containing heteromers as targets for antipsychotic drugs

S-01-001 Antipsychotics – are we targeting the right system but the wrong end

S. Kapur, Institute of Psychiatry, London, United Kingdom

Objective: Antipsychotics were discovered by serendipity nearly 60 years ago. Since then efforts to make antipsychotics that avoid the dopamnergic system entirely have not been successful. This raises the question why dopamine blockade is essential for antipsychotic action. Despite several studies looking for an increase in dopamine D2 receptors – the data remains equivocal.

Methods: We have recently completed a meta-analysis of all the available neuroimaging studies (44 studies with 618 patients) of the dopamine system and find only weak evidence for an increase in D2 receptor numbers – a finding that was driven by a few studies using butyrophenone tracers in previously treated patients.

Results: This raises the possibility of whether an increase in D2 receptors is missed as this increase is restricted to the high states of the D2 receptor, a state that can be missed by the standard antagonist radioligands. Therefore, using 11C-PHNO, a ligand that can image the high states of the D2 receptor and D3 receptors we have examined patients with schizophrenia – and find no evidence of an increase in D2/3 receptors – though treatment seems to induce an upregulation of the D3 subtype. The most striking finding in the meta-analysis is an increase in the presynaptic uptake of 18F-Dopa, suggestive of increased synthesis capacity (effect size 0.79). More recent data suggests that it is not the level of D2 blockade (provided it is in the sufficient range) that determines antipsychotic response – but, the level of presynaptic DA synthesis capacity.

Conclusion: Thus, it seems, that for the last sixty years the antipsychotics have been blocking dopamine transmission by focussing on the wrong end of the DA synapse. The implications of this view for further antipsychotic development will be presented.

S-01-002 Dopamine, D1 receptors and noradrenergic mechanisms in the modes of action of antipsychotic drugs


Objective: Recent clinical data show, using in vivo imaging techniques, a reduced cortical DA release in schizophrenia (SZ), contrasting the previously observed enhanced striatal DA release that correlates with psychosis. The reduced prefrontal DA release is thought to be of antipsychotic response – but, the level of presynaptic DA synthesis capacity.

Methods: Experiments were performed in rats using electro-physiological intracacellular recording in pyramidal cells in a prefrontal cortical slice preparation to assess NMDA-R function, microdialysis in freely moving animals to assess regional monoamine efflux in brain, and behavioral methodologies, including the conditioned avoidance response (CAR) test to assess antipsychotic activity, the 8-arm radial maze to study working memory (WM) and a catalepsy test to assess extrapyramidal side effects (EPS).

Results: Since the clinical effects of quetiapine are partly mediated by its metabolite norquetiapine, which is not formed in rodents and qualitatively differs from quetiapine only by its potent NET inhibitory action, we compared the behavioral and neurobiological effects of clozapine and a combination of quetiapine and the selective NET inhibitor reboxetine with those of raclopride, a typical D2-R agonist. In contrast to raclopride, both clozapine and the combination of quetiapine and reboxetine effectively suppressed CAR at low D2 occupancy levels, markedly and selectively enhanced DA outflow in the medial prefrontal cortex (mPFC) and, via D1-R activation, facilitated NMDA-R mediated transmission in this region, an effect that was able to reverse the WM impairment induced by the selective NMDA-R antagonist MK-801. The effects of clozapine could largely be mimicked by a combination of raclopride with idazoxan, an alpha2R antagonist, and those of quetiapine plus NET inhibition by a combination of raclopride and the NET inhibitor reboxetine.

Conclusion: The results clearly implicate brain noradrenergic mechanisms in the modes of action of clozapine and quetiapine. Blockage of presynaptic alpha2-R on NE terminals may release both NE and its precursor DA and, moreover, the increased extracellular NE concentration may elevate cortical DA levels as both transmitters compete for the same transporter, thus producing D1-R activation in the mPFC. A recent meta-analysis (Hecht & Landy 2011) provides further support for he utility of noradrenergic targets in antipsychotic therapy.

S-01-003 Putative D2 receptor containing heteromers in the ventral striatum and their relevance for treatment of schizophrenia

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Objective: Our working hypothesis is that one or several of the D2R containing heteromers in the ventral striatum especially A2AR-D2R, D2R-5-HT2AR and NT5-D2R heteromers may be targets for typical and atypical antipsychotic drugs. The activation of the A2AR, 5-HT2AR and NT5 protomers of the respective heteromers could largely be mimicked by a combination of raclopride with idazoxan, an alpha2R antagonist, and those of quetiapine plus NET inhibition by a combination of raclopride and the NET inhibitor reboxetine.

Methods: We have used in situ PLA, FRET/BRET, coimmunoprecipitation, biochemical binding, receptor autoradiography, dual-probe microdialysis and behavioural measurements.

Results: The A2AR-D2R heteromer has been indicated through biochemical-biophysical methods. On the basis of the existence of the antagonistic A2AR-D2R interactions, A2AR agonists were proposed to be atypical antipsychotic drugs. A2AR agonists counteract the D2R-induced reduction of the glutamate drive from the mediodorsal thalamic nucleus to the prefrontal cortex via their reduction of D2R signaling in the nucleus accumbens. There may also exist extrasynaptic A2AR-D2R-mGlur5 receptor mosaics located on the dentritic spines of the local circuits of the ventral and dorsal striato-pallidal GABA neurons. Behavioral evidence indicates that the A2AR agonist CGS21680 and the mGlur5 agonist CHPG synergize in counteracting phencyclidine-induced motor activity. Furthermore, we demonstrated that the D2LR and the 5-HT2AR form stable and specific heteromers in mammalian cells. Costimulation of D2LR and 5-HT2AR within the heteromer led to inhibition of the D2LR functioning, thus suggesting the existence of a 5-HT2AR-mediated D2LR trans-inhibition.
phenomenon. Also, antagonistic NTS1-D2 receptor interactions in postulated NTST1-D2R heteromers in the ventral striatum have been repeatedly proposed to be the molecular mechanism involved in the postulated antipsychotic effects of neurotensin.

**Conclusion**: D2R heteromers may be disrupted or dysfunctional in schizophrenia leading to removal of the brake on D2R signaling in the striato-pallidal GABA circuits. 

Receptor-receptor interaction between cortical NA and DA receptors in potential heteromers should also be considered as targets for antipsychotics.

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**S-02. Management of treatment-resistant major depression**

**S-02-001** TRD: Pharmacotherapeutic strategies for adults with major depressive disorder

**G.J. Papakostas**, Massachusetts General Hospital, Boston, MA, USA

**Objective**: Major depressive disorder can, often, be chronic, recurrent, and associated with significant disability, morbidity, and mortality. Numerous pharmacologic and non-pharmacologic treatment options exist for the treatment of major depressive disorder, with full and sustained symptomatic remission being the goal of treatment. However, it has been estimated than as many as half of all patients may not experience a remission of their depressive episode despite a treatment trial of adequate dose (in the case of drug therapy) and duration, while a significant burden of (subsyndromal) depressive symptoms may persist among those patients who do achieve remission of their depression. Thus, in most cases, subsequent treatment approaches are required to help achieve full and sustained symptomatic remission. The progressive increase in recognition of the prevalence and burden of TRD, has sparked a rapid growth of research in this treatment area, with a number of novel therapeutic options emerging. Ultimately, these approaches combined may help improve the standard of care for major depressive disorder. The goal of the symposium is to review the prevalence and burden of treatment-resistant major depressive disorder (TRD), and to review novel as well as established therapeutic strategies for TRD.

**Methods**: Literature will be searched for randomized, double-blind, placebo-controlled trials of pharmacologic interventions for TRD.

**Results**: Numerous studies are found and discussed.

**Conclusion**: Numerous studies support the use of various interventions for TRD. Their evidence-base, relative efficacy, tolerability, and safety are discussed.

**Policy of full disclosure**: Dr. Papakostas has served as a consultant for Abbott Laboratories, AstraZeneca PLC, Brainway Ltd, Bristol-Myers Squibb Company, Cephalon Inc., Depharma, L.P., Eli Lilly Co., GlaxoSmithKline, Evotec AG, Infabloc Pharmaceuticals, Jazz Pharmaceuticals, Osuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc., Pierre Fabre Laboratories, Ridge Diagnostics (formerly known as Precision Human Biologicals), Shire Pharmaceuticals, Theracos, Inc., and Wyeth, Inc. Dr. Papakostas has received honoraria from Abbott Laboratories, AstraZeneca PLC, Bristol-Myers Squibb Company, Brainway Ltd, Cephalon Inc., Depharma, L.P., Eli Lilly Co., Evotec AG, GlaxoSmithKline, Infabloc Pharmaceuticals, Jazz Pharmaceuticals, Lundbeck, Osuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc., Pierre Fabre Laboratories, Ridge Diagnostics, Shire Pharmaceuticals, Theracos, Inc., Titan Pharmaceuticals, and Wyeth Inc. Dr. Papakostas has received research support from AstraZeneca PLC, Bristol-Myers Squibb Company, Forest Pharmaceuticals, the National Institute of Mental Health, PAMLAB LLC, Pfizer Inc., and Ridge Diagnostics (formerly known as Precision Human Biologicals). Dr. Papakostas has served (not currently) on the speaker’s bureau for Bristol-Myers Squibb Co and Pfizer, Inc.

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**S-02-002** Pharmacotherapeutic strategies for adults with bipolar depression

**M. Bauer**, Univ. Hosp. Carl Gustav Carus, Technische Universität Dresden, Germany

**Objective**: The burden of depression represents the most debilitating dimension for the majority of patients with bipolar disorder and dominates the long-term course of the illness. The purpose of this presentation is to review the evidence base of the available treatment options for bipolar depression assigned to two frequent clinical scenarios A and B.

**Methods**: The evidence is largely based on a systematic literature search. All relevant randomized controlled trials were critically evaluated.

**Results**: Scenario A: if a patient with bipolar depression is currently not being treated with a mood stabilizing agent (de novo depression), then quetiapine or alternatively olanzapine are an option, carbamazepine and lamotrigine can be considered. Antidepressants are an option for short-term use, but whether they are administered as mono- or combination treatment with mood stabilizing agents is still controversial. Most clinicians prefer to use antidepressants in combination with an antimanic substance. Scenario B: If a patient is already treated with a mood stabilizing agent (breakthrough depression) once adherence has been confirmed and the dose has been adjusted, lamotrigine is an option in patients on lithium. There is no evidence for further effects of antidepressants in cases where a patient is already receiving a mood stabilizer, however, an additional antidepressant is preferred by most clinicians.

**Conclusion**: Overall, the evidence from treatment trials in bipolar depression is relatively sparse compared with the number of controlled trials in unipolar depression and as such the choice of treatment is governed by a multitude of factors. While clinical trials provide evidence on the efficacy of a certain intervention in a specific population, they cannot necessarily determine which intervention will be optimal for a given patient in a given specific situation. They can however inform the choice of intervention and in particular prevent clinicians from choosing interventions that have been shown to be ineffective.

**Policy of full disclosure**: Grant/Research Support from The Stanley Medical Research Institute, NARSAD and the European Commission (FP7), Consultant for AstraZeneca, Lilly, Servier, Lundbeck, Bristol-Myers Squibb and Otsuka. Speaker Honoraria from AstraZeneca, Lilly, GlaxoSmithKline, Lundbeck, Bristol-Myers Squibb and Otsuka.
Objective: This talk overviews recent advances using Brain Stimulation therapies for treating medication or treatment resistant depression.

Methods: A literature review shows that these methods range from relatively non-invasive (e.g., transcranial direct current stimulation (tDCS) and prefrontal transcranial magnetic stimulation (TMS)), to more invasive (vagus nerve stimulation (VNS)) to very invasive (deep brain stimulation (DBS) and epilepti
cal cortical stimulation (EPCS)).

Results: To date, tDCS studies in acute depression are mixed. TMS is now US FDA approved and a recent NIH pivotal study (OPT-TMS) provides class 1 evidence of treating acne depression. The level of treatment resistance affects TMS response rates. New work involves accelerated TMS over 3 days, or for use in suicidal crisis. ECT continues to be the most effective treatment for acute depression.

New advances in ECT pulse width (ultrabrief unilateral ECT) are showing promise with similar efficacy but less toxicity than older methods. We will show data on 17 patients treated with a new directional ECT to prefrontal and VNS does not have class I evidence of effectiveness in acute depression but two longitudinal studies in either Europe or the US showed similar long-term benefit in TRD patients followed over several years. The onset of action is slow (months) but appears durable. DBS controlled trials are underway with preliminary promise in patients who have failed to respond to many of the above interventions. There are at least 4 different brain regions being targeted by different groups. While preliminary results are promising, DBS remains an investigational technique without convincing class I evidence of either acute or chronic effects.

Conclusion: Clinicians are now beginning to offer the brain stimulation methods in a staged approach, similar to cancer management, starting with less invasive methods and then gradually advancing.

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S-02-002 Treatment of adolescent depression: Some substantive issues

J.K. Buitelaar. St. Radboud and Karakter Child and Adolescent Psychiatry, Nijmegen, Netherlands

Objective: The objective of this presentation is to discuss the challenges in treating pediatric depression, and balance medication and psychological approaches to treatment.

Methods: Narrative review of the results of key clinical trials with medication and psychological interventions in child and adolescent depression, based on PubMed search and consultation of authoritative reviews.

Results: More severe depressive episodes will generally require treatment with antidepressants. Depressed children and adolescents treated with SSRIs have a relatively good response rate (40%–70%), but the placebo response rate is also high (30%–60%). With the exception of the fluoxetine studies (e.g., Emslie et al., 1997), significant differences between SSRIs and placebo were, due to the high placebo response, only found in depressed adolescents but not in depressed children (Bridge et al., 2007). The TADS compared fluoxetine, cognitive behaviour therapy (CBT), and their combination (TADS, 2004). In adolescents with moderate to severe depression, treatment with fluoxetine alone or in combination with CBT accelerates the response. Adding CBT since it enhances the safety of medication. Taking benefits and harms into account, combined treatment appears superior to either monotherapy as a treatment for major depression in adolescents (TADS, 2007). Results of the TORDIA study show that depressed adolescents who have failed to respond to an adequate trial with a SSRi, a switch to another antidepressant plus CBT resulted in a better response than a switch to another antidepressant without additional psychotherapy (Brent et al., 2007). Fluoxetine was shown to normalize brain activity in multiple brain regions, including the frontal, temporal, and limbic cortices after 8 weeks of treatment (Tao et al., 2012).

Conclusion: Though a reasonable percentage of depressed adolescents respond to treatment, remission rates are rather low in short-term trials. Treatment should be continued after remission for at least 6–9 months. Most patients recover after 2–4 years, but in the meantime, another 50% of these show already recurrence.

Policy of full disclosure: Jan K Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, Bristol-Myer Squibb, Shering Plough, UCB, Shire, Novartis and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

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S-03. Cocaine-induced changes in glutamate neuroplasticity in developing and mature neuronal circuits

S-03-001 Cocaine-induced changes in glutamate neuroplasticity in developing and mature mesolimbic circuits

C. Bellone1, T. Yuan2, M. Mameli3, C. Lüscher1, 1University of Geneva, Dept. Basic Neuroscience, Switzerland; 2University of Geneva, Switzerland; 3Institut du Fer a Moulin, Paris, France

Objective: As in many parts of the central nervous system of the mouse, glutamatergic synapses onto dopamine (DA) neurons in the ventral tegmental area (VTA) mature postnatally. We have recently demonstrated that at birth many AMPARs lack GluA2 and most NMDARs contain the GluN2B subunit. Within two weeks these receptors are replaced with GluA2- and GluN2A- containing AMPARs and NMDARs respectively. Here we now show that a single injection of cocaine triggers not only the redistribution of AMPARs, but also rearranges NMDARs.

Methods: In order to test our hypothesis, we use in vitro whole-cell patch-clamp recording in VTA acute slices from neonatal and juvenile mice.

Results: After the drug exposure the synapses express GluN2B containing NMDARs along with GluA2-lacking AMPARs, as if addictive drugs re-open a developmentally critical period. Both during the development and after single cocaine exposure, mGluRI activation drives the insertion of NMDARs (mGluRI-LTPNMDA). This is associated with an overall increase in NMDAR-EPSGs (mGluRI-LTPNMDA) and involves PLC, Ca2+ release from the internal stores as well as PKC activity. Moreover, we identify the Shanks/Homer interaction as an important player in the mGluRI-LTPNMDA interaction.

Conclusion: While we are only beginning to understand the repercussions of drug-evoked receptor redistribution, the striking resemblance with the processes occurring during early postnatal development brings a new, exciting perspective that may help us to understand both normal development and the development of addiction.

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S-03-002 Cocaine experience modulates synaptic transmission in the habenula complex

M. Mameli1, M. Maroteaux1. 1Institut du Fer a Moulin, Bâtiment INSERM, 75005 Paris, France

Objective: Goal directed actions, aimed to obtain a reward, motivate our behaviors and influence our decisions. Midbrain dopamine neurons activity and therefore dopamine release are enhanced by external cues predicting a reward. Lateral habenula (LHb) neurons play a central role in this regulation since they instruct dopamine neurons during reward learning. Addictive substances induce an abnormal increase in dopamine neurons and recent theories posit that addiction develops by hijacking the reward system promoting strong association between drug and context. Given the critical importance of LHb neurons in tuning dopamine neurons firing and participating to cue-reward association we tested whether synaptic transmission and plasticity at glutamatergic synapses in this nucleus are sensitive to drug exposure.

Results: We have used patch clamp recordings and identify peculiar biophysical properties of AMPA receptors that suggest that such proteins lack the subunit GluA2. Cocaine experience strengthens excitatory transmission and alters synaptic plasticity in treated animals compared to saline injected ones.

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Policy of full disclosure: The authors declare no potential conflicts of interest.
Conclusion: These results suggest that cocaine exposure alters the synaptic inputs onto LHB neurons, which in turn could explain some of the mechanisms during drug-context association occurring in the reward circuit.

S-03-003 Neuronal changes following repeated exposure to cocaine during adolescence: Focus on the glutamatergic system

F. Fumagalli, L. Caffino, G. Gianotti, G. Racagni, 1University of Milan, Dept of Antidrug Policies, Italy; 2University of Milan, Italy

Objective: To investigate changes in glutamate receptors expression and phosphorylation following repeated exposure to cocaine during adolescence.

Methods: We therefore treated male rats from post-natal day (PND) 28 to PND 42 with saline or cocaine (20 mg/kg). Animals were sacrificed 3 days (PND 45) after the end of treatment or at adulthood (PND 90) and the brain regions of interest (prefrontal cortex and nucleus accumbens) were removed. Analyses were carried out by Western blots.

Results: No major changes were found in the phosphorylation or expression of the main subunits of NMDA receptors in the prefrontal cortex of PND 45-old rats with only a slight reduction in the major AMPA subunit, i.e. GluR1; conversely, in nucleus accumbens, we found increased phosphorylation, but not expression, of NR1, NR2B and GluR1. At adulthood, we primarily found a significant reduction in GluR1 expression and phosphorylation in the prefrontal cortex with no major changes in the nucleus accumbens. Additionally, when we challenged the animals with an acute stress to evaluate whether exposure to cocaine during adolescence had altered the response of the glutamatergic system to the stress itself, we found a dysregulation in response in the phosphorylation of the main glutamatergic subunits, i.e. the NR-1 NMDA subunit and the GluR1 AMPA subunit.

Conclusion: Our results suggest 1) an early activation of the glutamate system in nucleus accumbens; 2) a persistent effect of the exposure to cocaine during adolescence on GluR1 subunit, which persists into adulthood 3) a dynamic role of glutamatergic receptors following adolescental exposure to cocaine which is not limited to changes at the steady state level of these receptors.

S-03-004 Corticostriatal glutamate dysregulation in an animal model of cocaine addiction and relapse

R. See, University of South Carolina, Department of Neurosciences, Charleston, South Carolina, USA

Objective: Cocaine-induced changes in corticostriatal glutamate regulation have been implicated in cocaine-seeking after prolonged cocaine self-administration in rats. Here, we examined changes in striatal glutamate release in rats with a history of daily cocaine intake. Based on evidence for normalization of glutamatergic function by the cysteine precursor, N-acetylcysteine (NAC), further experiments tested whether repeated NAC administration would produce lasting reductions in GLU release in the dorsal striatum. Results: Male rats self-administered intravenous cocaine during daily sessions, followed by daily extinction (no reinforcement) or abstinence (alternate environment) sessions. To assess glutamate release in the dorsal striatum, in vivo microdialysis procedures were used in awake animals to collect samples that were then analyzed by HPLC-EC. For assessment of chronic NAC effects, rats received daily injections of saline, 60, or 100 mg/kg NAC (IP). Subsequently, rats were tested for cocaine-seeking via conditioned cue-induced, cue+cocaine primed, and context induced cocaine seeking. Results: Rats with a history of chronic cocaine self-administration showed enhanced striatal glutamate efflux under both context induced conditions and after acute injection of cocaine. Chronic NAC administration blunted cocaine-seeking under multiple experimental protocols. Specifically, NAC attenuated responding during cue and cue+cocaine-primed reinstatement tests following extinction, and context, cue, and cue+cocaine tests of drug seeking following abstinence. Reduction of cocaine seeking by NAC persisted well after treatment was discontinued, particularly when the high dose was combined with extinction trials.

Conclusion: Dysregulation of striatal glutamate release likely plays a key role in persistent cocaine seeking following abstinence. The finding that NAC reduced cocaine-seeking after treatment was discontinued supports recent preclinical and clinical evidence that NAC may serve as an effective treatment for inhibiting relapse in cocaine addicts.

S-04. Insights for personalized medicine in psychiatry

S-04-001 Complex regulation of gene expression in brain

C. Wahlestedt, The Scripps Research Institute, Jupiter, USA

Objective: This lecture will present our view on how gene expression is dynamically regulated by protein and RNA mechanisms in contexts of different epigenetic states and psychiatric disorders.

Methods: We have conducted a wide variety of transcriptomic and epigenetic experiments over a number of years.

Results: Rather than a fixed hierarchy of transcription factors, the cell creates an entirely new paradigm for all aspects of genome-related research.

S-04-002 Gene x environment interactions in the prediction of response to antidepressant treatment

E. Binder, Max-Planck Inst of Psychiatry, Munich, Germany

Objective: High hopes have been held for the field of pharmacogenetics in the prediction of antidepressant response, but so far no associations could be consistently replicated. As for the development of psychiatric disorders per se, treatment response is likely not moderated by major genetic effects but also environmental factors and gene x environment interactions.

Methods: This presentation will focus on early life trauma and present molecular genetic data, including gene x environment interaction data, epigenetic data and gene expression data in human pharmacogenetic trials.

Results: Several lines of evidence are presented suggesting the importance of gene x environment interactions in predicting response to antidepressant treatments. First, a number of genetic polymorphisms, including polymorphisms within the serotonin transporter gene and the stress hormone system genes CRHR1 and FKBP5, have been shown to interact with early trauma to predict mood disorders. The same polymorphisms have also been shown to predict response to antidepressant treatment. Second, gene x environment interactions lead to highly different biological disturbances in mood disorders. This will be illustrated with FKBP5 polymorphisms as an example, for which we could show allele-specific epigenetic changes following exposure to early trauma. These are accompanied by distinct systemic-wide molecular changes, suggesting that different pathways need to be targeted to elicit antidepressant response depending on both, the FKBP5 genotype and exposure to early trauma. Finally, preliminary data supporting the importance of early trauma x gene interaction in the overall and differential prediction of response to current antidepressant treatments (medication vs. cognitive behavioral therapy) will be presented.

Conclusion: Different combinations of environmental and genetic risk factors likely lead to biologically distinct subsets of mood disorders that could show preferentially response to certain treatment types. This can be related to the prediction of response to currently used antidepressant therapies but may also aid in the identification of novel antidepressant targets.
S-04-003 Personalized medicine and the management of TRD
C. Nemeroff, University of Miami, USA

Although there are several effective pharmacotherapeutic and psychotherapeutic treatments for major depression, a large majority of patients do not obtain remission after an adequate monotherapy trial with one of these modalities. There is increasing evidence that biologically distinct subtypes of major depression, so-called endophenotypes, are to a large extent responsible for this current unfruitful state of treatment outcomes in depression and related mood and anxiety disorders. One subtype of depression that has repeatedly been shown to exhibit a lower than expected rate of treatment response to antidepressants is patients with major depression and a history of child abuse and neglect. This presentation will summarize the evidence that such patients represent a neurobiologically distinct subgroup as revealed by structural magnetic resonance imaging (MRI) and functional brain imaging (PET and fMRI) findings, alterations in neuroendocrine and immune function and a distinct pattern of distribution of several genetic polymorphisms (CRHR1, FKBP5, PAC1, BDNF) that mediate gene-environment interaction. In addition, unique symptom profiles of this patient group including cognitive impairment will be described. Taken together these data support the development of novel treatment strategies based on this subgroup-specific pathophysiology for optimal personalized management of a sizeable percentage of the treatment refractory depressed population.


S-04-004 Pharmacogenetics of alcohol reward and therapeutic response to naltrexone
M. Helig1, A. Thorsell1, J. Linköping Health Unit, Linköping, Sweden

Objective: Mu-opioid (OPRM1) receptors are key to rewarding properties of alcohol, and the target for the approved alcoholism medication naltrexone. Functional 118A→G variation at the OPRM1 locus was suggested to represent a genetic vulnerability factor for alcohol and heroin addiction, and to moderate therapeutic efficacy of naltrexone, but these findings remain controversial.

Methods: We first examined alcohol responses, consumption and efficacy of naltrexone in a functionally equivalent rhesus OPRM1 77C→G model. Next, DA release in response to alcohol was examined using PET and [11C]raclopride displacement in social drinkers recruited by OPRM1 118 genotype. Finally, the causal role of the 118 variant to predispose human carriers to endorphin-dependent DA-release and consumption. These findings are consistent with a role of this variant to predispose human carriers to endorphin-dependent alcoholism, but also to render patients more responsive to opioid antagonist treatment.

S-05. Mechanism of PTSD: From genes and epigenetics to neurocircuits and endophenotype

S-05-001 Searching for epigenetic biomarkers in PTSD
S. Morinobu1, M. Fuchikami1, S. Okada1, S. Yamawaki1, I. Liberzon2, A. King3, J. Seng1, 1Hiroshima University, Japan; 2Yale University, New Haven, USA; 3University of Michigan, Ann Arbor, USA

Objective: The development of posttraumatic stress disorder (PTSD), follows exposure to a traumatic/highly stressful event. Since it is well known that stress exposure changes the mRNA levels of genes in the rodent brain, it is conceivable that changes in gene expression mediated by alterations in the DNA methylation in the brain are involved in the pathophysiology of PTSD. In this context, it is hypothesized that the DNA methylation status may be a potent diagnostic biomarker in PTSD.

Methods: We examined the methylation profile of 35 CpGs located in one CpG island (799 bp), covering the exon 1 of the serotonin transporter (5-HTT) gene using genomic DNA from peripheral blood of 173 patients with PTSD and 48 healthy controls. Methylation rate at each CpG unit was measured using a massARRAY® system (SEQUENOM).

Results: Two-dimensional hierarchical cluster analysis (diagnosis × methylation rate) of all CpG units did not yield correct diagnostic classification to healthy controls and patients groups. The methylation rates of 6 CpG units out of 35 CpG units were significantly different in patients having current PTSD diagnosis and the methylation rates of 5 CpG units were significantly different in patients with lifetime PTSD diagnosis as compared to healthy controls. Among these, two CpGs units were common to the lifetime and the current PTSD diagnosis groups. In addition, we will present the results from the analyses of the methylation status of one CpG island at the promoter of the exon 1 of the brain-derived neurotrophic factor gene.

Conclusion: These findings suggest the possibility that the methylation rate of a certain CpG at the promoter of the 5-HTT gene may be a diagnostic biomarker in PTSD.

S-05-002 Genetic approaches to understanding posttraumatic stress disorder
K. Ressler, Emory University, Atlanta, USA

Objective: Posttraumatic Stress Disorder (PTSD) is an anxiety disorder which can develop as a result of exposure to a traumatic event and is associated with significant functional impairment. Family and twin studies have found that risk for PTSD is associated with an underlying genetic vulnerability and that more than 30% of the variance associated with PTSD is related to a heritable component.

Results: Using a fear conditioning model to conceptually model the neurobiology of PTSD, three primary neuronal systems have been investigated - the hypothalamic-pituitary-adrenal axis, the locus coeruleus-noradrenergic system, and neurocircuits interconnecting the limbic system and frontal cortex. The majority of the initial investigations into main effects of candidate genes hypothesized to be associated with PTSD risk have been negative, but studies examining the interaction of genetic polymorphisms with specific environments in predicting PTSD have produced several positive results which have increased our understanding of the determinants of risk and resilience in this aftermath of trauma. Promising avenues of inquiry into the role of epigenetic modification have also been proposed to explain the enduring impact of environmental exposures which occur during key, often early, developmental periods on gene expression. Studies of PTSD endophenotypes, which areheritable biomarkers associated also consumed higher amounts of alcohol than 118AA mice of the corresponding sex, in particular at higher alcohol concentrations.

Conclusion: These studies collectively establish that the functional OPRM1 118G variant is sufficient to confer greater alcohol-induced DA-release and consumption. These findings are consistent with a role of this variant to predispose human carriers to endorphin-dependent alcoholism, but also to render patients more responsive to opioid antagonist treatment.
with a circumscribed trait within the more complex psychiatric disorder, may be more directly amenable to analysis of the underlying genetics and neural pathways and have provided promising targets for elucidating the neurobiology of PTSD.

**Conclusion:** Knowledge of the genetic underpinnings and neural pathways involved in the etiology and maintenance of PTSD will allow for improved targeting of primary prevention amongst vulnerable individuals or populations, as well as timely, targeted treatment interventions. This article is part of a Special Issue entitled ‘PTSD’.

**S-05-003** Stress, emotion and cognition: Lessons from studying PTSD neurocircuitry

**J. Liberson**, University of Michigan, Ann Arbor, USA

**Objective:** Functional neuroimaging studies identified abnormalities in amygdala, Anterior Cingulate Cortex, Medial Prefrontal Cortex and insula in Post-traumatic stress disorder. Our presentation will describe recent studies and state of the art knowledge of neurocircuitry involved in PTSD vulnerability, neurophysiology and symptom formation.

**Methods:** The original conceptualization linked Amygdala and mPFC abnormalities to abnormal fear learning and expression, however more recent models examine the potential contribution of these regions to processes of emotional regulation, memory recall and reinstatement and contextual modulation. fMRI studies using these methods in PTSD will be discussed.

**Results:** In addition, novel analytical approaches to fMRI data allow for study of connectivity among various brain regions both during resting state and during specific tasks, providing additional information about the status of functional networks of brain regions. Initial findings of functional network abnormalities in PTSD are emerging, and they offer additional insights into abnormal brain processes potentially contributing to PTSD pathophysiology and symptom formation.

**Conclusion:** Together, these novel and more complex models of information processing in PTSD allow for more nuanced understanding of PTSD pathophysiology and symptom formation, as well identifying potentially more sensitive endophenotypic endpoints for treatment studies. Finally, recent integration of genetic and neuroimaging approaches offers a new and powerful tool to further describe intermediate phenotype (endophenotype) in PTSD, and to better identify the specific contribution of genetic vulnerability or resilience in PTSD development.

**S-05-004** Intrinsic network abnormalities in PTSD

**R. Lanius**, 3; J. Daniels, 3; P.C. Williamson, 4; A.C. McFarlane, 1; K.A. Morey, 1; C.R. Clark, 1; M. Shavit, 1; London, Canada; 2; Millwood, Australia; 3; Adelaide, South Australia, Australia; 4; Heidelberg, Germany

**Objective:** Previous neuroimaging studies in healthy controls have shown the existence of a “default mode network” of correlated brain regions active during rest. These regions include the posterior cingulate, anterior cingulate and medial prefrontal cortex, and lateral parietal areas. The current studies examined (1) the nature of the abnormalities in the default network in chronic PTSD related to early life trauma; (2) whether default network connectivity could predict PTSD symptomatology in an acutely traumatized sample; and (3) the pattern of default network connectivity during rest versus a working memory task in PTSD.

**Methods:** Patients with acute and chronic posttraumatic stress disorder (PTSD) related to early-life trauma and healthy controls underwent a 5.5-minute functional magnetic resonance imaging scan with their eyes closed. Areas of the brain whose activity is positively and negatively correlated with that of the PCC/precuneus were assessed in both groups. In addition, a working memory task and psychophysiological analyses with the posterior cingulate cortex and the medial prefrontal cortex as seed regions during fixation in patients with chronic PTSD and healthy controls were conducted.

**Results:** In healthy controls, activity in the posterior cingulate seed region was found to positively correlate with other regions of the default network. This correlation was significantly altered in the chronic PTSD group. Altered connectivity between the posterior cingulate and brain regions associated with the task positive network were observed in chronic PTSD during a working memory task. Results in the acutely traumatized sample suggest that resting state connectivity of the PCC with the right amygdala predicts future PTSD symptoms.

**Conclusion:** These results suggest that the integrity of the default network is compromised in acute and chronic PTSD and that the extent of the deficit reflects clinical measures of PTSD.

**S-06-001** Targeting glutamate clearance in the development of treatments anxiety and depression: Focus on EAATS

**C. Saracino**, Yale University, New Haven, USA

**Objective:** There is increasing evidence suggesting altered regulation of glutamate neurotransmission contributes to the pathophysiology of major mood and anxiety disorders. Recent reports demonstrating the antidepressant-like effects of several glutamatergic agents has further spurred interest in gaining a greater understanding of the role of glutamate in mood disorders. In a parallel line of research several postmortem studies have demonstrated marked giall cell pathology and altered levels of excitatory amino acid transport (EAAT) expression associated with several neuropsychiatric disorders. As giall cells are primarily responsible for the clearance and metabolism of glutamate in the brain there is strong motivation to understand the interaction between giall cell glutamate neurotransmission and psychiatric disorders.

**Methods:** The rodent chronic unpredictable stress (CUS) model was employed to investigate the effects of stress on giall cell function and glutamate cycling. Additional studies using drugs such as riluzole and cerebroxone, shown to alter giall cell clearance of glutamate were used to investigate potential antidepressant-like effects in the CUS model. Molecular, cellular and physiological measures were made to determine the effects of stress and the drugs on giall cell markers, metabolism and glutamate/glutamine cycling. Dihydroykainic acid (DHK) an EAAT blocker, was used to specifically investigate the role of glutamate uptake in relation to the effects of stress and antidepreessant actions. Lastly, studies using GLT-1 (EAAT2) knockout mice were performed to further evaluate the effects of glutamate clearance. Clinical trials evaluating the efficacy of these drugs will be discussed.

**Results:** CUS resulted in reduced levels of GLT-1 protein in the pre-and infra-limbic brain regions and reduced levels of glutamate/glutamine cycling. Riluzole and cerebroxone both produced anti-depressant-like effects in several rodent models that could be attenuated with DHK. The drugs also had a reduced antidepressant-like effect in heterozygous GLT-1 knockout mice.

**Conclusion:** Similar to previous findings form postmortem studies of depressed patients the findings suggest CUS produces changes in giall cells and glutamate transporters. Drugs targeting glutamate transporter activity appear to have antidepressant-like effects in rodent models and possibly in clinical trials.

**S-06-002** Modulating the NMDA receptor complex in developing therapeutics for bipolar disorder and major depressive disorder

**C. Zarate**, NIH/NIMH, Bethesda, USA

**Objective:** Current treatments are generally unsuccessful for a number of patients with severe and recurrent mood disorders. Reasons for this lack of better therapeutics include our limited understanding of the neurobiological basis of mood disorders, and of the mechanism of action of existing effective medications. A key limitation of existing therapeutics is that they are associated with a significant lag of onset of action. Pharmacological strategies that...
rapidly reverse depressive symptoms including suicidal ideation would have an enormous impact on public health. Several converging lines of evidence suggest that dysfunction of the glutamatergic system—particularly the N-methyl-D-aspartate (NMDA) receptor complex—may play an important role in the pathophysiology of major depression. Therefore, testing the efficacy of NMDA receptor modulators and subunit modulators could yield an improved knowledge of the neurobiological processes involved in these complex illnesses, and lead to the development of radically improved treatments.

Methods: Several trials examining drugs that affect the NMDA receptor complex have been conducted to date at NIH in major depressive disorder (MDD) and bipolar depression (1 double-blind placebo-controlled study with memantine, 1 with ketamine followed by continual am thriprenyl nitroprusside, 3 controlled studies with the NMDA antagonist ketamine, and 1 with a selective NR2B antagonist). In addition, we have obtained biomarker data with including peripheral and electrophysiological and neuroimaging measures such as magnetoencephalography (MEG), neuroimaging (position emission tomography [PET], magnetic resonance spectroscopy [MRS]) looking for peripheral and neural signals of antidepressant response to NMDA antagonists.

Results: In the three controlled studies with ketamine, a rapid antidepressant response was found. In the first study in MDD, we found an onset of antidepressant action within 110 minutes. The effect size for the drug difference was very large (d = 1.46) after 24 hours and large (d = 0.68) after 1 week. In two BPD studies, we found an antidepressant response within 40 minutes; this improvement remained significant throughout the course of the week for up to 3-5 days. In the latter controlled study, we found significant anti-suicidal effects within 4 minutes last 3 days. An antidepressant signal was also found with an oral selective NR2B antagonist in TRD. The use-dependent NMDA antagonist memantine was not found to have significant antidepressant effects. With regards to biomarkers predicting antidepressant response, we found that increases in slow wave activity (SWA), a putative marker of synaptic plasticity and gamma power cortical activity correlated with decreases in depressive symptoms following ketamine infusion. Furthermore, premenstrual anterior cingulate cortex, an emotional and cognitive task predicted antidepressant improvement to ketamine.

Conclusion: Modulating the glutamatergic system, particularly at the NMDA receptor complex appears to be important to the mechanism of immediate antidepressant and anti-suicidal response. Electrophysiological and neuroimaging studies are yielding important insights into the neural correlates of rapid antidepressant action.

S-06-003 Targeting glutamate release as a testing ground for compounds with antidepressant/anxiolytic action
M. Popoli. University Milano, Italy

Objective: Stressful life events impact on memory and cognition and are known to precipitate mood/anxiety disorders. It is increasingly recognized that stress and its neurochemical and endocrine mediators induce changes in glutamate synapses morphology and transmission.

Methods: We showed previously that unpredictable footshock (FS)-stress induces enhancement of depolarization-dependent glutamate release from synaptosomes of prefrontal and frontal cortex (P/FC), due to a rapid increase in corticosterone (CORT) levels. Activation of glucocorticoid receptor and presynaptic SNARE complexes accumulation. Intriguingly, chronic pretreatments with several antidepressants, with distinct primary mechanisms, completely abolish the increase of glutamate release induced by FS-stress. Patch-clamp recordings from prefrontal cortex pyramidal neurons revealed that FS-stress induces changes in paired-pulse facilitation (PPF) and its calcium-dependence consistent with an increase in glutamate release. Chronic desipramine, as observed for glutamate release, completely prevented the changes in PPF and calcium-dependence. However, desipramine does not block the increase of the size of the readily releasable pool (RfP) of vesicles induced by FS-stress (measured as hyperpolarizing sucrose-induced glutamate release), suggesting that the dampening action of the antidepressant does not affect the RfP size.

Results: Overall, our results show a novel effect of antidepressants that could be related to their therapeutic action in mood/anxiety disorders. Chronic treatments with benzodiazepines and antipsychotic drugs have been performed before the stress protocol, to understand whether this dampening effect of antidepressants is shared by other psychiatric drugs.

Conclusion: We are currently testing if measurement of stress-induced glutamate release can be used as a test to assay the preventing action of antidepressants in stress response. Understanding the action of traditional drugs on glutamate transmission could be of great help in developing compounds that may work directly at this level.

S-06-004 Metabotropic glutamate receptors as therapeutic targets for anxiety and depression: Focus on mGlu7
J. Cryan. University College Cork, Ireland

Growing evidence suggests that the glutamatergic system may be a regulator of glutamatergic function and modulates behaviours relevant to depression, anxiety, and cognitive dysfunction. Metabotropic glutamate (mGlu) receptors are poised to participate in a wide variety of functions of the CNS. The presynaptic mGlu7 receptor shows the highest evolutionary conservation within the family and is thought to regulate neurotransmitter release. The mGlu7 receptor is also the most widely distributed of the presynaptic mGlu receptors and is present at a broad range of synapses that are postulated to be critical for both normal CNS function and a range of psychiatric and neurological disorders. A growing body of evidence suggests that the mGlu7 receptor is a key player in shaping synaptic responses at glutamatergic synapses as well as being a key regulator of inhibitory GABAergic transmission. The development of selective pharmacological and genetic tools has allowed for the unravelling of mGlu7 receptor function in a host of physiological and behavioural processes. Knockout mice and siRNA knockdown has pointed to a role of the mGlu7 receptor in anxiety, extinction of fear and aversion learning, spatial memory and the hormonal response to stress. In addition, these studies are largely supported by pharmacological manipulation of mGlu7 receptor although controversies exist and better in vivo selective ligands are necessary. Finally, selective antidepressant drugs and models of depression have alterations in hippocampal mGlu7 expression which may contribute to their behavioural effects. Together, these data suggest that the mGlu7 receptor is an important regulator of glutamatergic function and modulates behaviours relevant to depression, anxiety and cognition. Thus this receptor presents an innovative therapeutic target for stress-related disorders at the interface of cognition and emotion.

Policy of full disclosure: None.
**S-08. The neurobiology of compulsivity and OCD: From basic science to clinical practice**

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**S-07-002 Genetic associations and gene-environment interactions between candidate genes related to stress-response and stressful life events, in severe suicide attempts.**

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¹Karolinska Institutet, National Prevention of Suicide, Stockholm, Sweden; ²NASP, Stockholm, Sweden.

**Objective:** Suicidal behavior (SB) is a major burden in most nations worldwide and a major public health concern, as ~1 million people commit suicide (SC) each year and 10-20 times more perform suicide attempts (SA). The causes of why certain people engage in SB are complex, involving both environmental and genetic factors, and interactions in-between. The aim of this study is to elucidate the interaction of certain genes with exposure to physical and sexual abuse amongst the young (G × E).

**Methods:** We performed G × E studies taking into consideration lifetime of trauma and gender concerning the corticotropin releasing hormone receptor 1 (CRHR1) gene, a major and systemic stress-modulator of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis. We assessed exposures to rape and/or physical assault (PA, below or over age of 18) or other lifetime stressful life events (SLEs) in male and females, by using a family-based design (n = 660 trios) complemented by case-control analysis, in relation to the outcome of severe lifetime SA in the offspring.

**Results:** We observed CRHR1 G × E among predominantly female SA between 5- SNP rs7209436 and PA below 18 years of age and a male-specific G × E between 3′-SNP rs1640465 and adulthood PA exposure, both sharing the SA characteristic of aggression. A third male-specific CRHR1 G × E was among depressed SA, between SNP rs4792887 and cumulative lifetime SLEs. Furthermore, excessive stress has the potential to induce unfavorable side-effects in a variety of brain-functions, by interactions of the HPA axis with other neurotransmitters.

**Conclusion:** We conclude that SA showed differences in their G × Es, concordant with a complex SB-aetiology, and that knowledge of specific G × Es might become helpful for focused prevention and intervention efforts in the future.

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**S-07-003 The pharmacogenetics of suicidal adverse reactions to SSRI medications in children and adolescents**

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¹University of Tel Aviv, Sacker School of Medicine, Petah Tikva, USA; ²University of Tel Aviv, Petah Tikva, Israel.

**Objective:** Depression is a common disorder in adolescents with serious morbidity and even mortality if not treated. SSRI medications are commonly used for such treatment but only about 55-60% of depressed subjects respond to treatment and 5% show severe side effects in including suicidal behavior and ideation.

**Methods:** Consecutive admissions (n = 121) to a Child and Adolescent Psychiatry outpatient were assessed and diagnosed by DSM-IV-TR criteria. The following assessment instruments were used: The Schedule for Affective Disorders and Schizophrenia for school aged children, Present and Lifetime, Screen for Child Anxiety and Related Emotional Disorders, Children’s Depression Inventory; Suicidal Ideation Questionnaire, Clinical Global Impression Scale, SSRI Side Effect Profile Inventory.

**Results:** We performed G × E studies taking into consideration lifetime of trauma and gender concerning the corticotropin releasing hormone receptor 1 (CRHR1) gene, a major and systemic stress-modulator of the neuroendocrine hypothalamic-pituitary-adrenal (HPA) axis. We assessed exposures to rape and/or physical assault (PA, below or over age of 18) or other lifetime stressful life events (SLEs) in male and females, by using a family-based design (n = 660 trios) complemented by case-control analysis, in relation to the outcome of severe lifetime SA in the offspring.

**Conclusion:** We conclude that SA showed differences in their G × Es, concordant with a complex SB-aetiology, and that knowledge of specific G × Es might become helpful for focused prevention and intervention efforts in the future.

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**S-08-001 Symptomatology and pharmacotherapy of obsessive-compulsive disorder**

D. Stein.
University of Cape Town, Department of Psychiatry, Capetown, South Africa.

**Objective:** Obsessive-compulsive disorder is an important neuropsychiatric disorder associated with significant morbidity. This presentation aims to review key questions about the symptomatology and nosology of obsessive-compulsive disorder, as well as current work on the pharmacotherapy of this disorder.

**Methods:** A number of systematic reviews have recently been undertaken of both diagnostic issues and pharmacotherapy approaches in obsessive-compulsive disorder; this presentation draws from this work, highlighting key questions for the field, and summarizing relevant data.

**Results:** There is growing acceptance in the field of the construct of “obsessive-compulsive related disorders”, although there continues to be debate about its optimal boundaries. There is good evidence for the efficacy of serotonin reuptake inhibitors (SRIs) as first line agents, some evidence for the efficacy of antipsychotic agents as augmenting agents in individuals refractory to SRIs, and ongoing interest in a range of other drug classes.

**Conclusion:** While there have been advances in diagnosis and treatment of obsessive-compulsive disorder, further work to delineate the underlying psychobiology of this disorder is needed to continue to progress the field.

**Policy of full disclosure:** Dr. Stein has received research grants and/or consultancy honoraria from Abbott, Astrazeneca, Eli-Lilly, GlaxoSmithKline, Jazz Pharmaceuticals, Johnson & Johnson, Lundbeck, Orion, Pfizer, Pharmacia, Roche, Servier, Solvay, Sumitomo, Takeda, Tikkah, and Wyeth.

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**S-07-004 Noradrenergic and serotonergic pathways and the stress diathesis model of suicidal behavior**

J. Mann¹, V. Arango², R. Parsy³, M. Oquendo⁴, H. Glassaly⁵.
¹Columbia University, NY State Psychiatric Institute, New York, USA.

**Objective:** To map the state of the noradrenergic and serotonergic neurotransmitter systems in suicide and nonfatal suicide attempts and link to identified components of psychopathology associated with suicidal behavior.

**Methods:** Postmortem brain autoreadiography was employed to map changes in pre and post-synaptic receptors in the serotonergic and noradrenergic neurotransmitter systems in suicides. PET in vivo imaging was used to map serotonin receptors and the transporter in brain in nonfatal suicide attempters with major depression compared with nonattempter major depression and healthy volunteers. Findings are related to clinical components of the stress diathesis model we have proposed for suicidal behavior.

**Results:** Noradrenergic deficiencies are related to lethality and probability of suicidal behavior and to its lethality. These deficits are correlated with hopelessness and depression. Serotonergic deficits are found in suicides in the brainstem nuclei, ventromedial prefrontal cortex and anterior cingulate. More recently we have confirmed some of these findings in living survivors of suicide attempts. Genetic and epigenetic causal factors have been identified for some of these findings.

**Conclusion:** The identification in nonfatal suicide attempters of biological abnormalities also found in suicides suggests that brain scanning may be a potential screening tool for those at risk for suicide. Treatment and prevention strategies using these findings as biomarkers of risk offer an alternative method for outcome indices in medication and psychotherapy trials.

**Policy of full disclosure:** Dr. Mann has past unrelated imaging grants from GSK and Novartis.
Objective: Obsessive-compulsive disorder (OCD) is a psychiatric disorder affecting 1–3% of the population. The orbitofrontal cortex, the striatum and the dopaminergic and serotonergic systems have been implicated in the pathophysiology of OCD, yet the ways in which these neural systems interact to produce obsessions and compulsions in patients is currently unknown. Data obtained using pharmacological manipulations, lesions, inactivation and electrical stimulation in the signal attenuation rat model of OCD suggest specific ways in which these neural systems interact to produce compulsive behaviors.

Methods: The signal attenuation model is a theory-driven rodent model of OCD which builds on the assumption that compulsive behaviors result from a deficient signaling that a response was effective in producing an outcome.

Results: Work in this model found that lesions to the orbitofrontal cortex decrease striatal serotonin and dopamine content and increase compulsive lever-pressing, and that this increase is blocked by intra-striatal administration of a selective serotonin reuptake inhibitor. Lesions to the subthalamus nucleus similarly decrease striatal serotonin and dopamine and increase compulsive lever-pressing. Consistent with these findings, high frequency stimulation of the subthalamic nucleus, which exerts an anti-compulsive effect in OCD patients and in the signal attenuation model, increases dopamine content in the striatum.

Conclusion: Taken together, these results suggest that alterations in striatal serotonin and/or dopamine may provide a final common pathway by which different brain pathologies may lead to compulsive behaviors.

Objective: Obsessive-compulsive disorder entails a tendency compulsively to perform repetitive acts and has traditionally been associated with anxiety states and obsessions, putatively reflecting pathology in the orbitofrontal cortex, striatum and amygdala. We have been searching for endophenotypic markers in the disorder that can also be related to these brain systems on the basis of studies with human neuroimaging and animal models.

Methods: A major candidate has been cognitive inflexibility, for example, in reversal learning and extra-dimensional set-shifting (a core component of the Wisconsin Card Sorting Test), previously shown in studies with monkeys and rodents to depend on distinct cortico-striatal loops involving the orbitofrontal and lateral prefrontal cortex. We used a human fMRI paradigm previously shown to separate these regions according to the BOLD responses during reversal and extra-dimensional set-shifting as well as parallel behavioural paradigms in rodents and monkeys.

Results: We demonstrated hypoactivity of the orbitofrontal network during reversal learning in an obsessive-compulsive group and in their first degree relatives without clinical symptoms. Parallel work with marmoset monkeys showed reversal learning to depend on cortico-striatal loops involving the orbitofrontal and lateral prefrontal cortex. We used a human fMRI paradigm previously shown to separate these regions according to the BOLD responses during reversal and extra-dimensional set-shifting as well as parallel behavioural paradigms in rodents and monkeys.

Conclusion: These data suggest that DBS induces acute increases in power in cortical regions, but over time this change undergoes compensation and is replaced with changes in coherence. Changes in coherence is likely to reflect alterations in information processing. Thus increased coherence between the OFC and its afferent structures would improve signal processing, potentially enabling the OFC to effectively devalue stimuli that are no longer relevant for behavior; a function impaired in OCD. In contrast, decreased coherence in the prefrontal FC and ventral striatum may reflect improved extinction. Whether DBS has different effects on power and coherence in animal models of OCD is currently being evaluated.

Policy of full disclosure: Cambridge Cognition (consultancy and royalties) (CANTAB) Consultancy and research grants from E. Lilly, Lundbeck and GlaxoSmithKline. This research was funded by a Programme Grant from the Wellcome Trust. The BCNI is funded by a joint grant from the MRC and the Wellcome Trust.

Animal models of obsessive-compulsive disorder: What deep brain stimulation may tell us about pathophysiology

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Objective: OCD patients exhibit hyperactivity in the orbitofrontal cortex (OFC), and effective treatments normalize OFC activity. Moreover, intractable OCD is responsive to deep brain stimulation (DBS) of the central striatum (VS). Therefore, we evaluated animal models of OCD, and examined the neuronal alterations produced by continuous DBS of the VS target used in OCD treatment in humans.

Methods: Two models of OCD were evaluated; the clomipramine model (15 mg/kg twice/day between postnatal days 9 and 16) and the quinpirole model (0.5 mg/kg twice/week for 7 weeks). Animals were evaluated for compulsive behavior and VTA DA neuron activity. DBS was administered to the VS site for 5 days continuously (130 Hz, 100 usec and 100 uA bilaterally), and local field potentials recorded.

Results: In our hands, the clomipramine model failed to show results consistent with OCD. Quinpirole treated rats showed significant perseveration and compulsive lever pressing, and increased VTA DA neuron population activity. DBS in control rats increased gamma power bilaterally in the VS, but decreased coherence between the VS and the prelimbic PFC, and between the VS and the thalamus. In contrast, there was an increase in coherence between the OFC and the thalamus, and the OFC bilaterally.

Conclusion: These data suggest that DBS induces acute increases in power in cortical regions, but over time this change undergoes compensation and is replaced with changes in coherence. Changes in coherence is likely to reflect alterations in information processing. Thus increased coherence between the OFC and its afferent structures would improve signal processing, potentially enabling the OFC to effectively devalue stimuli that are no longer relevant for behavior; a function impaired in OCD. In contrast, decreased coherence in the prefrontal FC and ventral striatum may reflect improved extinction. Whether DBS has different effects on power and coherence in animal models of OCD is currently being evaluated.

Policy of full disclosure: Johnson & Johnson, Lundbeck, Pfizer, GlaxoSmithKlein, Merk, Takeda, Dainippon Sumitomo, Otsuka.

Role of orexin/hypocretin in panic and other stress disorders

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Objective: Panic disorder (PD) is a severe anxiety disorder characterized by recurrent panic attacks affecting about 2–5% of the population and resulting in severe disability in about a third of those subjects. We recently identified that orexin (hypocretin) neurons are one of the key regulators of a coordinated panic response and that patients with panic but not depression symptoms do indeed have high levels of orexin in their cerebrospinal fluid. Panic patients also have enhanced vulnerability to conditioned fears, avoidance and phobias. The present study was conducted to elucidate the mechanisms of these long term consequence of panic disorder utilizing preclinical model system.

Methods: Utilizing chronic disinhibition of orexigenic neurons in the perifornical/dorsomedial hypothalamus (PeF/DMH) we tested the effects on disrupted network functions on induction of 1) chronic anxiety states; 2) enhanced fear conditioning; and 3) delayed extinction of conditioned fear. We measured behavioral, molecular and electrophysiological endpoints, utilizing pharmacological and gene silencing experiments in both whole animal and slice preparations.
Results: Chronic disinhibition of ORX neurons in the DMH/Pf e
inducing molecular and network changes in the bed nucleus of the
striatal terminals (BNST) to decrease GABAergic and to enhance glutamatergic neurotransmission in order to induce a chronic anxiety-like phenotype. Hyperactivation of orexin system enhanced acquisition and expression of conditioned fears seen in panic-prone rats, and re-sulted in excitation and reduced inhibition in the central nucleus of
the amygdala (CeA), thus facilitating neuronal plasticity in the CeA.

Conclusion: These results provide a mechanistic model to under-
stand the pathophysiology of PD and its disabling consequences and
provide insight into the functional network electrophysiology as well
as basic cellular and molecular changes within key limbic circuits.
Finally, at the translational level, these results provide novel insights
into the persistent and hard to extinguish nature of agoraphobia and
anticipatory anxiety in patients with panic disorder.

Policy of full disclosure: Supported by the US National Institute
of Mental Health grant, R01 MH52619.

S-09-002 CRH1 Receptor antagonists – Back on the map
F. Holsboer, Max-Planck-Institut, für Psychiatrie, Munich, Germany

Objective: Strong evidence emerged from basic and clinical research that
many of the signs and symptoms prevalent in depression are
mediated by CRH via CRH1 receptors. Key findings were behavioral
tests in animals that were chronically stressed, received centrally
CRH or were overexpressing transgenically CRH. The CRH1 sub-
type was among other techniques identified by conditional CRH1
gene deletions. Clinical support for targeting the CRH/CRH1 system
stem came from enhanced CRH concentrations in the brains and cere-
bral spinal fluids of depressed patients, neuroendocrine and sleep-
EEG studies and a first open label trial with R121919, a nonpeptide
CRH1 antagonist. All major pharmaceutical companies developed
CRH1 antagonists and compared them with current standard com-
 pounds and placebo. Without exception all so far reported controlled
trials yielded negative results, i.e. the test drugs were equal to placebo
and comparators were superior. The reason was that in the absence of
laboratory tests identifying patient subgroups where CRH hyper-
activity accounts for the clinical condition, a specific intervention such
as CRH1 blockade will be inferior to a current unspecific anti-
depressant.

Methods: We developed a genestest allowing to accumulate potent-
tial CRH hypersecretors. In addition, we observed in transgenic mice
overexpressing CRH a disinhibition of REM-like sleep. REM-
disinhibition was associated with beneficial response to CRH1
antagonist treatment among severely depressed patients. Therefore
we argue that a genestest combined with sleep-EEG analysis will
identify potential CRH1 antagonist responders.

S-09-003 Duplications of the neuropeptide receptor gene
VIPR2 confer significant risk for schizophrenia
J. Sebat, Chief, Regenter Center for Genomics of Neuropsychiatric, La Jolla,
USA

Rare copy number variants (CNVs) have a prominent role in the
ontology of schizophrenia and other neuropsychiatric disorders.
Substantial risk for schizophrenia is conferred by large (>500-kilo-
base) CNVs at several loci, including microdeletions at 1q21.1 (ref. 2), 3q29 (ref. 3), 15q13.3 (ref. 2) and 22q11.2 (ref. 4) and microduplication
at 16p11.2 (ref. 5). However, these CNVs collectively account for
a small fraction (2-4%) of cases, and the relevant genes and neuro-
biological mechanisms are not well understood. Here we performed
a large two-stage genome-wide scan of rare CNVs and report the
significant association of copy number gains at chromosome 7q36.3
with schizophrenia. Microduplications with variable breakpoints
occurred within a 362-kilobase region and were detected in 29 of 8,290
(0.35%) patients versus 2 of 7,431 (0.03%) controls in the combined
sample. All duplications overlapped or were located within 89 kilo-
bases upstream of the vasoactive intestinal peptide receptor gene
V1PR2. V1PR2 transcription and cyclic-AMP signalling were signifi-
cantly increased in cultured lymphocytes from patients with micro-
duplications of 7q36.3. These findings implicate altered vasoactive
intestinal peptide signalling in the pathogenesis of schizophrenia and
indicate the VPA2 receptor as a potential target for the development
of new antipsychotic drugs.

S-09-004 Galanin and galanin receptors in depression – focus
on the human brain
T. Hökfelt1, E. Le Maître2, S. Barde2, E. Kuteeva3, M. Palkovits3,
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3Semmelweis University & HAS, Budapest, Hungary

Objective: Galanin is a 29 (30 in humans) neuropeptide that is ex-
pressed in many regions of the rodent brain, including locus coeruleus
(LC) and dorsal raphe nucleus (DRN), where it in rat coexists with
noradrenaline and serotonin, respectively. There is evidence from
animal experiments that galanin is involved in mood regulation, in
fact also from human genetic studies. Animal experiments suggest
that a galanin antagonist should have antidepressant actions. The aim
of this work is to reveal to what extent distribution of the galanin
system in the human brain is similar to that reported in rodents.

Methods: We have used riboprobes and in situ hybridization to
localize galanin and its receptor (GalR1-3) mRNAs in LC and DRN.
Some other markers like transcripts for tyrosine hydroxylase, trypto-
phan hydroxylase 2, vesicular glutamate transporters and nitric oxide
synthase were also analysed.

Results: In the human post mortem brain LC galanin and GalR3,
but not GalR1 and -R2 could be detected. In the DRN galanin was not
found in areas harbouring serotonin neurons, but GalR3-positive and
serotonin neurons overlapped.

Conclusion: These findings indicate that the galanin system ex-
hibits considerable species differences, which should be taken into
account in work aiming at development of novel antidepressants. Our
results based on analysis of the human post mortem brain, and on animal
experiments, suggest that antagonists at the GalR3, but not the
GalR1, receptor would be potential antidepressants. In fact, such an-
tagons have been generated.

S-10. Putative abnormalities in Orexin and
GABA metabolism in panic disorder

S-10-001 Orexin and psychiatric symptoms in suicide
attempters
I. Brandin1, L. Träskman-Bendz2, 1Lund University, Psychoneuroimmunology
Unit, Sweden; 2Lund University, Sweden

Objective: The orexins (hypocretins) are hypothalamic peptides ini-
 tially discovered to be involved in the regulation of sleep, appetite
and state of arousal. We analyzed orexin levels in the cerebrospinal
fluid (CSF) of patients who were hospitalized after a suicide attempt.

Methods: At the day of the lumbar puncture, psychiatric symptoms
were carefully rated using the Comprehensive Psychopathological
Rating Scale (CPRS) as well as the Suicide Assessment Scale (SUAS),
and the patients underwent a thorough diagnostic interview.

Results: We found that suicide attempts with a diagnosis of
Major Depressive Disorder had significantly lower levels of orexin in the
CSF than patients with adjustment disorder and dysthymia. Further-
more, we found that orexin levels increased significantly dur-
ing the first year after the suicide attempt, together with an improve-
ment of the scores on the SUAS. We also found that low CSF-orexin
levels were related to pronounced symptoms of inertia and reduced
motor activity in suicidal patients.

Conclusion: The lower the orexin levels, the higher were ratings of
overall illness, as observed by a specialist in psychiatry. Interestingly,
depressed patients with anxiety display significantly higher orexin
levels than patients without such symptoms. Thus, high vs. low levels
of orexin might be coupled to different spectrums of psychiatric
symptoms.

S-10-002 GABA imaging findings in panic disorder measured
by 1H MRS
U. Dyvdal1, Z. Long2, Y.-W. Shin3, M. Dzemidzic1, A. Goddard4,
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West Lafayette, USA; 3Department of Psychiatry, Seoul, Republic of
Korea; 4Indiana Univ. School of Med., Indianapolis, USA

Objective: Several 1H Magnetic Resonance Spectroscopy (MRS)
studies found decreased levels of the inhibitory neurotransmitter

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y-aminobutyric acid (GABA) in cortical regions of unmedicated patients with panic disorder (PD). Furthermore it has been suggested that a positive family history of PD may play a role in cortical GABA changes in PD patients. This talk will review published 1H-MRS/GABA findings in PD and present data from a recent study investigating the influence of family history on GABA levels in unmedicated PD patients.

Methods: A GABA-editing MRS technique was used for GABA detection in anterior cingulate cortex (ACC) and occipital cortex (OCC) in five family history-positive (FHP) patients, six family history-negative (FHN) patients and 11 matched controls.

Results: While no significant difference in GABA levels was expressed as the ratio of GABA over total Creatine (iCr), were found between the groups in either brain region, ACC GABA/iCr levels had a numerical trend to be lower in FHP patients versus controls. A significant correlation was found between OGG ACC/iCr levels and the trails B test scores (a test of visual attention) (r = 0.8, p < 0.05) in this patient group. Interestingly, the correlations between prescan state anxiety scores and GABA/iCr levels seem to be opposite for ACC and OCC, as well as for FHP and FHN patient groups: a positive correlation is found for FHN patients in ACC (r = 0.95, p < 0.01) and for FHP patients in OCC (r = 0.92, trend only); however, a negative correlation was seen for FHN patients in OCC (r = -0.88, p < 0.01) and for FHP patients in ACC (r = -0.62, trend only).

Conclusion: Our results agree with previous reports on GABA deficits in PD patients. Decreased GABA in family history-positive patients suggests a unique GABAergic mechanism in these patients.

Methods: As mentioned by other symposium speakers, perturbations in GABA (MRS measures) and neuroepetide/ORX function (CSF ORX) may contribute to a panic vulnerability state, which may be reflected in variations in resting-state fMRI parameters. A series of recent preclinical and clinical studies (Johnson, Truitt et al., 2010), has led us to hypothesize that PD is associated with specific cortical and subcortical GABA deficits that result in disruption of normal inhibitory regulation of ORX neurons. This disruption promotes excessive ORX release, sympathetic activation, and vulnerability to spontaneous or lactate-induced panic.

Results: Follow-up animal and human work within our anxiety research team has identified evidence of ORX neuronal hyperactivity in association with CO2-induced anxiety. Furthermore, other investigators have reported ORX metabolic abnormalities at rest in patients with chronic PTSD, another anxiety disorder with pathophysiologic similarities to PD (Strawn et al., 2010).

Conclusion: Our collaborative research effort has implications for elucidating key ORX-GABA interactions that contribute to human panic states, as well as for defining the therapeutic mechanisms of actions of known effective antipanic therapies (e.g. benzodiazepines, SSRIs, CBT), and novel pananxiety agents (e.g. ORX1 receptors antagonists).

Policy of full disclosure: Pfizer-Consultant, Janssen-Independent grant awardee, Astra-Zeneca-Independent grant awardee.

RS-01. Neuroimaging applications in neuropsychopharmacologyCINP Asia Regional Committee

RS-01-001 Imaging evaluation of drug target molecule: translational perspective from animal model and human brain

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Positron emission tomography (PET) techniques have enabled the visualization of transporter protein and functions. In the field of neuropsychopharmacology, monoamine transporters such as serotonin transporter and norepinephrine transporter (NET) are the major target of antidepressants and efflux transporters such as P-glycoprotein is a major component of blood brain barrier. The serotonin transporter occupancy has been used as a reliable index for therapeutic drug monitoring. Previous PET studies on antidepressants have suggested over that 80% of occupancy provides the desired therapeutic effects. On the other hand, the NET occupancy by antidepressants in human brain has not been reported because of a lack of suitable radioligands for NET. (S,S)-[18F]FMeNER-D2 was recently developed as a radioligand for the measurement of NET binding with PET. The mean NET occupancies of norryptiline doses were 16.4 % at 10 mg, 33.2 % at 25 mg, and 41.1 % at 75 mg, respectively. The mean plasma concentration of norryptiline was 0 ng/ml at 10 mg, 23.7 ng/ml at 25 mg, and 50.5 ng/ml at 75 mg. Estimated ED50 (50 % effective dose) was 76.8 mg of administration dose and 59.8 mg/ml of plasma concentration.

RS-01-002 Drug-receptor occupancy study in predicting proper dose of psychotropic drugs with PK-PD modeling

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Objective: To predict proper dose of antipsychotic drugs in terms of receptor occupancy, it is necessary to determine the relationship between plasma drug concentration and receptor occupancy. Typically, most studies of antipsychotic drugs have applied the Emax model alone to characterize the relationship. However, a limitation of this approach is that it does not account for the discrepancy between the time courses of plasma drug concentration and receptor occupancy by antipsychotic drugs. This prompts the necessity of combined pharmacokinetic-pharmacodynamic (PK-PD) modeling for the reliable analysis of the concentration-occupancy relationship. We will introduce PK-PD modeling in the concentration-occupancy analysis and compare it with conventional approach (Emax model alone).

Methods: We will introduce PK-PD modeling in the concentration-occupancy analysis and compare it with conventional approach (Emax model alone).
Methods: We measured dopamine receptor occupancy using [11C]raclopride PET and plasma concentration of aripiprazole to a number of time points after the administration of aripiprazole. We built the PK-PD model and simulated the time effect on the concentration-occupancy relationship.

Results: The hysteresis characteristics were observed in the concentration-occupancy relationship and the value of EC50 was different according to the analysis approach (EC50 = 11.1 ng/ml (95% CI = 10.1 – 12.1) from Emax model alone; EC50 = 8.63 ng/ml (95% CI = 7.75 – 9.51) from PK-PD model).

Conclusion: This finding suggests that PK-PD modeling is required to obtain reliable results in study about the antipsychotic concentration-occupancy relationship.

RS-01-003 Association of brain serotonin transporter (SERT) availability and brain-derived neurotrophic factor in models of SERT genotypes in human subjects: a new insight for the development of antidepressant

Y.-H. Chou, Taipei Veterans General Hospit, Taiwan

Objective: The S-allele of functional polymorphisms of the serotonin transporter (SERT) gene has been demonstrated to have lower transcriptional activity compared with the L-allele, which shows low expression of SERT in the brain. However, this finding cannot be consistently replicated in vivo. Importantly, the frequency of polymorphism is different from Asian and Caucasian. The aim of this study was to determine the availability of SERT based on SERT genotype in an Asian population. We also examined the relationship between brain-derived neurotrophic factor (BDNF) and the availability of SERT.

Methods: Sixty-two healthy subjects were recruited. Each subject underwent single photon emission computed tomography (SPECT) with 123I-ADAM for imaging SERT in the brain. The specific uptake ratio (SUR) was measured and venous blood was drawn when the subject underwent SPECT to evaluate plasma BDNF levels and SERT genotype. All subjects expressed SERT genotypes that were consistent with a bi-allelic model, and 26 subjects had SERT genotypes that were consistent with a tri-allelic model.

Results: No differences in SUR were detected in the midbrain, putamen, caudate and thalamus based on the SERT genotype using the bi-allelic and tri-allelic models. Interestingly, linear regression revealed a positive correlation between plasma BDNF and SERT availability. In particular, this relationship was observed in homozygous S-allele expression and a genotype with low functional expression (Ss/Ss/Lg) in the bi-allelic and tri-allelic models of SERT genotypes, respectively.

Conclusion: This finding might explain why the SS genotype of SERT did not increase the risk of MDD in Asian populations and implicate an important role of BDNF in the patients, who has the SS genotype of the SERT gene.

RS-01-004 A two-year follow-up study on the functional connectivity abnormality in first-episode drug-naive schizophrenia in a Chinese population

T. Li. Chengdu, China

Objective: By first episode of illness and prior to treatment, diffusion tensor imaging (DTI) studies confirm patients with schizophrenia have lower regional white matter fractional anisotropy (FA) measures than typically developing controls. However, it is not clear whether antipsychotic drugs ameliorate or worsen microstructural changes in white matter systems during the very early phase of treatment. To explore longitudinal alterations in white matter (WM) microstructure in antipsychotic-naive patients with first-episode schizophrenia during the very early phase of treatment.

Methods: High-resolution diffusion tensor imaging (DTI) was obtained from 35 first-episode drug-naive patients with schizophrenia and 22 controls as baseline and 6 weeks later, respectively. The patients received standard antipsychotic treatment during the 6-week period. The differences in Positive and Negative Syndrome Scale (PANSS) scores and Global Assessment of Functioning (GAF) scores between baseline and 6 weeks later were evaluated and expressed as a 6-week/baseline ratio. In addition a 6 week ‘difference map’ was generated from the follow-up image minus the baseline DTI image. The FA difference maps in cases and controls were compared and potential correlations between FA changes and changes in PANSS, outcome scores and antipsychotic drug dosages were explored.

Conclusion: This finding suggests that PK-PD modeling is required to obtain reliable results in study about the antipsychotic concentration-occupancy relationship.
Dr. Raison has served as a consultant to Brystol Myers Squibb and Pamlab and has developed and presented disease state promotional material for Pamlab.

S-11-003 The immune system and the kynurenine pathway in schizophrenia: Pathophysiological and therapeutic aspects

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Objective: The paradigm of a disturbed dopaminergic neurotransmission being a key-feature in the neurobiology of schizophrenia has more and more been replaced by more complex hypotheses including the interaction between distinct neurotransmitter systems and the immune system. One highly intriguing functional link is represented by the kynurenine pathway of the tryptophan metabolism.

Methods: This presentation will sum up results of several studies.

Results: The immune response in schizophrenia seems to be a two-sided sword: There are data clearly indicating an enhanced activation of the T-helper2-like immune system associated with more pronounced positive symptoms, which fit with the findings of an enhanced production of the NMDA and alpha2A-nACh receptor antagonist kynurenic acid. On the other hand there are data showing that the immune system is clearly activated, characterised by an enhanced production of pro-inflammatory cytokines. This pro-inflammatory state is associated with the activation of the enzyme indoleamine 2,3-dioxygenase (IDO) resulting in an increased production of neurotoxic kynurenine metabolites including 3-hydroxykynurenine. The immunological effects of antipsychotics partly reverse the immune imbalance and there is evidence for their modulating effect on the kynurenine pathway as well.

Conclusion: Substances acting directly on the kynurenine metabolism are still in early stages of development, while anti-inflammatory drugs acting indirectly on this metabolism are discussed as therapeutic or preventive agents in schizophrenia. Most of the current data are related to COX-2 inhibitors, which have been tested in animal experiments and in clinical trials, pointing to favourable effects in schizophrenia.

Policy of full disclosure: The author is involved in two patents on kynurenine metabolites as biomarkers for psychiatric disorders.

S-11-004 Oxidative and immune biomarkers as targets for the development of novel therapies

M. Berk. University of Melbourne, Swannston Centre, Geelong, Australia

Objective: There is abundant evidence that inflammatory and oxidative processes play a role in mood disorders. There is evidence of increased inflammatory activity in mood disorders, including elevations in cytokines.

Methods: The brain is the most metabolically active tissue, and disruptions in mitochondrial energy generation are now well described in mood disorders. Administration of pro-inflammatory cytokines is amongst the best models of depression. The consequences of inflammatory and oxidative stress include lipid peroxidation, DNA fragmentation protein carboxylation and an increased vulnerability to apoptosis. Inflammatory and oxidative stress lead to decreased BDNF and other trophic factors. Established antidepressants and mood stabilisers including lithium and valproate have a role in ameliorating oxidative stress, and additionally alter immune markers.

Conclusion: There is data that these agents may reduce risk for mood disorders. Such biomarker data have the potential to lead to the development of novel therapies for mood disorders outside of traditional monoamine targets.

Policy of full disclosure: Grant/Research support: Stanley Medical Research Foundation, MBF, NHMRC, BeyondBlue, Geelong Medical Research Foundation, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Servier. Speaker: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Pfizer, Sanofi Synthelabo, Servier, Solvay, Wyeth. Consultant: AstraZeneca, Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Janssen Cilag, Lundbeck, Servier.

S-12. Oxidative stress, and the development of mental disorders

S-12-001 Mood disorders and mitochondrial dysfunction

T. Young. University of Toronto, Canada

Mood disorders present an enormous burden of illness and many patients do not respond to available treatments. While we continue to focus on neurocognitive changes and cellular loss and damage in specific brain regions, the exact etiology remains uncertain. Genome wide association studies support multiple genes of small effect which confer increased for these illnesses. Continued progress on studying post-mortem brain tissue and blood cells from patients have demonstrated new possibilities for biological causes of these disorders. Evidence from a number of investigators has shown that oxidative stress and damage is increased in patients with bipolar disorder which may be related to abnormalities within the electron transport chain. Build up of oxidative metabolites may lead to cellular damage and loss. Studies from animal models and patients suggest that treatment with mood stabilizers may reduce oxidative damage and ultimately prevent cellular damage and loss. Oxidative stress has long been held as a mechanism in other neurodegenerative disorders including Parkinsonism. Of particular interest is the relation of oxidation to dopamine metabolism which may be important in the mechanism of action of mood stabilizing drugs. These findings help to broaden yet focus the search for the specific causes of mood disorders, lead to the development of biomarkers and make way for novel effective treatments.

S-12-002 Long term consequences of brain oxidative-stress during early postnatal life

M. Behrens. Salk Institute, La Jolla, CA, USA

Objective: Through its involvement in the generation of gamma oscillatory activity, the fast-spiking parvalbumin-positive (PV+) neuronal system is essential for shaping neuronal circuits during postnatal brain development. Discrete functional disruptions in this GABAergic system are expected to alter the excitatory/inhibitory balance in brain and to produce cognitive deficiencies, as those observed in schizophrenia. We have studied the postnatal developmental periods in which a redox imbalance produced by NMDA receptor antagonists leads to a permanent alteration of the PV+ neuronal system in the rodent cortex.

Methods: Our studies encompass molecular determinations, slice electrophysiological recordings, and in vivo EEG recordings of mice exposed to ketamine during the perinatal period. This data is then used in computer simulation studies of prefrontal cortex function.

Results: Our work has shown that repetitive exposure of rodents to ketamine during the perinatal period increases brain levels of IL-6 and activates the superoxide-producing enzyme NAPDH oxidase (Nos2). This, in turn, produces a lasting redox imbalance that leads to a permanent loss of PV and GAD67 expression in PV+ neurons, to a decreased response of the interneurons to excitatory transmission and to a diminished inhibitory drive to pyramidal neurons. At the systems level, it leads to pronounced alterations in auditory evoked related potentials, with decreased stimulus-induced gamma oscillatory activity and to a shift in the evoked gamma/beta ratio. Computational simulations that incorporate the reductions in PV and GAD67 observed in the mouse model lead to networks showing a diminished gamma-band oscillatory activity in response to stimuli, and to a reduced evoked gamma/beta ratio as observed in vivo.

Conclusion: Our data suggest that a period of oxidative-stress, caused by activation of the IL-6/Nos2 pathway during early life, may alter the normal development of PV+ neurons leading to the alterations in gamma oscillatory activity observed in schizophrenia patients.

S-13. Molecular mechanisms and prophylaxis in PTSD, contributions from prospective and longitudinal studies

S-12-003 Oxidative stress in prefrontal cortical parvalbumin interneurons in the neonatal ventral hippocampal lesion model of schizophrenia

P. O’Donnell1, P. Pantazis2, J.H. Cabungcal3, K. Do4, 1University of Maryland, Baltimore, Md, USA; 2University of Lausanne, Switzerland

Objective: Prefrontal cortical interneurons are affected in a variety of rodent models of schizophrenia, including the neonatal ventral hippocampal lesion (NVHL) and genetic models. Together with post-mortem studies showing altered markers related to GABA transmission in the prefrontal cortex (PFC) of schizophrenia patients, these findings suggest inhibitory interneurons in the PFC may be affected by many genetic and environmental factors during development. As there is increasing evidence of redox dysregulation in schizophrenia, we tested whether NVHL rats exhibit signs of oxidative stress in PFC interneurons and whether antioxidant treatment improves outcome.

Methods: Sprague-Dawley rats received a bilateral injection of ibotenic acid (lesion) or vehicle (sham) in the ventral hippocampus at postnatal day (P) 6-7. Some rats received the antioxidant N-acetylcysteine (NAC) between P5 and P56. Rats were euthanized and parvalbumin (PV) cell counts were assessed with unbiased stereology; additional rats were tested for prepulse inhibition deficits and electrophysiological measures.

Results: Juvenile rats with a NVHL, but not sham controls, exhibited a higher level of the oxidative stress marker 8-oxo-DG but no differences in PV staining. Most PV neurons exhibited 8-oxo-DG staining, indicating this cell type is susceptible to oxidative damage. At P64, we observed a marked reduction in parvalbumin labeling in untreated NVHL. PFC. NAC treatment reversed the deficit in PV cells as well as the PPI deficits in NVHL rats.

Conclusion: The data indicate that a neonatal hippocampal lesion has deleterious effects on PFC development, yielding PV interneurons with oxidative damage during the pre-pubertal stage and a loss of PV labeling and behavioral deficits in the adult stage, which are reversed with NAC treatment. The findings suggest that PFC interneurons may present oxidative stress in rodent models of schizophrenia, and this could be the mechanism that renders them into a reduced level of activity, eventually causing cognitive and other deficits associated with the disease.

S-12-004 Redox dysregulation, inhibitory-excitatory imbalance and myelination impairment in schizophrenia

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Objective: Glutathione (GSH), a major cellular redox regulator and antioxidant, is decreased in chronic schizophrenia (SZ) patients. Polymorphisms of key GSH-synthesizing enzyme genes, glutamate-cysteine ligase catalytic and modifier (GCLM) subunits, are associated with SZ. GSH dysregulation was investigated now in early psychosis patients (EP). Impaired GSH synthesis of genetic origin, when combined with environmental risk factors generating oxidative stress, may play a crucial role in inducing connectivity anomalies, a hypothesis tested in GCLM-/- mice (70% lower GSH).

Methods: In EP, GSH genes were genotyped and their expression cross-sectionally in PTSD in association with treatment. It is also the first to provide an indication that molecular mechanisms associated with GR activity are involved in PTSD risk, pathophysiology, and resilience. We conclude that the molecular biology of the GR should be further examined as this may be a potential target for PTSD prevention and treatment.

S-13-001 Biological correlates of PTSD: From endocrinology to molecular biology

R. Yehuda, New York, USA

Objective: Many endocrine and glucocorticoid alterations have been examined with PTSD, prompting an interest in molecular biology. Epigenetic and molecular mechanisms that may influence glucocorticoid alteration in PTSD. This study examined cytosine methylation of the 1F exon on the human GR gene (NR3C1) and gene expression of the GR related genes in order to determine the relevance of these measures to PTSD risk, pathophysiology, or recovery.

Methods: Cytosine methylation of the GR gene along with other neuroendocrine measures (cotisol, glucocorticoid receptor sensitivity, and neuropeptide Y) were measured over time in association with symptom change following prolonged exposure psychotherapy. We will present data from 16 patients, all combat veterans, obtained prior to treatment, at treatment end, and at follow-up.

Results: At treatment end, 50% of patients no longer met diagnostic criteria for PTSD. Treatment response was significantly predicted by cytosine methylation of the GR gene. Cytosine methylation, in turn, predicted neuroendocrine changes in urinary cortisol excretion (which was significantly elevated) and plasma neuropeptide Y (also elevated) in responders compared to non-responders.

Conclusion: This is the first study examining gene methylation and expression cross-sectionally in PTSD in association with treatment. It is also the first to provide an indication that molecular mechanisms associated with GR activity are involved in PTSD risk, pathophysiology, and resilience. We conclude that the molecular biology of the GR should be further examined as this may be a potential target for PTSD prevention and treatment.

S-13-002 True prospective studies in military cohorts; central and peripheral regulation of combat stress

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Objective: The course of central and peripheral regulation of severe stress can provide information on preexisting vulnerability factors as well as neuronal responsivity to severe stress. Prospective studies can be informative in understanding trajectories of resiliency as well as desensitization.

Methods: We conducted a large epidemiological study in which functional stress-related biological parameters were used in association with predicting PTSD symptoms prior to and on two separate time points within the first year after deployment. We also looked at neural responsivity to salient stimuli which was correlated to high threat perception during deployment, in comparison to a group that was not deployed during the same time period.
This normalized in the first year after deployment. Yet, we observed persistent changes in amygdala-dACC connectivity.

**Conclusion:** The results from this study have enhanced our ability to understand biological concomitants of vulnerability and resilience. Preexisting high GR number in PBMCs as well as FKBP5 and GILZ mRNA expression are vulnerability factors for subsequent development of PTSD symptoms. Central regulation of combat stress at the level of the amygdala appeared highly plastic and adaptive to environmental demands. We speculate that a normalization failure may underlie the pathophysiology of PTSD which is presumably related to preexisting vulnerabilities.

**S-14-004** Prospective study of risk and resilience factors for posttraumatic stress in police officers

C. Marmar. New York, USA

**Objective:** Results will be presented on a prospective longitudinal study of risk and resilience for PTSD symptoms in 400 police academy recruits, assessed during academy training and followed during the first 7 years of police service.

**Methods:** Utilizing Latent Growth Mixture Modeling (LGMM) we have established three symptom trajectories, highly resilient, initially distressed with gradual improvement and increasing distress.

**Results:** We will present findings on the relations of the following predictors ascertained during academy training to the three PTSD symptom trajectories: I.Q., family histories of anxiety, depression, alcohol and drug abuse, neighborhood, socioeconomic conditions, educational programs or childhood education, alcohol or adolescent traumatic exposure, levels of awakening cortisol, fear-potential of acoustic startle, MHPG and cortisol responses to a critical incident video challenge, sleep quality as measured by actigraphy, and candidate polymorphisms including serotonin transporter (SLC6A4), adrenergic pathway genes, (ADRB1, ADRB2, ADRA2C), brain derived neurotrophic factor gene (BDNF), genes for several critical components of the HPA axis such as the glucocorticoid receptor (NR3C1), CRH receptor 1 (CRHR1), and FKBP5 binding protein 5 (FKB5P) and Catechol-O-methyltransferase (COMT). Multivariate models of risk and resilience will be presented utilizing a multinomial logistic regression nested in the unconditional LGMM.

**S-14-002** Pharmacogenetics of antidepressant therapies

A. Serretti. University of Bologna, Italy

**Objective:** The response to antidepressant treatment is still unsatisfactory: about 40–50% of depressed patients do not respond to first antidepressant and about 60% do not reach remission at all. Evidence suggests that genetic factors contribute for about 50% of the antidepressant response therefore the knowledge of the patient genetic profile may lead to an individualized therapy in the next years.

**Results:** Several gene variants have been reported in association with short term antidepressant response. A growing number of evidence has been reported for the functional polymorphism in the upstream regulatory region of the serotonin transporter gene (5-HTTLPR), particularly 1 allele has been associated with a better response in Caucasian. A significant number of replication findings are presented in literature also for 5-HT2a, 5-HT1a, BDNF, COMT, MAOA, NET, Glu3a, FKB5P, Ppp, TPH, ACE and GSK-3b variants, although an high number of failure of replication is reported for these genes. Furthermore new candidate genes have been recently identified through the genome-wide scan approach and multi-sites projects like STAR*D and GENDEP. Among these the more promising are GRK4, GRK2 and DNTB1. A pathway analysis performed by us on the large STAR*D and STEPBD databases yielded promising results.

**Conclusion:** Until now genetics was not able to predict the overall response to antidepressant. However there are increasing evidences of a genetic modulation on treatment response, both directly and through a modulation or an interaction with clinical variables that could influence the response to antidepressant, like personality and social modulators.

**Policy of full disclosure:** Dr. Serretti is or has been consultant/speaker for: Abbott, Astra Zeneca, Clinical Data, Boheringer, Bristol

**S-13-003** Hydrocortisone in the golden hours and PTSD trajectory – Clinical and animal studies

J. Zohar. Tel Hashomer, Israel

**Objective:** Animal studies and anecdotal human case reports point out the importance of adaptive response of the HPA axis in response to traumatic events. Along these lines, it is possible that the administration of cortisol immediately after exposure (in the “golden hours”) to a trauma might alter the trajectory of trauma exposure by promoting recovery. A series of studies using a well-validated animal model for PTSD has demonstrated a greater susceptibility to experimentally induced PTSD-like behavioral changes in rats with hyperactive/reactive vs. hyperactive/reactive HPA axis, i.e., Lewis strain vs. Fischer strain. Exogenous administration of cortisol to Lewis rats prior to the stressor significantly reduced this difference. Further animal studies examined the effect of a single intervention with high-dose corticosterone immediately after exposure to a stressor. A significant reduction in the incidence of PTSD-like behaviors and improved resilience to subsequent trauma was observed.

**Methods:** We conducted a double blind, placebo-controlled clinical pilot-study, in which patients were randomly assigned to one of two treatment groups: placebo or hydrocortisone treatment (100-140 mg iv, injected 1.5-5.5 hours following the traumatic event).

**Results:** Results based on 2-week and 3-month follow-up support a potential therapeutic role for administration of hydrocortisone in the “golden hours”.

**Conclusion:** Potential interventions, once explored in a systematic way in an animal model can then, via a process of translational research, be implemented into the clinical arena. Early intervention after psychological trauma is an area which may specifically benefit from translational research. Changing the focus from treatment once PTSD is already established to secondary prevention of PTSD in the “window of opportunity” – the first few hours after exposure to a traumatic event – has opened the door to new exciting possibilities in PTSD research and treatment.

**Policy of full disclosure:** Prof. Zohar has received research funding from Lundbeck, Servier and Pfizer, and has been a speaker/consultant for Lundbeck, Servier, Pfizer, Abbott, Pierre Fabre, BMS and Roche.

**S-13-001** Genomics of response and side effects of antipsychotics

D. Rujescu. University of Munich, Dept. of Psychiatry, Germany

**Objective:** A major drawback of the therapy with antipsychotics is the lack of efficacy and the occurrence of extrapyramidal symptoms (EPS) in some patients that can both limit therapy and compliance. Thus, the availability of a predictive tool for response to antipsychotics is desirable.

**Methods:** To search for genes associated with response to antipsychotics or EPS, a hypothesis free approach was used including animal models, neural cell cultures, and differential gene expression analyses. Immunohistochemical analyses were performed in rats that received an agent mimicking aspects of psychosis (MK-801), haloperidol, a combination of these agents, or saline. Genes differentially expressed between the different groups had been genotyped in one hundred four patients with acute psychosis (schizophrenia, schizoaffective, brief psychotic, and substance-induced psychotic disorder) treated with haloperidol for up to 28 days. Diagnosis was established by applying the SCID I and II interview. Patients were assessed at baseline and on days 3, 7, 14, 21 and 28. Improvement and response were measured by using the Positive and Negative Syndrome Scale.

**Results:** Furthermore, genome wide studies were performed for parkinsonism, dyskinesia and akathisia.

**Conclusion:** Dan Rujescu will present novel data on this ongoing genetic study on response to haloperidol and discuss that in the context of the literature.
S-15. Oxytocin in normal and abnormal psychology: Promises and caveats

Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Lundbeck, Pfizer, Sanofi, Servier.

S-14-003 | Pharmacogenomics of nicotine addiction
B. Lerer1, L. Greenbaum1, K. Sarner2, A. Righi1. 1Hadassah-Hebrew University Med Ctr, Jerusalem, Israel
Nicotine dependence (ND) is a complex, multifactorial phenotype, in which both genetic and environmental factors are involved. The heritability of ND is estimated at more than 50%. Due to their prominent biological relevance, brain nicotinic acetylcholine receptor (nAChR) – encoding genes are among the most widely studied candidate genes for ND. Traditionally, much attention has been paid to two nAChR genes, encoding the alpha4- and beta2-subunits respectively. However, the focus has shifted substantially in the last few years with the discovery of the major contribution of the chromosome 15q24 nAChR gene loci, CHRNA5-CHRNA3-CHRNBD4, to several smoking phenotypes as well as to substance abuse in general. At least three common independent ND risk variants located within these loci are associated with several ND-related phenotypes, each with a small effect size. The association results are robustly supported by multiple replications in various populations. Less clear, however, is their association with smoking cessation in pharmacogenetic trials. One of the ND associated SNPs, rs16969968, changes an amino acid in the CHRNA5 protein, and thus alters the electrophysiological properties of the nicotinic receptor. Other associated SNPs may influence receptor expression level. Many interesting questions are currently emerging, such as the possible influence of rare variants within the loci on the phenotype, relation of ND genetic risk variants to lung cancer susceptibility and interaction with other genes and environmental factors. On the other hand, functional biological understanding of the novel genetics findings is relatively limited and translational approaches are needed (for example, in transgenic mouse models), exploration of the interaction of these gene variants with environmental factors and their role in cognitive processes influenced by nicotine. Findings may have important implications for the neurobiological understanding of addiction, as well as for the development of pharmaceutical agents to aid in nicotine withdrawal.

S-14-004 | The role of leptin in the pharmacogenomics of obesity
M.-L. Wong. John Curtin Institute, ANU, Canberra, Australia
Objective: Pharmacogenomics is based on the premise that genomic heterogeneity will be reflected in treatment heterogeneity. Common and complex disorders such as obesity are the outcome of genetic and environmental factors. Each person has different contributions of genetic and environmental to their body weight. In obesity, 3 to 5% of cases are due to genes of major effect. In those situations the effect of a genetic mutation overrides environmental effects. Such is the case with functional mutations of the leptin gene. Leptin is an adipokine that is synthesized principally by white fat and for which there are receptors in the brain. It sends a satiety signal to the central nervous system by activating anorectic pathways, mediated by POMC and MC4-R, and by suppressing orexigenic pathways, mediated by NPY and AgRP. Leptin is also a trophic factor for the maturation of the reproductive system.

Methods: We have studied a Turkish family with a Mendelian recessive missense mutation in the leptin gene that results in the same truncated and non-functional molecule as that found in the ob/ob mouse. Those patients were morbidly obese and hypogonadal, with a body mass index (BMI) of 50.

Results: Treatment with recombinant human leptin, while not generally effective for obesity, had a major effect in those patients and drastically reduced their weight and brought about normalization of reproductive function.

Conclusion: Our results show that indeed genetic heterogeneity is the basis of treatment heterogeneity in the therapeutics of obesity.

S-15. Oxytocin increases the salience of social agents: Evidence from psychopathology
S. Shamay-Tsoory. University of Haifa, Israel
Objective: Recent classes of theories explaining the role of oxytocin in social behavior have focused mainly on prosocial positive behaviors such as trust, generosity and empathy. A plausible hypothesis suggested here is that oxytocin has a general effect on increasing the salience of social agents, and therefore administration of oxytocin may provoke a wide range of emotions and behaviors related to social behavior. To show that oxytocin is involved mainly in increasing the salience of social agents we conducted two experiments that examined the effects of oxytocin on competitive as well as collaborative behaviors.

Methods: In the first experiment we investigated the influence of a single intranasal administration of oxytocin on cooperative behavior. Cooperation was assessed using a computerized drawing task (a coordinated Etch a Sketch game) which required participants to work together in coordination with each other. In the second experiment participants played a game of chance with another (fake) participant who won more money (envy manipulation), lost more money (schadenfreude manipulation) or won/lost equal amounts of money.

Results: In the first experiment we demonstrate that the administration of oxytocin improves subject’s accuracy in the cooperation task when completing the task in the couple condition, as compared to the performance of the same subjects subsequent to the administration of placebo. In the second experiment, oxytocin, compared with placebo, had an effect of increasing envy ratings during unequal monetary gains conditions involving relative loss and increased ratings of gloating during relative gain conditions.

Conclusion: It is concluded that rather than being involved solely in positive prosocial behaviors (as believed so far), the oxytocinergic system probably plays a key role in a wider range of social emotion-related behaviors.

S-15-002 | Oxytocin modulates cooperation and competition within and between groups
C. de Dreu. University of Amsterdam, Netherlands
Objective: Examines the possibility that hypothalamic release (or infusion) of the neuropeptide oxytocin modulates the regulation of cooperation and conflict among humans.

Methods: Reviews research programs focusing on effects of intranasal administration of oxytocin (v.s placebo) in healthy volunteers.

Results: First, oxytocin enables social categorization of others into in-group versus out-group. Second, oxytocin dampens amygdala activity and enables the development of trust. Third, and finally, oxytocin up-regulates neural circuitry (e.g., inferior frontal gyrus, ventromedial prefrontal cortex, caudate nucleus) involved in empathy and other-concern.

Conclusion: Consistent with an evolutionary perspective on the functionality of cooperation, oxytocin-motivated cooperation is mostly parochial—it motivates (i) in-group favoritism, (ii) cooperation towards in-group but not out-group members, and (iii) defense-motivated non-cooperation towards threatening outsiders. In addition to its well-known role in reproduction and pair-bond formation, oxytocin’s primary functions include in-group “tend-and-defend.”

S-15-003 | Oxytocin treatment in schizophrenia reduces psychotic symptoms and improves theory of mind and social perception
C. Pedersen1, S. Rau1, K. Salimi1, C. Gibson1, J. Leserman1, D. Penn1.
1University of North Carolina, Chapel Hill, USA
Objective: Because oxytocin (OT) has prosocial and antipsychotic-like effects in animals and recent human studies, we hypothesized that a trial of OT treatment would reduce social cognition deficits as well as psychotic symptoms in schizophrenia.

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Methods: A double blind study compared twice daily intranasal OT (24 IU/dose, N=14) vs. placebo (N=11) for 14 days on social cognition tests, PANSS scores and Paranoia Scale self-ratings. Subjects' symptoms (PANSS >60) and psychotropic medications were stable for >1 month prior to starting the treatment trial and medications were unchanged during the trial.

Results: From baseline to treatment day 14, the OT group: 1) significantly increased accuracy in recognition of 2nd and 3rd order false belief on the Brune Theory of Mind Task; 2) trended toward greater accuracy in recognizing deception on the Brune Task and more trustworthy ratings of faces on the Trustworthiness Task. Also, mean scores on PANSS social items (suspiciousness, hostility, social withdrawal [passive/aphatic, active], uncooperativeness) declined dramatically. There were significant reductions in PANSS total, positive, negative and general subscale scores, the individual suspiciousness and anxiety item scores as well as Paranoia Scale scores. In the placebo group, only PANSS suspiciousness and anxiety item scores declined significantly. ANCOVAs controlling for baseline revealed that the OT group vs. placebo group had significantly greater declines in PANSS total scores and trends toward greater declines in PANSS mean social item and positive subscale scores.

Conclusion: Enhancement of social cognition suggests that OT treatment may improve social dysfunction, which responds poorly to antipsychotic medications and is the major cause of disability in schizophrenia. OT may augment antipsychotic efficacy and should be tested as a monotherapy for schizophrenia. Our results indicate that the OT group vs. placebo group had significantly greater declines in PANSS total scores and trends toward greater declines in PANSS mean social item and positive subscale scores.

S-15-001 Does oxytocin have a role in borderline personality disorder?

M. Brüne, A. Ebert, Ruhr-University Bochum, Germany

Objective: Oxytocin (OT) is an evolutionarily conserved nonapeptide which attenuates fear responses, improves empathy, exerts major effects on pair-bonding and attachment, and has the potential to improve social aspects of disability. Oxytocin (OT) may play an important role in the pathophysiology of psychotic symptoms in schizophrenia and associated social cognition and social function deficits.

S-16-001 Alpha7 nicotinic acetylcholine receptor crosstalk with the lipid microenvironment in health and disease

E. Barrantes, National Science & Technology, Res. Council (CONICET), Bahía Blanca, Argentina

The homomeric alpha7-subtype of nicotinic acetylcholine receptors (nAChR) is one of the pentameric ligand-gated ion channels that mediate fast synaptic transmission. It is broadly distributed in the central nervous system, where it plays important roles in synaptic signaling, neurite outgrowth, synaptic plasticity, learning, memory formation and neuroprotection, and constitutes an important target for the treatment of cognitive deficits in schizophrenia and Alzheimer's disease (AD). The alpha7-AChR is highly expressed in brain regions relevant to cognitive and memory processing. The alpha7-AChR subunit gene (CHRNA7) is located in the highly duplicated 15q13–q14 region implicated in several neuropsychiatric diseases, including schizophrenia and bipolar affective disorder. Postmortem brains show decreased amounts of AChRs in AD patients; the most vulnerable neurons appear to be those expressing high levels of alpha7-AChR. In cortical neurons, alpha7-AChRs are expressed post-synaptically at over 70% of synapses, where they may regulate glutamate receptor trafficking. There is increasing evidence showing a misregulation of lipid, and in particular cholesterol metabolism in the development of AD. Since cholesterol affects the AChR protein at multiple levels (distribution in the membrane, degree of aggregation, endocytosis, association with the cytoskeleton, trafficking, single-channel conductance) we have speculated that some of the neurological correlates of AD might be partly associated with abnormal crosstalk between the receptor protein and the sterol in this synaptopathy (see e.g. Barrantes, Valles and Borroni, FEBS Lett. 584 (2010) 1856–1863).

S-16-002 Alpha7 nicotinic receptors as important targets for neuroprotective mechanisms in new drug targets for Alzheimer’s disease


Objective: The neuronal acetylcholine receptors (nAChRs) play an important role in cognitive processes in brain regulating and modulating several neurotransmitters. The nAChRs also seem to be involved in pathological processes as amyloid (Aβ) toxicity in Alzheimer’s disease (AD).

Methods: Fibrillar Aβ was measured using 3H-PiB binding, astrocytes using 3H-Deprenyl and 131-I-Bungarotoxin in AD autopsy brain tissue. Fibrillar and oligomeric and its interactions with Aβ and with α7 nAChRs and α7 nicotinic agonists were characterized in PC cells.

Results: Binding studies showed a significant negative correlation between regional 3H-PiB binding and β-amyloid plaques. A combination of fibrillar (Aβ-3H-PiB binding) in autopsy AD brains (Kadir et al., 2011). Fibrillar Aβ may at least partly exert its toxic effect by forming a complex and blockade of α7 nAChRs while oligomeric Aβ may instead act as ligand activating α7 nAChRs (Lilja et al., 2011). The α7 nAChR agonist JN403 as well as the partial α7 nAChR agonist vararyl enicline but not the α4 nAChR agonist cytosine induced an increase in the 3H-PiB binding in AD autopsy brain tissue homogenates as a sign for interaction and release of Aβ from preformed complex Aβ/nAChR complex (Ni et al., submitted). The α7 nAChRs are also found in astrocytes and thereby also related to neuroinflammatory processes in AD.

Conclusion: Activation of α7nAChRs might be a promising strategy to prevent Aβ toxicity and obtain neuroprotective effects in early stages of AD. Kadir et al., Brain 2011;134: 301–317. Lilja AM et al., J Alzheimers Dis 2011;23: 335–347.

S-16-003 Neuronal circuits and mechanisms involved in the cognitive enhancing properties of α7 nicotinic acetylcholine receptor (nAChR) modulators

I. Mikkelsen, M.S. Thomson, K. Alexander, M. Pershing, D. Borte, R. Schwartz, J.P. Bruno, 1 Center Integrated Molecular, Brain Imaging, Copenhagen, Denmark; 2 Neurobiology Research Unit, University Hospital Copenhagen, Copenhagen, Denmark; 3 Dept Psych Neuroscience, The Ohio State University, Columbus, USA; 4 Dept Psychol Neurosci, The Ohio State University, Columbus, USA; 5 Maryland Psych Res Ctr, University of Maryland, Baltimore, USA

Objective: Alpha7 nicotinic acetylcholine receptor (nAChR) selective agonists have been reported to exhibit pro-cognitive effects in patients with schizophrenia (SCZ). We have carried out behavioural, biochemical and neuroanatomical studies in the rat to investigate the neuronal systems and mechanisms involved in this effect.

Methods: Systemic administration of kynurenine (KYN, 100 mg/kg, ip), the precursor of kynurenine acid (KYN, an endogenous, astrocyte-derived, antagonist of α7nAChR whose levels are increased in the brains of schizophrenics) produced selective deficits in the initial
reversal and extra-dimensional shift stages of an attentional set-shifting task. These deficits mirror the performance of patients with SCZ in such tasks.

Results: Pre-treatment with the α7nAChR agonist SR180711 (3 mg/kg, ip) returned the performance of KYN-treated rats back to control levels. Performance in this task is highly dependent on increases in glutamatergic and cholinergic transmission within the prefrontal cortex (PFC). However, the mechanisms within the PFC through which these α7nAChR modulators work to enhance performance are poorly defined. Systemic administrations of a number of α7nAChR agonists produce an increase in c-Fos activation in the prelimbic region of the PFC as well as in cholinergic cells of the basal forebrain projecting directly to the PFC. This increase in gene expression is mediated via the cholinergic neurons in the basal forebrain, because a selective lesion of the cholinergic input to the PFC eliminates c-Fos induction after administration of an α7nAChR agonist. Furthermore, intra-PFC infusion of SR180711 led to a dose-dependent increase in local extracellular glutamate as measured by a microelectrode array.

Conclusion: The α7 nAChR-dependent increases in prefrontal acetylcholine and glutamate may be critical components of the pro-cognitive effects of SR180711 in KYN-treated rats. These data further support the potential value of the α7nAChR as a therapeutic target for the development of drugs to treat the cognitive deficits associated with SCZ.

S-16-004 Alpha7 nicotinic acetylcholine receptors as a potential target for imaging of brain disorders with positron emission tomography

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S-17. Neurodevelopmental bases for progress in pharmacotherapy in autism spectrum disorders

S-17-001 Neurophysiological biomarker of impaired social interaction in ASD

K. Yui1, M. Koshiba2, S. Nakamura3, 1Ashiya University, Japan; 2Tokyo University of Agriculture, Koganei, Japan

Objective: The core symptoms of Autism spectrum disorders (ASD) (i.e., impaired social interactions; communication, and restricted and repetitive patterns of interests and behavior) can be attributed to the impaired delivery of afferent signals To understand neuropsychological underpinnings of ASD, it is important to specify clear biomarkers of neurobiological abnormalities. Our original integrated multivariate analysis of the neuropsychological cues may be useful in diagnosis for ASD. Furthermore, we tried arachidonic acid as supplementation since this has neuronal signal transduction effect.

Methods: The core symptoms of Autism spectrum disorders (ASD) (i.e., impaired social interactions; communication, and restricted and repetitive patterns of interests and behavior) can be attributed to the impaired delivery of afferent signals To understand neuropsychological underpinnings of ASD, it is important to specify clear biomarkers of neurobiological abnormalities. Our original integrated multivariate analysis of the neuropsychological cues may be useful in diagnosis for ASD. Furthermore, we tried arachidonic acid as supplementation since this has neuronal signal transduction effect.

Results: The 17 individuals with ASD exhibited increases of preference for high spectral power and the standard deviation of the head surface temperature based on IRIS in response to unfamiliar male approach, which reflect heightened central nervous system arousal. While, plasma prolactin and cortisol levels didn’t increase. Our supplementation regimen improved the repetitive and stereotyped interests and behavior, and the impaired communication (Yui K). Improvement of neurophysiological function by ARA remains to be clarified.

Conclusion: The neurophysiological responses to unfamiliar adults may reflect functional vulnerability of the limbic system relevant to social cognition. Altered signal transduction might contribute to pathophysiology of impaired social interaction in individuals with ASD.

S-17-002 The predictive value of multiparameter image of whole-brain structures in autism spectrum disorders

C. Ecker, Section of Brain Maturation, Institute of Psychiatry, London, United Kingdom

Objective: The objective of this research was therefore to characterize the complex and subtle structural pattern of gray matter abnormalities in adults with ASD on the basis of multiple morphometric parameters, and to disentangle spatially distributed patterns of regional differences with potentially different neuropathological underpinning. Furthermore, we aimed to examine the predictive value of individual morphometric parameters for group membership (i.e. diagnostic value).

Methods: Structural MRI data was collected on 20 well-characterized male adults with ASD, and 20 age/IQ matched healthy controls. All individuals with ASD met algorithm cut-offs for ASD on both the ADI & ADOS. For each participant, a set of 5 morphological parameters including both volumetric and geometric features were obtained at each spatial location on the cortical surface (i.e. vertex) was obtained using FreeSurfer software. This set of measures was then used to (1) discriminate between individuals with ASD and controls using a Support Vector Machine analytical approach, and to (2) finding a spatially distributed pattern of regions with maximal discriminative power for each of the five morphometric features describing brain volume and geometry. For all parameters, the left hemisphere provided higher classification values than the right hemisphere.

Results: SVM achieved good separation between ASD and control group and was able to identify individuals with ASD at a sensitivity and specificity of up to 90% and 80% respectively using cortical thickness. In addition, SVM revealed spatially distributed, independent patterns of regions with maximal discriminative power for each of the five morphometric features describing brain volume and geometry. For all parameters, the left hemisphere provided higher classification values than the right hemisphere.

Conclusion: Our results confirm the hypothesis that the neuro-anatomy of ASD is truly multi-dimensional. These differences also provided significant predictive power for group membership, and could thus be used as a potential biomarker for ASD. The spatial patterns detected using SVM may also help further exploration of the specific genetic and neuropathological underpinnings of ASD, and provide new insights into the most likely multi-factorial aetiology of the condition.

S-17-003 Neurobiological marker in ASD

R.L. Davis, Neuroinflammation Research, Laboratory, Tulsa, USA

Objective: We are particularly interested in mercury-induced effects on neuroimmune signaling given that mercury exposure and neuro-inflammation are both implicated in autism. Thus, our studies are focused on the hypothesis that environmental triggers of autism are mediated through disruption of neuroimmune signaling.

Methods: We utilized the prairie vole as an animal model. Prairie voles have been used extensively to study the physiological and neurochemical underpinnings of social behaviors. Prairie voles are highly social and these social behaviors are remarkably similar to those of humans. However, their preference for social proximity is quite sensitive to exposure to environmental toxins. Adult prairie voles were chronically exposed to 60 ppm HgCl2 in drinking water for 10 weeks. Mercury was therefore used as a tool to induce a male-specific change in social behavior as a model for autism-like behavior. Following mercury exposure, social behavior was assessed; then brain tissue was collected and cytokine/chemokine protein expression measured in select brain regions by ELISA.

Results: Following chronic mercury exposure, these normally highly social animals avoided strangers and displayed social withdrawal. Importantly, these social deficits were more prevalent in male voles than in females. Acute oral chronic mercury exposure resulted in a male-specific, increase in TNFβ protein expression in the cerebellum and hippocampus; whereas, chemokine (CCL2 and CXCL10) expression was not affected by mercury exposure.
**Conclusion:** Further investigation is expected to more fully define the brain regions, cell types and immune factors involved in the altered neuroimmune signaling. Together, these findings are expected to lend insight into the role of altered neuroimmune signaling in autism.

**Objective:** The main objective of this set of studies is to characterize the brain structure, function, and connectivity in autism spectrum disorders.

**Methods:** Functional MRI and Diffusion Tensor data were collected from several participants (adults and children) with autism spectrum disorders. The tasks mainly focused on theory-of-mind, emotion recognition, action understanding, and resting state.

**Results:** In addition to decreased engagement of critical brain areas in autism, such as the mirror neuron system, theory-of-mind networks, and cortical midline structures, we found disrupted connectivity across several brain areas. Functional and anatomical underconnectivity were found primarily in long-distance connections, and overconnectivity was found in short-distance or local connections, especially in frontal and in relatively posterior brain areas.

**Conclusion:** Overall, the results of these studies point to disrupted cortical connectivity as a characteristic feature of the brain in autism.

**Objective:** Fibromyalgia/chronic fatigue patients are usually treated by rheumatologists and/or neurologists but since there is frequently comorbid depression and anxiety, psychiatrists are likely to be confronted with patients suffering from fibromyalgia. However, the patients do not want to be a “psychiatric case” and therefore a neurobiological approach has been reported to be most successful. The symptoms associated with fibromyalgia/chronic fatigue vary from person to person but there is one common syndrome—they ache all over, demonstrate fatigue and have difficulties concentrating. The pain can be a deep ache, a stabbing or burning pain or a tingling sensation. Pain can be mild at times but in other moments so severe that it becomes unbearable.

**Methods:** For a formal diagnosis of fibromyalgia the ACR (American College of Rheumatology) criteria require the patient to have widespread pain for at least 3 months together with tenderness in at least 11 of 18 specific tender points. Treatment of fibromyalgia requires a comprehensive approach involving education, aerobic exercise, physiotherapy and cognitive behavioural therapy in addition to pharmacotherapy.

**Results:** The most effective drugs available (or will shortly be available) for the treatment for fibromyalgia are amitryptiline, the selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), milnacipran and duloxetine and the anti-epileptic, pregabalin, are all well known to psychiatrists.

**Conclusion:** Improvement in pain severity is a key element of response to a treatment programme but reduction of other symptoms of the Fibromyalgia Inventory Questionnaire including fatigue, poor concentration, stiffness, anxiety and depression are also essential indicators of the patient’s improvement.

**Policy of full disclosure:** Siegfried Kasper received grants/research support, consulting fees and honoraria within the last three years from AstraZeneca, Bristol-Myers Squibb, CSC, Eli Lilly, GlaxoSmithKline, Jansen, Lundbeck, Merck Sharp and Dome (MSD), Novartis, Organon, Pierre Fabre, Pfizer, Schwabe, Sepracor, Servier, Wyeth.

**S-18-002** Treating CFS—It may not be rocket science, but at least it works

S. Wessely. Academic Department of Psychological Medicine, London, United Kingdom

Chronic fatigue syndrome (CFS) has an undeserved reputation for being difficult or impossible to treat, which allows a wide variety of unorthodox and sometimes unscrupulous treatments to flourish at the literal and metaphorical expense of patients. However, a long programme of work over two decades, culminating in the recent Lancet multi centre large PACE trial, now provides compelling evidence that neither nihilism nor opportunism is necessary. There are now two rehabilitative treatments that are both safe and effective. Neither are perfect, but then not much in medicine is. Both can be recommended now to patients as the best currently available options. I shall review the evidence for both, and show how non expert practitioners can use basic CBT principles in clinical practice.

**S-18-003** The concept of ‘Mental Fatigue’ in a broader dimensional context

C. Tammenga. USA

Psychiatric nosology is being encouraged these days to become dimensional in its organization and to consider cognitive and affective disease symptoms as altered and pathological dimensions of normal brain functions. The NIMH has designed and discussed a system call the RDoCs approach, a system that will encourage a biological conception and formulation for all diseases of the brain. The RDoCs approach has already generated a set of dimensions of function, along with a unique anatomy, physiology and potential pharmacology for the dimensions. Along this continuum of function and dysfunction, the task for any single syndrome is to fit its primary symptoms into the defined dimensions. For a syndrome like “Mental Fatigue” this is a most useful and clarifying exercise. In this talk, I will suggest a framework for defining the intermediate phenotypes of mental fatigue in dimensional constructs. It will suggest its relationships to other psychiatric disease constructs and to behavioral aspects of medical disease diagnoses. These relationships might suggest new formulations for pathophysicsology and certainly for treatments.

**S-18-004** Effect of the dopamine stabilizer OSU 6162 on mental fatigue in neurological patients

A. Carlsson. Göteborg, Sweden

**Objective:** The (-)-enantiomer of OSU6162 is a phenylpiperidine derivative characterized as a dopamine stabilizer, given its affinity for dopamine D2 receptors leading to mixed activating and inhibitory effects on behavior. More recently this compound has also been found to be a partial agonist on a number of serotonergic receptors, which further contributes to its behaviorally stabilizing properties. Early clinical studies have shown beneficial actions in patients with Parkinson’s disease, Huntington’s disease, schizophrenia, and mental fatigue. The present report deals with the actions of this agent in patients with mental fatigue of long duration following upon stroke or traumatic brain injury (TBI).

**Methods:** OSU6162 was given orally for four weeks in doses increasing from 15 to 45 mg b.i.d. to twelve patients suffering from mental fatigue, following upon stroke (N = 6) or TBI (N = 6). OSU6162 was compared with placebo using a double-blind, randomized crossover design. Patients included were well rehabilitated physically with no gross impairment in cognitive functions other than those related to the mental fatigue.

**Results:** OSU6162 caused a remarkable improvement in mental stamina, as evaluated by a self assessment scale on mental fatigue. Statistical significance was reached on the primary end-point (Mental Fatigue Scale). Principal component analysis demonstrated an overall positive treatment effect in seven of 12 patients. Beneficial responses were seen already during the first few days of active drug treatment. Increasing dosage caused no further improvement. Side effects
S-19. Recent advances in research on serotonergic hallucinogens: Implications for treatment of schizophrenia

L. Gonzalez, L. Massa
Mount Sinai School of Medicine, Department of Psychiatry, New York, NY, USA

Objective: Traditionally, G protein-coupled receptors (GPCRs) were thought to function as monomeric units. However, over the past few years, GPCRs have been shown to be located in close molecular proximity at the plasma membrane in living mammalian cells, implying the existence of dimers or even higher-order oligomers. The neurotransmitters serotonin and glutamate have been the target of considerable attention regarding psychosis and antipsychotic drug development. Atypical antipsychotics, such as clozapine, olanzapine and risperidone, all have in common a high affinity to block the function of the 5-HT2A receptor. The psychotomimetic effects of hallucinogenic 5-HT2A receptor agonists, such as lysergic acid diethylamide (LSD) and psilocybin, share several features with schizophrenia, including perceptual disturbances and alterations in cognition and mood. A new class of potential antipsychotic drugs acting as agonists at metabotropic glutamate 2/3 (mGlu2/3) receptors has recently received attention in preclinical and clinical studies.

Methods: We used biophysical assays to characterize the oligomerization of 5-HT2A and mGlu2 receptors, and mouse behavior models to determine the molecular mechanisms contributing to antipsychotic efficacy.

Results: We found that 5-HT2A and mGlu2 receptors form a GPCR heterocomplex in tissue culture and mouse frontal cortex. Our results suggest that the 5-HT2A-mGlu2 receptor heterocomplex is necessary for the cellular and behavioral responses induced by hallucinogenic and antipsychotic drugs.

Conclusion: These observations provide a mechanistic insight into antipsychotic action.

S-19-001 Hallucinogenic signaling in a GPCR heterocomplex

M. Grever
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Objective: Both glutamatergic and serotonergic hallucinogens are used as model psychoses in humans and animals. Recent studies suggest that both drug classes increase levels of synaptic glutamate, suggesting some overlap in their pharmacological effects despite differing primary mechanisms of action. Here we compare the behavioral profiles of these drug classes in measures related to psychotic disorders.

Methods: Startle habituation and prepulse inhibition (PPI) have been measured in both schizophrenia and psychotic bipolar patients and in parallel animal models after administration of hallucinogens. Similarly, these psychiatric groups have been examined in terms of dopamine antagonists, but are blocked by 5-HT2A antagonists and some atypical antipsychotics. In motor activity paradigms, manic bipolar patients exhibit hyperactivity in a novel environment, while schizophrenia patients instead exhibit normal initial levels of activity but reduced rates of habituation over time. In rodents similarly tested for locomotor activity, serotonergic hallucinogens produce an exaggerated neophobia response characterized by initial reductions in exploratory behavior only in novel environments, while glutamatergic antagonists exhibit motor hyperactivity in both novel.

Conclusion: Thus, across behavioral paradigms in rodents, there are both similarities and differences in the profiles exhibited by serotonergic and glutamatergic hallucinogens. Further exploration of the neurobiological substrates of these similarities and differences is likely to help elucidate the domains of overlap and differentiation between the syndromes of schizophrenia and bipolar mania.

Policy of full disclosure: Work supported by the U.S. National Institute on Drug Abuse and the National Institute of Mental Health.

S-19-003 Suppression of slow cortical oscillations by hallucinogens: Relationship to schizophrenia

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Objective: Psychotomimetic drugs, such as non-competitive NMDA receptor antagonists and serotonergic hallucinogens are used as animal models of schizophrenia. However, their neurobiological basis of action is poorly known. Our objectives are 1) to characterize the actions of hallucinogenic drugs (the NMDA receptor antagonist phencyclidine –PCP- and 5-HT2A receptor agonists) on neuronal activity in prefrontal cortex, and 2) to examine the potential reversal of these actions by antipsychotic drugs.

Methods: Electrophysiological recordings in the medial prefrontal cortex of anesthetized rats and mice: single unit extracellular recordings of identified pyramidal neurons and local field potential recordings.

Results: The non-competitive NMDA receptor antagonist phencyclidine (PCP) and the preferential 5-HT2A agonist DOI share the ability to disrupt prefrontal cortex (PFC) activity in anesthetized rodents. These drugs markedly increase the discharge of ~40% of pyramidal neurons and decrease that of ~30%, reducing also slow cortical oscillations (SCO; <4 Hz) to which neuronal discharge is temporally coupled. Interestingly, these effects are reversed by the subsequent treatment with haloperidol and clozapine, acting also via different pharmacological mechanisms. In line with these observations, the 5-HT1A/2A receptor agonist 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT), natural component of the Amazonian beverage Ayahuasca, evokes similar changes in PFC and other cortical areas (V1 and S1). The reduction of SCO induced by 5-MeO-DMT is also reversed by antipsychotic drugs (haloperidol, risperidone, clozapine) and by the mGlu2/3 agonist LY337926.

Conclusion: The disruption of PFC function is a common action of hallucinogens, irrespectively of their primary site of action (NMDA or 5-HT receptors). These drugs evoke a chaotic PFC activity, characterized by a randomly occurring, discharge imbalance which may account for the perceptual and cognitive changes induced by these drugs. The reversal by antipsychotic drugs with different mechanisms of action reinforces their relationship with schizophrenia symptoms.

S-19-004 Neurophysiological studies of psilocybin-induced hallucinations: role of 5-HT2A receptors

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Objective: Serotonergic hallucinogens such as psilocybin produce positive-like symptoms and perceptual disturbances including visual hallucinations and deficits in visual contour processing that are reminiscent to that observed in some patients in early or acute stages of schizophrenia. However, the neurophysiological mechanisms and 5-HT receptor sites that mediate these visual perceptual alterations remain largely unknown.

Methods: To further elucidate the role of 5-HT2A receptors in visual processing, we performed a double-blind placebo-controlled randomized trial in healthy human subjects (n=20) to assess the effects of psilocybin (215 μg/kg p.o.), on prestimulus and subsequent visual stimulus-induced parieto-occipital alpha oscillations and
early visual-evoked potentials and to determine whether these psilocybin-induced effects are (II) reversed by the preferential 5-HT2A antagonist ketanserin (50 mg p.o.) or the partial 5-HT1A agonist buspirone.

**Results:** Analysis of the visual-evoked potentials revealed that psilocybin selectively increased the medial P1 potential, whereas ketanserin selectively decreased the medial P1 potential. The subsequent N170 potential was strongly decreased over the lateral occipital cortex by psilocybin and associated with the appearance of visual hallucinations and audiovisual synesthesia, both of which were completely blocked by the 5-HT2A antagonist ketanserin. A correlation analysis showed that the decrease the N170 potential correlated with the intensity of psilocybin-induced subjective alterations in visual perceptions. In contrast to this, the partial 5-HT1A agonist buspirone did only moderately reduce psilocybin-induced visual disturbances and partially reversed the reduction in the N170 potential.

**Conclusion:** The present results show that 5-HT2A rather than 5-HT1A receptor stimulation is the key mechanism for the generation of visual hallucinations and audiovisual synesthesia in psilocybin states and suggests that such a mechanism may also be responsible for the visual disturbances observed in early schizophrenia and/or Parkinson’s disease.

**S-20. The translocator protein (18 KDa) as a novel target in neurology and psychiatry**

**S-20-001 Translocator protein 18 KDa ligands as novel anxiolytics without benzodiazepine like side effects**

R. Rupprecht, Medizinische Einrichtungen des, Bezirks Oberpfalz GmbH, Regensburg, Germany

**Objective:** The translocator protein 18 KDa (TSPO) mediates the transport of cholesterol from the outer to the inner side of the mitochondrial membrane. TSPO ligands offer a broad spectrum of diagnostic and therapeutic possibilities.

**Methods:** We assessed GABAergic neurotransmission by means of slice studies with the selective TSPO ligand XBD173. Moreover, we studied the effects of XBD173 on behavioral anxiety paradigms in rats and humans.

**Results:** XBD173 stimulated neurosteroidogenesis and enhanced GABAergic neurotransmission in slices of the mouse prefrontal cortex. Moreover, XBD173 displayed antanic activity in rats and in humans employing the CCK-4 challenge paradigm. In contrast to alprazolam there was no sedation and no induction of withdrawal symptoms.

**Conclusion:** TSPO ligands may offer therapeutic potential as anxiolytics but also for other indications such as pain and neurodegenerative disorders.

**Policy of full disclosure:** The studies with XBD173 were sponsored by Novartis, Switzerland. Rainer Rupprecht has been a consultant for Novartis and Grünenthal.

**S-20-002 Structure and function of the translocator protein (18kDa) in steroid and neurosteroid biosynthesis**

V. Papadopoulos, Montreal, Canada

**Objective:** Translocator protein (18-kDa; TSPO) is the product of a gene family that is evolutionarily conserved from bacteria to humans and expressed in most mammalian tissues. Among all tissues TSPO is expressed at the highest levels in those with the ability to synthesize steroids. Subsequently, TSPO was shown to be primarily localized to mitochondria and to be associated with cholesterol import into mitochondria, a key function in steroidogenesis. Indeed, cholesterol transfer from the outer mitochondrial membrane (OMM) to the inner mitochondrial membrane (IMM) is the rate-limiting and hormone-sensitive step in the regulation of steroid biosynthesis.

**Methods:** Using cellular, molecular, biochemical, biophysical and genetic methods we demonstrated that TSPO binds with high affinity to cholesterol, identified a cholesterol recognition amino acid consensus and investigated the mechanism underlying TSPO-mediated cholesterol import.

**Results:** Our studied demonstrated that the transfer of cholesterol into OMM occurs through a protein complex termed the transducosome which is composed both of cytosolic proteins and the OMM proteins TSPO and voltage-dependent anion channel (VDAC). Steroid production is proposed to be initiated at this complex by the mitochondrial-targeted Steroidogenic Acute Regulatory protein (STAR) which acts on the OMM to facilitate cholesterol transfer to the IMM through the assistance of TSPO. Further studies demonstrated photo-activatable cholesterol binding to two native cholesterol binding-protein mitochondrial complexes of 66- and 800-kDa. STAR was found to mobilize cholesterol from the 800-kDa complex and induce cholesterol metabolism to pregnenolone, the precursor of all steroids. Immunoblot and mass spectrometry analyses revealed that this complex contains the OMM TSPO and VDAC and IMM proteins, including CYP11A1, the enzyme metabolizing cholesterol to pregnenolone. We then demonstrated that the 800-kDa complex contains CYP11A1 activity.

**Conclusion:** These results identify a bioactive, TSPO-anchored multilayer protein complex spanning the OMM and IMM that is responsible for the cholesterol import, segregation, targeting, and metabolism to steroids and neurosteroids.

**S-20-004 Peripheral nerve regeneration: Therapeutic perspectives for TSPO ligands**

M. Schumacher, Paris, France

**Objective:** We investigate the potential therapeutic benefits of translocator protein (TSPO) drug ligands for neuroprotection, axonal regeneration, neuroinflammatory responses and neuropathic pain symptoms. TSPO expression is strongly upregulated in response to nerve injury, primarily in Schwann cells and macrophages, but also in neurons. Importantly, TSPO levels only return to low control values when nerve regeneration is completed, strongly supporting a role in regenerative processes. The mechanisms of action of TSPO ligands involve the regulation of mitochondrial activity and function and the stimulation of steroid biosynthesis.
S-21. From gene to drug response: Multi-method approach to the pharmacogenomics of response to antidepressants


Results: Treatment with the benzoxazine etifoxine, which binds to TSPO and GABAA receptors, resulted in a 2-fold acceleration in axonal regeneration after sciatic nerve injury and in a marked improvement of both the rate and quality of functional recovery. Walking track test, automated grid walk assay and nerve pinch test showed that the recovery of both motor and sensory functions was accelerated and improved. Treatment with etifoxine also strongly reduced the number of macrophages and blunted the production of inflammatory cytokines. This effect appeared earlier in the proximal stump than in the part of the injured nerve distal to the lesion site. Importantly, etifoxine has been shown to reduce mechanical and thermal pain induced by the chemotherapeutic agent vincristine. Thus, TSPO ligands are also promising agents for reducing neuropathic pain symptoms.

Conclusion: Etifoxine, an already clinically approved drug for the treatment of anxiety disorders, and TSPO ligands in general, offers promise for the treatment of peripheral nerve injuries and axonal neuropathies.

S-21-001 Multi-method approaches to pharmacogenomics in animal models

M. Popoli, University Milano, Italy

Objective: Preclinical research in rodent models may contribute to the identification of genomic determinants of response to drugs. Different techniques, from transcriptomics and proteomics to the more recent epigenetic methods can be employed to reach this objective. Aim of this presentation will be to draw from different animal studies a number of converging, validated genes and pathways that may inform human pharmacogenetic studies.

Methods: Results from a number of different studies will be discussed: (1) Transcriptomics of the Flinders Sensitive Line (FSL) genetic model of depression (2) Synaptoptroteomics of FSL subjected to early-life stress (gene x environment model) (3) Synaptoptroteomics of the Learned Helplessness (LH) model (4) Epigenetic analysis of transgenic mice carrying the BDNF Val66Met human mutation (5) Analysis of microRNAs (miRs) involved in the action of antidepressants.

Results: A common finding of the FSL and LH models was that energy metabolism and cellular remodeling pathways are involved in both the depressive-like phenotype and in the response to antidepressants. A number of interesting biomarkers was regulated in opposite directions by stress and antidepressants in both models. Results with the BDNF Val66Met mice have been obtained both from candidate gene studies and from a genome-wide CHIP-Seq study. Bioinformatic analysis of genes with epigenetic changes in their promoters revealed the involvement of networks related to lipid metabolism, small molecule biochemistry, cell death, cellular development functions, among others. In addition, consistent changes in epigenetic tags and in expression have been found in select splice variants of BDNF transcripts.

Conclusion: Overall, the results obtained in the different rodent studies allowed to select a number of genes and pathways that may be involved in pathophysiology as well as in response to drug treatments. Converging results from different studies and models will be implemented to inform human pharmacogenetic research.

S-21-002 Transcriptomic and epigenetic correlates of antidepressant response

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Objective: There is significant variability in antidepressant treatment outcome, with approximately 30–40% of patients with major depressive disorder (MDD) not presenting with adequate response even following several trials. To identify potential gene expression and epigenetic biomarkers of response we investigated peripheral gene expression patterns of response to antidepressant treatment in MDD.

Methods: We used Affymetrix HG-U133 Plus2 microarrays in blood samples from untreated individuals with MDD (N = 63) ascertained at a community outpatient clinic, pre- and post eight-week treatment with citalopram and used a regression model to assess the impact of gene expression differences on antidepressant response. We carried out technical validation of significant probesets by qRT-PCR and conducted CNS follow-up of the most significant result in post-mortem brain tissue samples from MDD and control individuals. We investigated epigenetic mechanisms that could explain differential expression of selected genes.

Results: A total of 32 probesets were differentially expressed according to response to citalopram treatment following FDR correction. Interferon Regulatory Factor 7 (IRF7) was the most significant differentially expressed gene and its expression was upregulated by citalopram treatment in individuals who responded to treatment. Consistent results were found in postmortem brain tissue of MDD subjects and epigenetic mechanisms seem to play a relevant role.

Conclusion: These findings are promising and support studies investigating genomic factors associated with antidepressant response.

S-21-003 Antidepressants and emotional processing

C. Harmer, University of Oxford, Psychiatry, United Kingdom

Objective: The neurochemical actions of antidepressant drug treatment are relatively well understood but there has been little work on how these changes become translated into the clinical effects on mood and psychological processes seen in the treatment of depression.

Methods: A recent series of studies suggests that antidepressants affect key psychological processes important in depression early in treatment and before therapeutic effects are seen. This has been investigated using behavioural and fMRI test batteries in healthy volunteers and acutely depressed patients.

Results: Antidepressant treatments have been observed to bias emotional processing towards positive vs. negative valenced information. This increase in positive bias could therefore provide a platform for subsequent cognitive restructuring and learning which contributes to later improvements in depression. Consistent with this, we have also found that changes in emotional bias in depressed patients with a single dose of an antidepressant predicted therapeutic response after 6 weeks of treatment. fMRI studies further suggest modulation of amygdala and extra-striate responses to emotional stimuli, indicating drug-modulation of attentional processing.

Conclusion: These results challenge long held assumptions that the delay in antidepressant drug action results solely from the need for neurophysiological processes to be completed. Rather, the role of psychological mechanisms may be important in antidepressant drug response as patients learn to re-evaluate themselves and their emotional context in the light of new processing biases. Such an approach may therefore help us to understand how drug treatments are working, how we might be able to improve treatment approaches and also may provide biomarkers for early candidate selection.

Policy of full disclosure: Advisory board and shareholder in Pivotal Ltd. Received consultancy from Eli-Lilly, Servier and Pivotal. Company director of Oxford Psychologists Ltd. Research work has been funded by the Medical Research Council.
S-22. ECT: Research and practice update

S-22-001 What we now know about ECT mechanisms of action
T. Bolwig, Copenhagen University Hospital, Denmark
Objective: To review the existing literature in search of a hypothesis for the working action of ECT.
Methods: The presentation has focused on hypotheses based on reproducible empirical data, and attempts to link clinical and para-clinical findings with the wealth of findings relevant for ECT emerging from animal studies conducted primarily during the last four decades.
Results: Especially three hypotheses have proven useful from a heuristic point of view: The Generalized Seizure Theory points to therapeutic efficacy being totally dependent on the elicitation of brain activity corresponding to a grand mal seizure. The neuroendocrine theory enunciates that ECT works by restoring neuroendocrine dys-function associated with melancholic depression. The Combined AnatomICAL-Ictal Theory enunciates that seizure activity in th limbic system induces neurotrophic effects crucial for the therapeutic efficacy of ECT.
Conclusion: Generalization of seizures (grand mal) is necessary for therapeutic effect of ECT. Among the theories to explain this effect the neuroendocrine theory, at the present time has the strongest foundation among the existing theories to explain the working action of ECT.

S-22-002 Latest NIH supported ECT data – efficacy and safety
C. Kellner, Mount Sinai School of Medicine, New York, USA
Objective: To review recent efficacy and safety data from recent NIH-supported multicenter clinical trials.

S-22-003 Impact of ECTAS on UK ECT
C. Freeman, Royal Edinburgh Hospital, Department of Psychiatry, Edinburgh, United Kingdom
Objective: To review the existing literature in search of a hypothesis for the working action of ECT.
Methods: The academic and industrial partners of the NEWMEDS consortium compiled a sample of over 2000 cases of moderate to severe depression with prospective outcome data for up to 12 weeks treatment. Individuals were given either a serotonin reuptake inhibiting (SRI) or norepinephrine reuptake inhibiting (NRI) antidepressant. The primary aim of the study was to obtain genetic predictors of antidepressant response thus power analyses and interpretation of results focused on detecting clinically significant effect for genetic markers. In 1790 individuals with high quality genotyping information, four genome-wide linear regressions tested the associations of half million genetic markers with percentage change in depression severity overall, with SRI, with NRI and with differential response to SRI and NRI.
Results: None of the more than half million genetic markers significantly predicted response to antidepressants overall, SRI, NRI or differential response to SRI and NRI. Pathway analysis in ALIGATOR revealed no biological pathways that were significantly overrepresented in the results. A meta-analysis undertaken with another large sample (STAR*D) detected no significant associations. Polygenic scoring found no convergence among multiple associations in NEWMEDS and STAR*D. Machine learning algorithms suggest that genetic information can meaningfully contribute to prediction of treatment outcome and predict approximately 3% of the variance in outcome.
Conclusion: The absence of pharmacogenetic associations with clinically meaningful effect suggests that genetic information is not ready to inform personalization of treatment for depression in the near future. Complex prediction algorithms allowing for non-additive effects may be able in the future to aid in the prediction of antidepressant response.

S-22-004 Cognitive effects of ECT
D. McLoughlin, M. Semkovska, R. Dunne, M. Noone, Trinity College Dublin, Ireland
Objective: Concerns about cognitive side-effects following ECT for depression limit its use. We sought to quantify ECT-associated cognitive changes, specify their pattern and progression and explore the effects of electrode placement.
Methods: We performed a series of meta-analyses to quantify changes in cognitive performance as measured using standardised tests after completing a course of ECT.
Results: Cognitive deficits were mainly limited to the first three days after completing an ECT course. During this period right unilateral (RUL) ECT was associated with significantly smaller deficits than bitemporal (BT) ECT. However, after three days there were no significant differences between BT and RUL ECT and after 15 days all levels of functioning were restored to at least baseline with many significantly improving beyond this. Meta-analyses of trials comparing bifrontal (BF) ECT to BT or RUL ECT found BF ECT to be no more effective than BT or RUL ECT with only modest benefits on visual recall compared to RUL ECT. It was not possible to meta-analyse autobiographical amnesia outcomes due to lack of use of standardised measures; and significant publication bias was found, favouring reporting of larger percentage loss. To address this we have validated a new scoring system for the Columbia Autobiographical Memory Interview – Short Form (CAMI-SF), the most commonly used such instrument in ECT studies, and have obtained normative data for retrieval consistency of its semantic, episodic-extended and episodic-specific components for both healthy controls and depressed persons. On initial assessment, depressed patients produced less episodic-specific memories than controls. Both groups showed equivalent changes in cognitive performance as measured using standardised tests after completing a course of ECT.
Conclusion: The majority of cognitive abnormalities associated with ECT appear to be transient and function improves over time. Research quantifying retrograde amnesia following ECT for depression needs to control for normal loss in consistency over time and contribution of persistent depressive symptoms.
S-23. Defining the neurobiological basis of cognitive impairment in schizophrenia through translational research

S-23-001 Serotonergic-glutamatergic-dopaminergic interactions: The basis for the cognitive enhancing effects of atypical antipsychotic drugs in schizophrenia and NMDA receptor antagonist animal models

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Objective: to identify contribution of various serotonin (5-HT), dopamine (DA) and glutamate (Glut) receptors to the ability of atypical antipsychotic drugs (APDs) to reverse or prevent the enduring deficit in novel object recognition (NOR) in female rats treated with phencyclidine (PCP), an NMDA receptor non-competitive antagonist, which has been considered to provide the best model of the cognitive deficit in SCZ.

Methods: The administration of PCP, 2 mg/kg ip for 7 days, followed by a 7 day washout period, to groups of 8 rats produced a deficit in NOR that lasted for many months. Various APDs, specific 5-HT, DA and Glut receptor agonists and antagonists were given along with PCP, or acutely or for 7 days following the PCP washout period. The effect on treatments on the discrimination index (novel-familiar/novel + familiar) during the retention period, which is 0.4-0.5 in control rats was assessed.

Results: Atypical APDs which are potent 5-HT2A inverse agonists with less potency for D2 receptors, e.g. lurasidone, as well as amisulpride, a D2/D3/D5-HT7 antagonist reversed the deficit in NOR produced by subchronic PCP. Shepholdine A, a putative atypical APD, with D1 and 5-HT1A agonist properties was also effective. Haloperidol (HAL), a D2 antagonist, did not. By means of selective agonists and antagonists, it was possible to establish that D1 agonism, 5-HT1A partial agonism, 5-HT2A inverse agonism, 5-HT7 antagonism, and mGlur2/3 agonism can positively impact the effects of subchronic PCP. Some, but not all of these mechanisms, also prevented the effect of subchronic PCP to impair NOR or produce an enduring reversal in the effects of PCP.

Conclusion: A variety of 5-HT, DA and glutamate mechanisms can be shown to ameliorate the deficit in a behavior analogous to declarative memory in PCP-treated rodents. The translational value of these findings will be discussed.

Policy of full disclosure: Grant support from Dainippon Sumitomo; Masakuni Horiguchi is an employee of Dainippon Sumitomo.

S-23-002 Effects of antipsychotic and antidepressant drugs, alone and in combination, on cortical dopaminergic and glutamatergic transmission and cognitive impairment in schizophrenia

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Objective: Clinical studies indicate that both atypical antipsychotic drugs and a combination of conventional antipsychotic and antidepressants may enhance neurocognition in schizophrenia. A reduced cortical dopamine release as well as impaired glutamatergic transmission in prefrontal cortical areas have also been proposed in this disease, which may underlie certain aspects of the cognitive impairment. The present studies aimed to elucidate the effects of atypical antipsychotic drugs such as clozapine as well as a combination of moderate doses of other antipsychotic drugs and conventional antidepressants on cortical dopaminergic and glutamatergic transmission, including both NMDA- and AMPA receptor functioning.

Methods: Experiments were performed in rats, using electro-physiological intracellular recording in pyramidal cells in a prefrontal cortical slice preparation, microdialysis in freely moving animals to assess regional monoamine efflux in brain, and behavioral methodol-ogies, including the conditioned avoidance response (CAR) test to assess antipsychotic activity, the 8-arm radial maze to study working memory function and a sensitive catalepsy test to estimate extrapyramidal side effect liability.

Results: Clozapine and a combination of suboptimal doses/concentrations of other antipsychotic drugs and conventional anti-depressants, i.e. reboxetine or SSRIs, that caused a sufficient suppres-sion of CAR to indicate an effective antipsychotic action, in parallel markedly increased prefrontal cortical dopamine outflow and also generated a significant potentiation of NMDA receptor-mediated transmission in this region. In the case of clozapine these effects were found to be associated with a reversal of impaired working memory induced by MK-801, a selective NMDA receptor antagonist, and to be mediated via dopamine D1 receptors which are coupled to the NMDA receptors. None of the drugs except clozapine was able to achieve these effects when given alone in the same doses/concentra-tions. Importantly, the combination of low concentrations of anti-psychotic and antidepressant drugs also facilitated prefrontal cortical AMPA receptor-induced currents in pyramidal neurons.

Conclusion: These results propose that clozapine as well as a combination of antidepressants and other antipsychotic drugs may improve neurocognition in schizophrenia by means of activation of prefrontal dopamine release, D1 receptors and an associated potentiation of glutamatergic NMDA receptor-mediated transmission in this brain region. The concomitant AMPA receptor facilitation may indicate a relatively rapid onset antipsychotic effect as well.

Policy of full disclosure: Funded by NIMH, NIDA.

S-23-003 Translational biomarkers of NMDA dysfunction in schizophrenia: Mechanisms and opportunities

D.C. Javitt, New York University Sch Med, Nashville, USA

Objective: Deficits in NMDA receptor function represent a core feature of schizophrenia and a primary target for new drug development. A key challenge is development of compounds to augment NMDA neurotransmission, and development of measures that can be used in preclinical studies to guide translational drug development. Deficits in auditory sensory event-related potentials (ERPs) including N1, mismatch negativity (MMN) and auditory steady-state response (ASSR) have become increasingly well documented over recent years. These studies evaluate generators of auditory ERP in animal models, and their relation to underlying NMDA function.

Methods: ERP were recording in both primates and rodents. In primates, ERPs were recorded using multichannel electrodes implanted into primary auditory cortex. Laminar profile of response was analyzed as well as response to the NMDAR antagonist ketamine. In rodents, effects were measured both of NMDA receptor antagonists and genetic manipulations relative to NMDA function.

Results: In primates, generators of N1, MMN, and ASSR were located to discrete layers of primary auditory cortex, reflecting differential function. Moreover, ketamine decreased N1 generation, while increasing ASSR, suggesting differential underlying circuit mechan-isms. In rodents, serine racemase and selective PV/NMDA KO led to selective modulations of N1 and ASSR generation, and increased sensitivity to ketamine.

Conclusion: These findings validate neurophysiological measures, including N1, MMN and ASSR as indices of NMDA receptor dys-function in both schizophrenia and in underlying primate and rodent models, and suggest their use as translational measures in early stage drug development processes.

Policy of full disclosure: Funded by NIMH, NIDA.

S-23-004 Effect of clozapine and ketanserin on S-ketamine-induced brain activation and psychotic symptoms in healthy humans

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Objective: NMDA antagonist such S-ketamine induces positive-like symptoms and cognitive impairments of schizophrenia in healthy humans.
subjects. In animals, NMDAR antagonists disrupt sensory gating (PPI) comparable to that observed in schizophrenia, a finding that is reversed by atypical 5-HT2A/2C/3 antagonists, but not by typical antipsychotics. Similarly, previous work in humans suggests that clozapine but not haloperidol partially ameliorates ketamine-induced symptoms. Here, we examined the functional network underlying S-ketamine-induced psychotic symptoms and whether clozapine and ketanserin reverse such symptoms, and if so, where these changes would be expressed.

Methods: S-ketamine-induced psychotic symptoms (OAV) and alterations in regional brain activity were assessed using H215O-PET. Twenty male subjects were tested (double-blind, randomized): 10 receiving placebo, 5-ketamine (0.006 mg/kg/min), clozapine (30 mg po), and S-ketamine plus clozapine; the other 10 receiving ketanserin (50 mg po) as pretreatment.

Results: S-ketamine produced positive symptoms and cognitive disturbances that were differentially associated with increased brain activity in an extended neural network including prefrontal regions, anterior cingulate, putamen, thalamus and the temporo-parietal and insular cortex. Reduced activity was found in parietal and occipital cortex regions, and cerebellum (p < 0.0001). Pretreatment with clozapine (30 mg) moderately reduced some of the S-ketamine-induced symptoms and partially reversed the S-ketamine-induced alterations in anterior cingulate, insula, temporal-medial and insular cortex. Moreover, clozapine reduced brain activity in left hippocampus and bilaterally in parahippocampus and increased the activity in pons and orbitofrontal cortex. Pretreatment with ketanserin (50 mg) partially reversed S-ketamine-induced mania-like symptoms and alterations in the left insula, putamen, anterior cingulate, cerebellum, and pons.

Conclusion: The present findings suggest that a disruption of NMDAR but not S-5HT2AR-mediated neurotransmission within fronto-temporal-striato-thalamic pathways mainly contributes to ketamine-induced psychotic symptoms.

S-24. Cytokines and psychiatric illness

S-24-001 Inflammation-induced depression: Evidence and mechanisms
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Exposure to pathogenic micro-organisms triggers an episode of sickness behavior. The development of sickness behavior is triggered by the proinflammatory cytokines that are produced by activated cells of the innate immune system when they sense specific pathogen-associated molecular patterns via toll-like receptors. These cytokines include mainly interleukin (IL)-1 (IL-1alpha and IL-1beta), IL-6, and tumor necrosis factor alpha (TNF-a). The same cytokines are produced in the brain by macrophage-like cells including microglia in response to peripherally produced cytokines. Brain cytokines ultimately act on neurons to alter body metabolism and behavior. In the same way as inflammation normally resolves and leaves room for repair mechanisms, sickness behavior is normally followed by recovery. However, when the peripheral immune responses is too intense or lasts too long, the behavioral response to cytokines can become maladaptive and culminate in an episode of depression. The mechanisms of transition from sickness to depression have been studied both in the clinics in patients receiving chronic cytokine immunotherapy for the treatment of chemotherapy-resistant tumors or hepatitis C virus, and at the bench, in animal models of inflammation-induced depression. The transition from sickness to depression is mediated by activation of the tryptophan-degrading enzyme, indoleamine 2,3 dioxygenase (IDO), which is the first and rate-limiting enzyme of the kynurenine metabolic pathway. Kynurenine is further metabolized in neurotoxic compounds including 3-hydroxy kynurenine and quinolinic acid. Inhibition of IDO by pharmacological or genetic means abrogates the development of depression but does not affect sickness in response to inflammation. In contrast inhibition of the cytokine response abrogates both sickness and depression. The way this research ultimately impacts on our understanding of the occurrence and treatment of non-specific symptoms in physically ill patients will be discussed.

Policy of full disclosure: Funded by NIH Honorarium from Janssen Consultancy with Lundbeck Laboratories.

S-24-002 Inflammation as a cause of suicidality?
L. Brundin1, S. Erhardt2, L. Träskman-Bendz2, 1Lund University, Psychosomatics Unit, Sweden; 2Lund University, Sweden

Objective: There is accumulating evidence that the immune system is involved in the pathophysiology of depression. Depressed patients display elevated levels of proinflammatory cytokines in the blood, and patients treated with interferons for other disorders often develop depression. It is currently not known whether inflammation gives rise to specific psychiatric symptoms. Suicideality is a comparatively well-defined phenomenon, present in some depressive patients but not others, which we hypothesized to be associated with inflammation.

Methods: In 2009, we found increased IL-6 in the cerebrospinal fluid (CSF) of suicide attempters, and that cytokine levels were related to severity of depression. In a subsequent study, we compared suicide attempters to non-suicidal depressive patients as well as healthy controls. We found that suicide attempters displayed higher plasma levels of IL-6 and TNF-a, than both depressed- and healthy controls.

Results: In a recent study we measured quinolinic acid (QUIN), a metabolite produced when the kynurenine pathway is induced by inflammation, in the CSF of suicide attempters. QUIN is an agonist of the NMDA receptor and thus an interesting link between the immune system and glutamate neurotransmission. We found increased QUIN in suicide attempters compared to healthy controls, and there was a correlation with the degree of suicidal intent as well as with IL-6 levels in the CSF.

Conclusion: Our studies provide evidence of both central and peripheral inflammation in suicide attempters. There were positive correlations between inflammatory factors and both depressive and suicidal symptoms. QUIN, affecting glutamate neurotransmission might be a key player in the symptom generation.

S-24-003 Neuroinflammation in psychiatric disorders
G. Engberg Karolinska Institutet, Stockholm, Sweden

Objective: Accumulating evidence suggests that psychotic disorders are associated with brain inflammatory processes. However, direct evidence for a central immune activation in schizophrenia is relatively sparse. Several studies have shown that brain kynurenic acid (KYNA), a neuroactive compound blocking the glycine site of the NMDA receptor and the alpha7nicotinic receptor, is elevated in schizophrenia. In the past few years it has become evident that CSF KYNA serves as a biological marker of brain immune activation. The present study was undertaken in order to investigate concentrations of cytokines in the CSF of psychotic patients.

Methods: Cytokines were analyzed by an electrochemiluminescence biosensor assay (Meso Scale Discovery, Gaithersburg, MD, USA). Also the relationship between cytokines and KYNA was studied in vitro settings.

Results: The pro-inflammatory cytokine interleukin (IL)-1beta is markedly elevated in the CSF of first-episode patients with schizophrenia (mean 6.5 ± 0.7 pg/ml) as compared to healthy volunteers (0.8 ± 0.04 pg/ml). Furthermore, in olanzapine-medicated patients with chronic schizophrenia we found that CSF IL-6 is elevated (3.2 ± 0.4 pg/ml ± ) compared to healthy volunteers (1.8 ± 0.2 pg/ml). Also in patients with bipolar disorder CSF KYNA and IL-1beta are elevated. In this regard, levels of KYNA correlate to life-time occurrence of psychotic episode, while CSF IL-1beta levels correlate to the occurrence of recent symptoms of mania. In vitro studies utilizing human astrocytes show that the rate limiting enzymes of the kynurenine pathway of tryptophan degradation, IDO and TDO, are induced by administration of IL-1beta, resulting in increased KYNA formation. These findings may rationably link together the elevation of KYNA and IL-1beta seen in patients with schizophrenia or bipolar disorder.

Conclusion: Present results provide direct evidence for brain immune activation in these disorders.

S-24-004 Cytokines in psychiatric disorders: Therapeutic approaches
N. Müller. Ludwig-Maximilian University, München, Germany

Proinflammatory cytokines, such as IL-6, IL-1 and TNF appear to be elevated at least in the peripheral blood of depressed patients. Thus
S-25. Genetic and non-genetic risk factors in translational models of psychiatric disorders

Royal College of Surgeons, Dublin, Ireland

Objective: As molecular genetic findings in schizophrenia advance, they are now being complemented by a new generation of epidemiological studies that implicate also both biological and psychosocial adversities acting across its developmental trajectory. This highlights a need for more incisive models of gene environment interactions that are rooted in these genetic and environmental findings. Thus, we have studied a series of such environmental adversities in mice mutant for two genes bearing different relationships to schizophrenia: neur- egulin-1 (NRG1) and catechol-O-methyltransferase (COMT).

Methods: Mice mutant for NRG1 were subjected to one of three environmental adversities: intrauterine compromise via maternal immune activation with Poly I:C; adolescent psychosocial stress via repeated social defeat; and adult, subchronic exposure to the psychotomimetic phencyclidine (PCP). COMT mutants were subjected to adolescent vs. adult, subchronic exposure to the psychotomimetic 9- tetrahydrocannabinol (THC). Phenotypic evaluations included ethological assessment, exploratory activity, prepulse inhibition, cognition, social behaviour and magnetic resonance imaging.

Results: Effects of genetic mutation on the functional consequences of each environmental adversity were characterised. For example, effects of maternal immune activation with Poly I:C were altered in NRG1 mutants effects of acute PCP were attenuated in NRG1 mutants given subchronic vehicle but heightened in NRG1 mutants given subchronic PCP; the effects of adolescent THC were heightened in COMT mutants while no such effects of adult THC were evident.

Conclusion: The present findings indicate that for a series of both biological and psychosocial environmental factors, resultant phenotype may be determined by their interaction with psychosis-related genes operating across the developmental trajectory of schizophrenia at critical time points.

Policy of full disclosure: The authors’ studies are supported by Science Foundation Ireland and the Health Research Board.

S-25-002 Infectious and immune factors modulate neurobehavioral abnormalities in DISC1 mice

M. Pletnikov, John Hopkins University, USA

Objective: Although infections contribute to schizophrenia, the mechanisms whereby microbes affect neurodevelopment remain unclear. Interaction between microbial and genetic factors may be responsible for the disease in predisposed individuals. We studied the neurobehavioral effects of prenatal immune activation or early postnatal parasitic infection in control and mutant DISC1 mice to model human conditions of gene-environment interactions in schizophrenia.

Methods: We evaluated neurobehavioral schizophrenia-like alterations in mice exposed to early or late postnatal infection with Toxoplasma gondii (T. gondii), a pathogen associated with schizophrenia. In a different animal model, control and mutant DISC1 mice were challenged with immune activation with Poly I:C at embryonic day 9. Gene expression profiles, brain pathology, neurochemical alterations and behavioral abnormalities were examined in adult mice in both models.

Results: Early but not late infection with T. gondii produced loco- motor hyperactivity and stimulants-induced impaired pre-pulse inhibition of the acoustic startle in male but not female mice. Sex-dependent effects of the parasitic infection were also present in abnormal gene expression in the cortex and cyts distribution in the brain although no differences in antibody titres were seen between sexes. Prenatal infection produced abnormal affective and social behaviors and associated smaller amygdala and periaqueductal gray matter, and decreased density of spines on dendrites of hippocampal granule cells. Mutant DISC1 modulated Poly I:C-induced secretion of cytokines in fetal brains, and levels of endogenous mouse DISC1 and GSK-3β.

Conclusions: The present data suggest the timing of infection and sex of the host could play major roles in modulating schizophrenia-like neurobehavioral changes in mice. In addition, genetic predisposition to schizophrenia may modulate behavioral consequences of immune activation produced by microbes in vitro. The present mouse models may facilitate a better understanding of the contribution of microbes to schizophrenia and related conditions.

S-25-003 Identifying interactions between genes and early environment in the mouse

V. Carollo, EMBL, Mouse Biology Programme, Santa Lucia Foundation, Rome, Italy

Objective: Much of the impact of genes on mood disorders is likely to depend on interactions between genes and the environment. Such interactions would lead to the expression of environmental effects only in the presence of a permissive genetic background. Human studies have demonstrated interactions between genes and life stressful events in the modulation of mood disorders. Research in this field can take advantages of animal models where the manipulation of the genetic and environmental components is easy to perform. During the past years in our laboratory we have been establishing mouse models of the interaction between genes and early environment in the modulation of anxiety and depression-like behavior.

Methods: In parallel experiments, we exposed mice carrying targeted mutations in selected genes (5HTT; BDNF; and SERT) to different maternal environment (“high” vs. “low” levels of maternal care) during early development. The effect of the gene-by-early environment interaction (G × E) was evaluated using behavioral tests in adult mice. To identify the molecular substrates of the G × E, brains of these mice were all processed by HPLC, In Situ Hybridization, and autoradiography techniques.

Results: For SERT mutation, we clearly observed G × E effect with heterozygous 5-HTT knockout mice exposed to “low” maternal
Advanced paternal age: Modelling non-genetic risk factors in psychiatry

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Objective: Advanced paternal age (APA) is associated with an increased risk of neurodevelopmental disorders, such as schizophrenia and autism. We have developed a mouse model to explore the neurobiological correlates of APA. In this presentation the effects of APA on brain morphology and behaviour with relevance to neuropsychiatric disorders will be discussed.

Methods: We investigated structure-function relationships in the adult offspring of young (3 month-old) Control and old (12-24 month-old, APA) C57Bl/6 sires. Mice underwent a behavioural battery comprising tests for locomotion, anxiety, exploration, learned helplessness, social behaviour, avoidance learning, prepulse inhibition (PPI) of the acoustic startle response and amphetamine (AMPH)-induced locomotion. Brains of these mice were examined ex vivo using a 36.4T animal MRI scanner.

Results: We find no evidence of behavioural phenotypes that are commonly associated with models of schizophrenia, such as increased amphetamine-mediated hyperlocomotion or PPI deficits. Social behaviour was also unaltered, suggesting that the APA mouse model does not recapitulate classical features of ASD. However, APA appears to produce a robust anxiogenic phenotype that is increased with increasing sire age. Although this behavioural phenotype was not significantly altered in either disorder in any region examined for either disorder (p > 0.05). [3H]4-DAMP binding was decreased in BA 10 in BPD (p < 0.05). [3H]pirenzepine, [3H]AFDX-384 and [3H]4-DAMP to CHRM1/CHRM3, respectively. Radioligand binding was measured in postmortem tissue obtained from Brodmann’s area (BA) 10, 46 and 40 in mood disorders and BA 9 from subjects analysed for effects of suicide.

Conclusion: There is no evidence of behavioural phenotypes that are directly related to increasing sire age. Although this behavioural phenotype would not appear to obediently map on to the neuropsychiatric conditions in which APA is implicated, structural and functional changes in cortex callosum have been consistently reported in both autism and schizophrenia. These studies have clarified APA “dose” as a possible explanation for the variable phenotype reported in both autism and schizophrenia. These studies have clarified APA “dose” as a possible explanation for the variable phenotype reported in both autism and schizophrenia.

S-26. Emerging opportunities to treat psychiatric disorders with muscarinic receptor agonists

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Objective: Decreased levels of muscarinic receptors have been widely reported to occur in the brains of people with schizophrenia. Studies have identified that cortical muscarinic M1 receptors are altered, whilst in the hippocampus the M4 receptors are decreased. We recently discovered that the decreases in M1 receptors did not occur in everyone with schizophrenia but are restricted to a small portion of subjects, who have large deficits. This raised the question of whether this subgroup has unique neurochemical deficits compared to people with schizophrenia who do not have the deficit in M1 receptors.

Methods: RNA was extracted from Brodmann’s area 9 from 15 non-psychiatric controls and 30 subjects with schizophrenia, half of who had low muscarinic receptor levels. cDNA was generated from all samples and run on Affymetrix Human Exon 1.0 ST microarrays. Using JMP Genomics, the quality control probes were checked and principle component analyses carried out prior to the data being analysed using an ANOVA. Genes with significantly different expression profiles were inputted into Ingenuity Pathway Analysis.

Results: 487 genes were differentially expressed. 157 were uniquely different between controls and schizophrenia with normal levels of M1 receptors and a further 330 between controls and schizophrenia with low levels of M1 receptors. Pathway analyses revealed that like other microarray studies, many of our transcripts were involved in metabolic processes. A number of pathways have been identified which differentiate between the three groups in the study including control of cell cycle and tyrosine metabolism.

Conclusion: This microarray study reveals a number of pathways that are altered in both groups with schizophrenia compared to controls. However, it also identifies pathways that are changed in only one group of subjects with schizophrenia, supporting the concept that people with schizophrenia who have low levels of M1 receptors may have a distinct pathophysiology.

Symposia, Wednesday 6 June 2012
S-26. Advances in translational research in serotonin neurobiology: Implications for mood disorders

S-26-003 Genetic variation in Cholinergic-Muscarinic-2 Receptor gene modulates Muscarinic2-Receptor binding in vivo and accounts for reduced binding in bipolar disorder

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Objective: Genetic variation in the cholinergic muscarinic-2 (M2) receptor gene (CHRM2) has been associated with the risk of developing depression. We previously reported that M2-receptor distribution volume (VT) was reduced in depressed subjects with bipolar disorder (BD) relative to depressed subjects with major depressive disorder (MDD) and healthy controls (HCs). In this study, we investigated the effects of six single-nucleotide polymorphisms (SNPs) for CHRM2 on M2-receptor binding to test the hypotheses that genetic variation in CHRM2 influences M2-receptor binding and that a CHRM2 polymorphism underlies the deficits in M2-receptor VT observed in BD.

Methods: The M2-receptor VT was measured using positron emission tomography and [18F]TZTP in unmedicated, depressed subjects with BD (n = 16) or MDD (n = 24) and HCs (n = 25), and the effect of genotype on VT was assessed.

Results: In the controls, one SNP (with identifier rs234650, in which the ancestral allele adenine (A) is replaced with one or two copies of thymine (T)), showed a significant allelic effect on VT in the pregenual and subgenual anterior cingulate cortices in the direction AA < AT < TT. In contrast, in BD subjects with the TT genotype, VT was significantly lower than in BD subjects with the AT genotype in these regions. The BD subjects homozygous for the T-allele also showed markedly lower VT (by 27 to 37% across regions) than HCs of the same genotype. Post hoc analyses suggested that T homozygosity was associated with a more severe illness course, as manifested by lower socioeconomic function, poorer spatial recognition memory and a greater likelihood of having attempted suicide.

Conclusion: These data represent novel preliminary evidence that reduced M2-receptor VT in BD is associated with genetic variation within CHRM2. The differential impact of the M2-receptor polymorphism at rs234650 in the BD and HC samples suggests interactive effects with an unidentifiable vulnerability factor for BD.

S-26-004 Potential roles for allosteric Muscarinic receptor modulators for the treatment of psychiatric and neurologic disorders

C. Jones, Vanderbilt University, Vanderbilt Program in Drug Dis, Nashville, USA

Objective: Preclinical and early proof-of-concept clinical studies have revealed that activators of specific muscarinic acetylcholine receptor (mACHr) subtypes are efficacious in animal models predictive of antipsychotic-like activity and cognitive enhancement, as well as in the treatment of the symptoms associated with schizophrenia and Alzheimer’s disease. More recently, our group and others have used an innovative strategy to identify highly subtype selective ligands that act at allosteric sites on mACHrs, which are less highly conserved as compared to the orthosteric site, including allosteric agonists and positive allosteric modulators (PAMs). In vitro studies using calcium mobilization assays were used in parallel to generate functional efficacy and potency data for all allosteric modulators and the pharmacokinetic properties of each ligand were determined in a rat plasma-brain-level study using LC/MS detection of drug levels after systemic dosing. In vivo efficacy was evaluated in several rodent models predictive of antipsychotic-like activity and enhancement of affective and/or cognitive functions.

Results: Here we report the pharmacologic characterization of several subtype selective mACHr activators, including the M1 allosteric agonist VU0152100, which is also efficacious in preclinical models of anti-psychotic-like activity and in reversal of disruptions in hippocampal memory tasks.

Conclusion: Collectively, these allosteric mACHr activators are serving as key tools for further understanding the relative roles of the different mACHr subtypes in the observed efficacy of nonselective mACHr agonists in vivo.

S-27. Advances in translational research in serotonin neurobiology: Implications for mood disorders

S-27-001 Molecular target of serotonin neurotransmission – implication in therapeutics of mood disorders

X Li, Birmingham, USA

Serotonin is a neurotransmitter with broad functions in brain development, neuronal activity, and behaviors; and serotonin is the prominent drug target in mood disorders. The multiple actions of serotonin are mediated by diverse serotonin receptor subtypes and associated signaling pathways. However, the key signaling components that mediate specific function of serotonin neurotransmission have not been fully identified. This presentation will provide evidence from biochemical, pharmacological, and animal behavioral studies showing that brain glycogen synthase kinase-3 (GSK3) is an important component in serotonin signal transduction. GSK3 is a protein kinase which abnormal activity is associated with mood disorders. Several classes of mood-modulating drugs, such as lithium, antidepressants, and atypical antipsychotics, regulate GSK3 by inhibiting its activity in brain, which reinforces the importance of GSK3 as a potential therapeutic target in mood disorders. In animal studies, brain serotonin regulates the activation states of GSK3, mainly through serotonin 1A and 2A receptors. In return, GSK3 directly interacts with serotonin receptors in a highly selective manner, with a prominent effect on modulating serotonin 1B receptor activity. Therefore, GSK3 acts as an intermediate modulator in the serotonin neurotransmission system, and balanced GSK3 activity is essential for serotonin-regulated brain activity and behaviors. With this prominent relationship between serotonin neurotransmission and GSK3, drugs targeting GSK3 may elicit mood stabilizing effects by normalizing brain serotonin activity.

S-27-002 Role of the serotonin receptor adaptor protein p11 in depression

P. Svenningsson, Stockholm, Sweden

Objective: The molecular mechanisms underlying depression and therapeutic efficacy of antidepressants remain largely unknown. This presentation will introduce the possible role of p11 in depression and its treatment.

Methods: Using yeast two hybrid and co-immunoprecipitation experiments, p11 (S100A10, annexin II light chain) was found as an adaptor to 5-HT1B and 5-HT4 receptors. To study the functional role of p11, subsequent studies have used histological, molecular biological, biochemical, electrophysiological and behavioral approaches.

Results: A pronounced reduction of p11 has been found both in post-mortem human tissue from depressed individuals or suicide victims and in a rodent model of depression. Conversely, p11 is increased in rodent brains by antidepressants or electroconvulsive therapy. The expression of p11 is also controlled by L-DOPA and BDNF. p11 knockout mice exhibit a depression-like phenotype, abnormal emotional processing and have reduced or paradoxical behavioral, neurogenic and neurochemical responses to antidepressants as well as 5-HT1B and 5-HT4 receptor agonists. Viral or transgenic overexpression of p11 recapitulates certain behaviors on mood and anxiety seen after antidepressant treatment in mice. While p11 is widespread in the brain, there is some enrichment in populations of interneurons. In addition to serving as an adaptor protein to 5-HT receptors, p11 interacts with ion channels (incl. ASIC-1, TASK-1,
TRPV5/6, intracellular enzymes (incl phospholipase A2, PCTAIRE-1, tPA and cathepsin B) as well as its principal partner annexin 2.

Conclusion: The inducible protein p11 may contribute to certain aspects of depression symptomatology and mediate antidepressant actions.

Policy of full disclosure: Swedish Research Council Servier Dainippon Sumitomo.

S-27-003 Contribution of animal models to the understanding of epigenetic mechanisms in affective disorders and resilience

K.P. Lesch. Wuerzburg, Germany

Objective: Adverse childhood experiences are associated with increased risk for psychiatric diseases later in life, especially anxiety disorders and depression. Several studies indicate that whether an individual develops disorders of emotion regulation following early-life stress is influenced by variation of the serotonin transporter gene (5-HTT).

Methods: Multimodal fMRI in humans suggested that life stress interacts with the 5-HTT genotype to influence amygdala and hippocampal resting activation. There are also compelling data from non-human primates. In rhesus monkeys (Macaca mulatta), maternal separation during the first months of life results in deficient social adaptation and peer interaction.

Results: These deficiencies are related to brain serotonin system function, based on testing for interactions between early life stress and 5-HTT. In addition to the main effects of 5-HTT genotype and early stress to variation in serotoninergic function in later life, 5-HTT also interacts with deleterious early rearing experience to influence attentional and emotional resources, stress reactivity, and alcohol preference and dependence. However, the molecular mechanisms by which stress increases disease risk in adulthood are not known, but may include epigenetic programming of gene expression. Various gene-by-environment interaction (G × E) paradigms in the mouse allow investigations of the molecular mechanisms underlying epigenetic programming by early adverse environment in an animal model amenable to genetic manipulation. Using these G × E paradigms it was shown that prenatal stress or dominant/subordinate social interaction on anxiety-related behavior is modulated by inactivation of 5-HTT.

Conclusion: These findings suggest that the molecular mechanisms involved in these G × E models are relevant to the etiology of disease in humans.

S-27-004 Molecular imaging of serotonin vulnerability in mood disorders

G. Smith. Baltimore, USA

Objective: Findings from studies of animal models (including amyloid transgenic mice) can be translated into testable hypotheses in humans using molecular imaging methods. Studies of the functional neuroanatomy of geriatric depression have shown elevated glucose metabolism in cortico-cortical networks that include regions of the 'default network'. Citalopram treatment decreased metabolism in cortico-cortico networks that include regions of the anterior cingulate, medial frontal, orbitofrontal cortices, posterior cingulate, precuneus, hippocampus/parahippocampal gyrus.

Conclusion: Serotonin depletion associated with Aβ is observed in amyloid transgenic mice, as well as in human neuroimaging studies. This may represent a neurobiological basis for the association between late life depression and vulnerability to cognitive decline, as well as the increased risk of cognitive decline associated with neuropsyciatric symptoms (depression, agitation, anxiety) in mild cognitive impairment. These data may have implications for identifying subjects at risk and for identifying therapeutic targets for early intervention.

S-28. Novel targets for antipsychotic medication development

S-28-001 Efficacy of selective GABA A alpha 5 positive and negative allosteric modulators in the MAM model of schizophrenia

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Objective: Using the MAM developmental disruption rat model of schizophrenia, we examined the efficacy of novel GABA A allosteric modulators in reversing the hyperdopaminergic state thought to underlie psychotic symptoms in schizophrenia in humans. Our studies showed that this model demonstrated parvalbumin GABAAergic interneuron loss in the hippocampus leading to hippocampal hyperactivity and increased dopamine neuron population activity and hyper-responsivity to amphetamine. Therefore, we used drugs that targeted the GABA A alpha 5 receptor, which is selectively concentrated in the hippocampus.

Methods: Methylazoxymethanol acetate (MAM) was administered at 20 mg/kg i.p. to pregnant rats at gestational day 17, and the offspring studied as adults. Recordings of dopamine neuron population activity (active neurons per electrode track) and locomotor response to amphetamine (0.5 mg/kg.i.p.) was evaluated.

Results: MAM treated rats exhibited significant elevations in the number of DA neurons firing in the ventral tegmental area and hyper-responsivity to amphetamine. The alpha 5 positive allosteric modulator SH-053-20R-R-CH3 and the negative modulator selectively attenuated ventral hippocampal excitability in controls, and reversed the increased DA neuron population activity and response to amphetamine to control levels without significantly affecting controls. Interestingly, the negative allosteric modulator Ro4938581 increased DA neuron population activity in controls, but decreased it in MAM to control levels.

Conclusion: Unlike D2 antagonist antipsychotic drugs, manipulation of the GABA A alpha 5 receptor appeared to restore the hyper-reactive DA system in the MAM rat to control levels. The fact that this worked with both the positive and negative modulator suggests that the important point is not increasing inhibition, but restoring balance within a disrupted interneuron network. By attacking schizophrenia at the site of disruption is likely to be a more effective treatment for schizophrenia than is dopamine blockade, which works at least 5 synapses downstream from the site of pathology.

Policy of full disclosure: Johnson & Johnson, Lundbeck, Galaxo Smith Klein, Otsuka, Takeda.

S-28-002 Translational pharmacodynamics of phosphodiesterase 10A (PDE10A) inhibitors for treatment of schizophrenia

J. Nielsen1, B. Steiniager-Brach1. 1H. Lundbeck A/S, Copenhagen, Denmark

Objective: Phosphodiesterase 10A (PDE10A) is a dominant phosphodiesterase in striatal Medium Spiny Neurons. Inhibition of PDE10A leads to an increase of cAMP in these neurons and negatively modulates dopamine D2 receptor signalling in the striatum. Preclinical evidence suggests that PDE10A inhibitors are anti-psychotic, pro-cognitive and hold potential for treatment of negative symptoms. PDE10A inhibitors are currently being evaluated in clinical settings for the treatment of schizophrenia.
S-29. Molecular and genetic substrates underpinning diagnosis of major depression

**Methods**: A novel PDE10A in vivo binding ligand was developed and validated. Rodents were dosed with selective PDE10A inhibitors and were tested in schizophrenia relevant assays. The occupancy of the PDE10A enzyme was monitored by in vivo binding.

**Results**: PDE10A inhibitors were efficacious in a number of in vivo assays relevant for schizophrenia including assays for positive and cognitive symptoms as well as motor side effect assays. The dynamic occupancy range overlaps between different efficacy assays although some differences are reported in this study. For most in vivo assays, relatively low PDE10A occupancy is needed, and in cognition assays as little as 15% occupancy has significant effect. Different selective PDE10A inhibitors had similar occupancies at efficacious doses in these assays.

**Conclusion**: The data supports the potential of PDE10A inhibitors as a drug target for treatment of schizophrenia across symptoms do-

**Policy of full disclosure**: All authors are employees of H. Lundbeck A/S.

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**S-28-003** The glycine reuptake inhibitor (GRI) bitopertin: Going beyond antipsychotics towards a non-dopaminergic treatment for schizophrenia

D. Umbrecht, M. Martin-Facklam, E. Wasse, D. Dorflinger, A. Baasch, Y. You, L. Santarelili, F. Hoffman – La Roche Ltd, Basel, Switzerland

**Objective**: Deficient NMDA receptor signaling is considered a leading hypothesis in the pathophysiology of schizophrenia, including negative symptoms. Targeting the co-agonist glycine site of the NMDA receptor offers a safe approach to enhance NMDA receptor function. The effects of the glycine reuptake inhibitor (GRI) bitopertin (RG1678) on negative symptoms of schizophrenia were investigated in a phase II proof-of-concept study.

**Methods**: 323 clinically stable patients with predominant negative symptoms were randomized to 8 weeks of treatment with three doses of bitopertin (10 mg, 30 mg, 60 mg) or placebo once daily in combination with a stable, efficacy antipsychotic. Efficacy parameters included the PANSS negative symptom factor score (NSFS): proportion of responders (≥20% improvement in NSFS); Clinical Global Impression – Improvement in Negative Symptoms (CGI-I-N), and Personal and Social Performance (PSP) scale.

**Results**: In the per protocol population (231 patients) the NSFS showed a significantly greater decrease from baseline (delta = 25%) in the 10 mg and 30 mg groups versus placebo (delta = 19%) (10 mg, p = 0.049; 30 mg, p = 0.034). The response rate was significantly higher for 10 mg group versus placebo (65% vs. 43%, p = 0.013). Differences in CGI-I-N were significant for the 10 mg dose group (p = 0.025). There was a trend towards functional improvement (PSP score) in the 10 mg dose group (p = 0.072). The largest effect sizes for the 10 and 30 mg were observed for NSFS items N1 (−0.32, −0.27), N2 (−0.37, −0.65) N4 (−0.39, −0.41) and G16 (−0.37, −0.36).

**Conclusion**: Bitopertin 10mg demonstrated a consistent reduction in negative symptoms, accompanied by the emergence of a positive trend on personal and social functioning. Bitopertin may exert its greatest effect on key negative symptoms that include emotional withdrawal and apathetic/social withdrawal. These results support glycine reuptake inhibition and enhancement of NMDA signaling as a therapeutic approach for negative symptoms in patients with schizophrenia.

**Policy of full disclosure**: All authors are employees of F. Hoffmann – La Roche, Ltd.

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**S-28-004** Modulation of glutamate function via mGlu5 receptor: Potential novel antipsychotic target?


**Objective**: An emerging hypothesis regarding the neurobiological cause of schizophrenia suggests that the disease is due to altered glutamate neurotransmission in general and reduced NMDA receptor function in particular. For this reason, pharmacological approaches are being pursued to normalize glutamate or enhance NMDA receptor function. Direct approaches to increase NMDA receptor function are limited by the risk of seizures and neurotoxicity. As a result, indirect NMDA modulation is of interest. Administration of high doses of the NMDA receptor co-agonists glycine, D-alanine, and D-serine improve positive and negative symptoms, as well as cognitive deficits in schizophrenic patients (Heresco-Levy et al., 2002; Tsi et al., 2006). A promising, alternative strategy to indirect NMDA facilitation is to activate metabotropic glutamate 5 receptors (mGlu5).

**Results**: We described structurally novel mGlu5 PAMs which are selective for mGlu5 receptors and exhibit anti-psychotic like activity. We demonstrated the potential for neurotoxicity in rats and wild-type mice but not in mice lacking the expression of mGlu5.

**Conclusion**: This study reveals for the first time that activation of mGlu5 with selective allosteric modulators (PAM) rather than agonists, in the hope that we might achieve subtype selectivity and have a reduced risk of toxicity through excessive mGlu5 activation.

**Methods**: Selective mGlu5 PAMs are active in various rodent models predictive of efficacy on positive, negative, and cognitive symptoms. Although these findings with mGlu5 receptor PAMs are exciting, little is known regarding the side-effect liability of these compounds.

**Results**: We described structurally novel mGlu5 PAMs which are selective for mGlu5 receptors and exhibit anti-psychotic like activity. We demonstrated the potential for neurotoxicity in rats and wild-type mice but not in mice lacking the expression of mGlu5.

**Conclusion**: This study reveals for the first time that activation of mGlu5 with selective allosteric modulators (PAM) rather than agonists, in the hope that we might achieve subtype selectivity and have a reduced risk of toxicity through excessive mGlu5 activation.

**Policy of full disclosure**: Employee of Merck & Co., Inc.

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**S-29-001** Molecular evidence for BDNF- and GABA-related dysfunctions in the Major Depression

E. Sibille, University of Pittsburgh, Department of Psychiatry, USA

**Objective**: (1) To investigate primary evidence in support of low brain-derived neurotrophic factor (BDNF) and reduced GABA function in the postmortem brain of subjects with depression and matched controls. (2) To test causal links between BDNF levels and expression of markers of GABA interneuron subtypes, using mice with genetically altered and reduced BDNF function (BDNF-HZ and BDNF-IV-KO). (3) To focus on corticolimbic regions (amygdala and anterior cingulated cortex).

**Methods**: Large-scale quantification of gene expression profiles in depressed and control human subjects (n = ~50/group; amygdala and anterior cingulated cortex). Robust downregulations were also observed for gene transcripts coding for GABA interneuron-related peptides that are known to be BDNF-dependent, including somatostatin (SST), ta-chykinin (TAC1), neuropeptide Y (NPY) and cortistatin (CORT). Changes extended to GABA markers (GAD1) that display low or no BDNF dependency. Notable regional (amygdala/cingulate cortex) and gender difference were observed. Out of all clinical and demographic factors investigated, only age further affected transcript levels of our genes of interest.

**Conclusion**: We provide both direct (low RNA/protein) and indirect (low BDNF-dependent gene pattern) evidence for reduced BDNF function in the amygdala and cingulate cortex of MDD subjects. Supporting studies in mutant mouse models suggest a complex mechanism of upstream BDNF-dependent and independent causal factors, thus partly linking the neurotropic and GABA hypotheses of depression. Notably, the most consistently findings identified reduced markers of GABA interneuron subtypes that target the
Objective: Suicide is a complex and heterogeneous phenomenon. We have recently described a molecular subphenotype characterized by extreme low expression of astrocytic genes. In this study, we investigated the potential role of genomic DNA methylation in this subphenotype.

Methods: Prefrontal brain samples from 184 subjects were screened using a combination of techniques to identify extreme low expressors (ELE) of these ELE and were matched to psychiatrically-unaffected controls according to gender, age, PMI and pH. Genomic DNA was sheared and methylated regions were isolated using methylated binding domain-2 (MBD) protein. Libraries were made using the Illumina ChiP-Seq library preparation protocol and each library used one lane of Illumina GAIIx, 36 base pair single read sequencing. Using the DESeq software, a negative binomial test was made using the Illumina ChIP-Seq library preparation protocol and each library used one lane of Illumina GAIIx, 36 base pair single read sequencing. The most significant results were validated by EpiTyper.

Results: A total of ~250 million reads were produced per group and were used to identify differentially methylated regions (DMRs). Reads were trimmed, duplicates removed and the resulting data was mapped to the human genome (hg19) using BWA. The genome was tiled using overlapping 500 bp windows at every 250 bp and reads were counted for each 500 bp interval. 989 DMRs passed multiple corrections using FDR.

Conclusion: These results point to a large number of genomic DMRs that may play a role in the neurobiology of suicides. Several of these DMRs may help explain the ELE phenotype. Studies using functional models will be useful to characterize these findings.

S-29-002 Identifying differentially methylated regions in depression and suicide by next generation sequencing

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Role of MicroRNAs in depression: Evidence from animal and human postmortem brain studies

Y. Dwivedi, University of Illinois, Chicago, USA

Objective: microRNAs (miRNAs) are newly discovered gene expression regulators that have recently been implicated in a variety of human diseases, including neuropsychiatric diseases. The present study was undertaken to examine whether the miRNA regulatory network is altered in depression.

Methods: Expression of miRNAs was measured in prefrontal cortex of depressed and well-matched non-psychiatric control subjects using multiplex RT-PCR plates. Levels of dicer, drosha, DGCR8 mRNA, and several pri-miRs were determined by qPCR. In addition, miRNAs were measured in frontal cortex of learned helpless (LH), non-learned helpless (LH), and tested control (TC) rats.

Results: miRNA expression was globally down-regulated in depressed suicide subjects and was accompanied by a significant decrease in inter-individual variability. Using individual tests of statistical significance, 21 miRNAs were significantly decreased. In addition, a set of 29 miRNAs, whose expression was not pairwise correlated in the normal controls, showed a high degree of correlation across individuals in the depressed group. Changes in some of the miRNAs were inversely correlated with target gene expression. Levels of dicer, drosha, DGCR8 mRNA and several pri-miRs were not significantly altered. NLH rats showed a robust adaptive miRNA response to inescapable shock whereas LH rats showed a markedly blunted response. One set of 12 miRNAs showed particularly large, significant down-regulation in NLH rats relative to tested controls. These were encoded at a few shared polycistronic loci, suggesting that the down-regulation was coordinately controlled at the level of transcription. We also identified a core miRNA co-expression module consisting of 36 miRNAs that were highly correlated with each other across individuals of the LH group but not in the NLH or TC groups.

Conclusion: These findings show that miRNAs contribute substantially to a reorganization of gene expression networks that occur in depression. miRNA profiling may assist in identifying factors that correlate with diagnosis, prognosis or response to treatment.

S-29-004 Genome-wide and candidate gene studies for neuroticism

D. Rujescu, University of Munich, Dept. of Psychiatry, Germany

Objective: The risk of suicide-related behavior is supposed to be determined by a complex interplay of sociocultural factors, psychiatric history, personality traits, and genetic vulnerability. This view is supported by adoption and family studies indicating that suicidal acts have a genetic contribution that is independent of the heritability of Axis I and II psychopathology. There is strong evidence for a heritability of suicidal behaviour as shown by family, twin- and adoption studies. Several studies suggest heritability between 45 and 55%. There is no doubt that suicidal behavior is not caused by any single gene but it is a disease with complex genetic features.

Methods: Personality traits could be an intermediate phenotype of suicidal behavior, which is a trait that reflects a tendency toward negative mood states, and has been linked to internalizing depressive conditions.

Results: Neuroticism is one example of such an intermediate phenotype of suicidal behavior and has been linked to internalizing depressive conditions.

Conclusion: Dan Rujescu will present genome-wide and candidate gene studies on neuroticism, demonstrating a genetic approach for discovering potentially important pathogenic pathways for which clinically powerful (bio)markers may eventually be developed.
Policy of full disclosure: Employee and share-holder of AstraZeneca, Sweden.

S-30-003 Plasma concentration based dosing of antipsychotics and antidepressants

C. Hiemke, University of Mainz, Germany

Objective: Psychotropic drug concentrations in blood resulting are highly variable between individual patients due to variability in drug metabolism or adherence to the medication. In 1971, it was reported for nortriptyline that drug concentrations in blood correlate well with clinical amelioration. Animal studies have shown that antidepressant and antipsychotic drug concentrations in the brain correlate much better with drug concentrations in plasma than with the dose. Plasma concentration based dosing, i.e. therapeutic drug monitoring (TDM), is therefore superior to symptom based dosing to attain maximal clinical effectiveness.

Methods: To promote an appropriate use of TDM the TDM expert group of the Association of Neuropsychopharmacology and Pharmacoepidemiology (AGNP) updated their guidelines for TDM in psychiatry.

Results: Evidence-based "therapeutic reference ranges" and "dose related reference ranges" were elaborated after intensive literature research and intensive discussions for 30 antipsychotic and 26 antidepressant drugs. A "laboratory alert level" was newly introduced above which the laboratory should immediately inform the treating physician. Recommendations are also given when TDM should be supported with pharmacogenetic tests. Supportive information such as substrate, inhibitor or inducer properties of medications is provided for the interpretative service.

Conclusion: This presentation will show how to use the updated guidelines to improve outcomes of psychopharmacotherapy of many patients, especially in case of pharmacokinetic problems.

Policy of full disclosure: Dr. Hiemke has served served on the speakers' bureau of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Pfizer, Servier, and Wyeth. He is managing director of the psiac company.

S-30-004 Dosing of antipsychotics and antidepressants: Guidance from PET imaging

G. Gründer1, C. Hiemke2, M. Paulzen3, T. Veselinovic, I. Vernaleken1

1RWTH Aachen University, Germany; 2Mainz, Germany

Objective: Rational pharmacotherapy is based on the assumption that the wanted and unwanted clinical effects of a specific psychotropic drug are directly related to its occupancy of the molecular target. Here we show that positron emission tomography (PET) of drug targets in the brain (neuroreceptors and transporters) allows for establishment of these relationships, thereby providing guidance for clinical dosing regimens.

Methods: Associations between brain target occupancy, plasma concentrations, and clinical effects and side effects will be discussed for the most commonly used antidepressant and antipsychotic drugs. It will also be demonstrated that PET studies unmasked some traditional dosing strategies as wrong and potentially harmful.

Results: Research over the past two decades has clearly established relationships between target engagement of the most commonly prescribed antidepressants (especially selective serotonin reuptake inhibitors) and antipsychotics and clinically useful doses of these drugs. This is especially true for the class of antipsychotics. However, it will be demonstrated that the recommended doses of haloperidol (and some other first-generation antipsychotics) are still too high based on PET studies. In addition, some newer antidepressants (e.g., bupropion) exemplify that questions related to rational dosing directly allude to problems of mechanism of action.

Conclusion: Nuclear imaging with PET is one of the most powerful tools to determine and validate rational drug doses and the respective plasma concentrations. In the future, PET studies on the relationship between brain target engagement and plasma levels should complement the development of every psychotropic drug. This will allow for the establishment of TDM services and, consequently, for rational dosing right from the introduction of a new drug to the market.

Policy of full disclosure: Dr. Gründer has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Chelapharm, Eli Lilly, Johnson & Johnson, Lundbeck, Otsuka, and Servier. He has served on the speakers' bureau of Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, and Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, Grant & Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH, Düsseldorf, Germany. Dr. Hiemke is a consultant for Servier. He has received grant support from Pfizer and Sanofi-Aventis and served on the speakers' bureau of AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Pfizer, Servier, and Wyeth. Dr. Paulzen declares no conflicts of interest. Dr. Veselinovic has received grant support from Bristol-Myers Squibb. Dr. Vernaleken has served on the speakers' bureau of Bristol-Myers Squibb, Eli Lilly, and GlaxoSmithKline.

S-31. Lithium and novel targets in bipolar disorders

S-31-001 Interfering with the activating effect of calbindin D28k on inositol mono-phosphatase activity to mimic lithium’s inhibitory effect on the enzyme at a different site of action

G. Agami1, L. Toker2, Y. Bersudsky3, I. Plaschkes1, V. Califa-Caspi3, G. Berry3, D. Moechars4, R. Beimkamer5, 6Beer-Sheva, Israel; 7Faculty of Health Sciences; 8Psychiatry Research Unit; 9National Institute for Biotechnology in the Negev; 10National Institute for Biotechnology in the Negev (NIBN), Beer-Sheva, Israel; 11Metabolism Program Division of Genetics; 12Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium; 13Beer Sheva, Israel

Objective: Clinical efficacy of lithium (Li) is characterized by a lag in onset of 1–3 weeks suggesting that the therapeutic effect requires reprogramming of gene expression. Previous studies have shown alteration in gene expression following mood stabilizing drug treatment in a variety of genes, including genes involved in inositol metabolism. Inositol-monophosphatase (IMPase)-1 is inhibited by therapeutically-relevant Li concentrations in an uncompetitive manner, possibly resulting in decreased inositol, subsequent down regulation of the phosphatidylinositol (PI) cycle and dampening of assumed hyperactive neurotransmission through this pathway (the "inositol depletion" hypothesis). Li was also shown to down-regulate the expression of sodium myo-inositol co-transporter (SMIT1), responsible for the uptake of myo-inositol from extracellular fluid. Both IMPA1 and SMIT1 homozygote knockout (KO) mice exhibit Li-like behavior in the forced-swim test (FST) and the pilocarpine-induced seizures paradigm. We aimed to identify gene networks and pathway effects in homzygote IMPA1 and SMIT1 knockout mice and in Li-treated mice compared with wild-type (WT) untreated mice.

Methods: Male, 2 month old, IMPA1 KO, SMIT1 KO and their littermate WT mice were used. Mice received powdered food. Li-treated WT mice received powdered food supplemented with 0.2% Li for five days, followed by 0.4% Li for another 10 days. DNA microarray analysis was performed using the Affimetrix platform. Results were analyzed using the software Ingenuity Pathway Analysis (IPA), GSEA and DAVID.

Results: We show that Oxidative Phosphorylation and Mitochondrial Function are the only significant pathways affected in the frontal cortex of SMIT1 and IMPA1 knockout mice and Li-treated mice. To verify this result the interrelationship between Li treatment and a pharmacological intervention in mitochondrial function by chronic mild treatment with rotenone, an inhibitor of the oxidative phosphorylation complex I, was studied behaviorally in bipolar disorder-related animal models. As hypothesized based on the microarray results, Li and rotenone counteracted each other's effects both in the FST model of depression-like despair behavior and in the amphetamine-induced hyperlocomotion model of mania-like behavior.

Conclusion: Our results corroborate previous finding in bipolar patients suggesting that improvement of mitochondrial dysfunction might underlie the therapeutic effect of Li, support the inositol depletion hypothesis of the molecular mechanism of mood stabilization and suggest that a consequent end point is amelioration of aberrant mitochondrial function in patients by its up-regulation.
Lithium is a gold standard in bipolar illness. Is it indicated for other conditions?

Objective: Lithium is established as a first-line long term treatment of bipolar disorder, but it may be beneficial in other conditions as well. In this presentation I will review the effects of lithium based on published evidence and present data from two large datasets.

Methods: First we studied risk factors for completed and attempted suicide in 737 families of probands with bipolar disorder in Nova Scotia and Sardinia. In the second study we examined lithium use and prevalence of neurodegenerative conditions in the Province of Nova Scotia. Specifically, we linked population databases containing data on persons diagnosed with Alzheimer’s disease, multi-infant dementia, Parkinson’s disease and stroke with prescription database of individuals older than 65 years.

Results: Published evidence suggests that lithium can be beneficial in major depression, aggressive behaviour, prevention of suicide, and cluster headaches among others; it is also being investigated for neuroprotective effects in neurodegenerative conditions such as amyotrophic lateral sclerosis or Alzheimer’s disease. In the family study, the risk of suicide was significantly reduced in those subjects who showed partial or full stabilization on lithium. In the population study, rates of all studied conditions were significantly elevated in those with bipolar disorder not on lithium (n=1173) compared with control subjects. History of at least one prescription of lithium (n=797) was associated with moderate reduction of the risk of Alzheimer’s disease and chronic stroke, but not the other diagnoses.

Conclusion: In addition to prevention of manic and depressive episodes in bipolar disorder, lithium appears beneficial in a range of conditions. The most intriguing are its antisudicial and neuroprotective effects. Interestingly, the prevention of suicide may be independent of the mood-stabilizing properties. However, it remains to be determined if the neuroprotective effects of lithium are at the core of its prophylactic action in bipolar disorder.

Neurocognition as a lithium target in bipolar disorder

L. Rybakowski, Poznan Univ Med Sciences, Department of Adult Psychiatry, Poland

Objective: The aim of this study is to assess the performance on neuropsychological tests in patients with bipolar illness receiving long-term lithium prophylaxis compared to matched healthy control subjects, and to relate the cognitive performance to the functional Val66Met brain derived neurotrophic factor (BDNF) gene polymorphism, BDNF serum level and the quality of lithium prophylaxis.

Methods: Patients with bipolar mood disorder on long-term (5-25 years) lithium treatment were genotyped for Val66Met BDNF gene polymorphism. The Wisconsin Card Sorting Test (WCST) was compared in 30 lithium treated-patients, among which 7 were lithium non-responders (NR), with 30 age- and gender matched healthy control subjects. Also, four tests from the CANTAB battery (Spatial working memory, Spatial span, Stockings of Cambridge and Rapid Visual Information Processing) and BDNF serum levels were compared between 60 lithium-treated patients, 13 of which were excellent lithium responders (ER) and 84 healthy control subjects.

Results: The patients with Met allele of BDNF polymorphism showed significantly better response to lithium prophylaxis suggesting that lithium could be more effective in subjects with lower activity of BDNF system. NR performed worse on WCST compared to matched healthy subjects, significantly so on perseverative errors (WCST-P) and conceptual responses (WCST-%conc). The performance on CANTAB tests was significantly worse in lithium-treated patients as a group, compared with matched healthy control subjects. However, the results of ER as well as serum BDNF lithium level were not different from those of the healthy persons.

Conclusion: Favorable response to lithium may be connected with preservation or even augmentation of cognitive functions. In ER after many years of successful lithium prophylaxis, the performance on neuropsychological tests and BDNF serum level was not different from that of matched healthy control subjects. ER may constitute a specific group of bipolar patients in which long-term lithium administration can produce complete normality.

The Consortium on Lithium Genetics (ConLiGen): Genome-wide association studies of lithium response phenotypes in bipolar disorder

T. Schulze, U. Boer.1 University of Goettingen, Germany

Objective: Lithium remains a mainstay in the long-term treatment of BD. Response to lithium is variable. About 30% of patients treated with lithium have fewer illness episodes over time, while about 20% have no response. Data from non-molecular genetic studies of lithium are comparatively sparse, and these studies have generally employed small sample sizes and varying definitions of response. Genetic markers of lithium response would be valuable for treatment planning and could provide insights into the biological mechanism of lithium action. To put that idea into practice, the international Consortium on Lithium Genetics (www.ConLiGen.org) was established.

Methods: ConLiGen has now collected over 1400 lithium-treated bipolar disorder (BD) patients. All patients have been characterized for lithium response with a 11-point treatment response scale ("Alda Scale". Grof et al., 2002). The Alda Scale assesses clinical improvement attributable to lithium, taking into account the history and frequency of episodes, duration of treatment, medication adherence, and concurrent treatment. Phenotype definitions were developed by consensus within ConLiGen. The whole sample has been genotyped using illumina arrays to perform a genome-wide association study (GWAS) of lithium response.

Results: Inter-rater reliability of lithium response assessment was good, with kappa values >0.7. Given a responder rate of 35%, the ConLiGen sample has >80% power to detect a common allele that confers a genotype relative risk of response of 1.5, at genome-wide significance. At the time of abstract submission (12/2011) genotyping has been completed, and preliminary quality control data indicates excellent call rates (>99% of samples have a call rate >98%) GWAS completion is expected for 04/2012.

Conclusion: Genetic findings from ConLiGen could have important implications for treatment planning and for developing new drugs that mimic the action of lithium but are better tolerated and more effective.

Novel NMMA amino acids for the pathophysiology and treatment of mental disorders

S-32-001 Novel mechanism of regulation of N-methyl-D-aspartate neurotransmission for CNS disorders

G. Tsuji, Harbor-UCLA Med CTR, Torrance, USA

Objective: D-amino acid oxidase activator (DAAOA, or named G72) is a primate specific regulator of DAAO. Both DAAO and DAAOA are strong susceptibility genes for schizophrenia. DAAO metabolizes D-serine, which is a potent coagonist at the "glycine" site of NMDA receptor (see figure). To date, trials of NMDA-enhancing agents, including glycine, D-serine, D-alanine, and sarcosine (a glycine transporter I inhibitor), reveal beneficial efficacy for the symptoms of schizophrenia. In addition, benzoate is a DAAO inhibitor which can elevate synaptic concentration of D-serine.

Methods: We explored the effect of benzoate on prepulse inhibition (PPI) and forced swimming test (FST) in rodent and examined the efficacy and safety of an 11 day treatment of benzoate for schizophrenia by a randomized, double-blind, placebo-controlled trial. We also determine whether G72 can serve as a biomarker for schizophrenia.

Results: Benzoate can reverse ketamine-induced deficit in PPI and reduce the duration of immobility in FST. Benzoate treatment produces substantial improvement in the scores of PANSS, SANS, QOL, CGI and HAMD as well as 3 cognitive domains of MATRICS battery (processing speed, verbal learning, and visual learning). The expression of plasma G72 protein in schizophrenia was significantly higher than in healthy controls. G72 protein expression is similar to that of matched healthy control subjects. ER may constitute a specific group of bipolar patients in which long-term lithium administration can produce complete normality.
between drug-free vs. medicated schizophrenia patients. PANSS-negative score showed a negative correlation with G72 levels. The logistic regression analysis suggests that plasma G72 protein can be a diagnostic biomarker for schizophrenia (OR = -6.90, 95% CI = 3.45–13.85). The ROC curve showed that a cut-off level of 1.48 pg/ml of plasma G72 protein cut-off and a 91% specificity for separating schizophrenia from control (AUC = 0.89).

**Conclusion:** Taken together the animal and human findings, DAA-DAAO-DAAOA is an novel NDMA pathway that can be exploited for the diagnosis and treatment of schizophrenia.

**Policy of full disclosure:** Dr. Tsai is the inventor for US patents 6228875, 6667297, 6420351, 6974821, 2010/0189818 for the use of NDMA agents in CNS disorders.

**S-32-002** GlyT-1 and DAAO inhibitors as potential therapeutic drugs for schizophrenia

K. Hashimoto, Chiba University, Japan

**Objective:** Accumulating evidence suggests that the glycine modulatory site on N-methyl-D-aspartate (NDMA) receptor is a potential therapeutic target for schizophrenia. Increasing synaptic levels of glycine by inhibition of glycine transporter-1 (GlyT-1) on glial cells will lead to enhanced NDMA receptor sensitivity. D-serine, an endogenous co-agonist for the glycine modulatory site on NDMA receptor, is metabolized by D-amino acid oxidase (DAAO) which may decrease oral bioavailability of D-serine. In this study, we examined the effects of GlyT-1 inhibitors and a combination of D-serine with a DAAO inhibitor on animal models of schizophrenia.

**Methods:** The effects of GlyT-1 inhibitor NFPs on cognitive deficits in mice after repeated administration of NDMA receptor antagonist phencyclidine (PCP) were examined. Furthermore, we measured the levels of GlyT-1 protein and amino acids in the frontal cortex and hippocampus of mice treated with PCP. The effects of D-serine with or without a potent DAAO inhibitor 5-chloro-benzo[d]isoxazol-3-ol (CBIO) on prepulse inhibition (PPI) deficits in mice after administration of NDMA receptor antagonist dizocilpine were examined. Moreover, the extracellular levels of D-serine in the brain were measured using in vivo microdialysis method.

**Results:** Cognitive deficits in mice after the repeated administration of PCP were significantly improved by subsequent subchronic administration of NFPs and D-serine. Repeated administration of PCP significantly increased the levels of GlyT-1 protein in the hippocampus, but not frontal cortex. Furthermore, we found that co-administration of CBIO increased the oral bioavailability of D-serine in mice, and that co-administration of CBIO significantly enhanced the efficacy of D-serine in attenuating dizocilpine-induced PPI deficits in mice.

**Conclusion:** These findings suggest that GlyT-1 inhibitors and a combination with D-serine plus a DAAO inhibitor would be new approaches for the treatment of schizophrenia.

**S-32-003** Treatment of NDMA agonist, glycine transporter 1 Inhibitor and D-Amino acid oxidase inhibitor for mental disorders

H.-Y. Lane, China Medical University, Taichung, Taiwan

**Objective:** Enhancement of NDMA neurotransmission has been proposed as a potential treatment of schizophrenia and other mental disorders. Several studies targeted at the glycine site of the NDMA receptor using full agonists (glycine, D-serine, D-alanine) or the partial agonist D-cycloserine. Another strategy to improve NDMA neurotransmission is increasing the synaptic glycine level by blocking the glycine transporter-1 (GlyT-1). The third strategy is increasing synaptic concentrations of D-serine and D-alanine by inhibiting D-amino acid oxidase (DAAO).

**Methods:** N-methylglycine (sarcosine), exiting in human tissues (including blood, muscle, brain) and many foods, is the prototype GlyT-1 inhibitor. Sodium benzoate, a legal food additive, is an inhibitor of DAAO. We conducted several receptor studies.

**Results:** A pilot clinical trial demonstrated that sarcosine adjuvant therapy improved positive and negative symptoms in patients with chronic schizophrenia. More recent studies further suggest that add-on sarcosine, superior to D-serine, can benefit the negative symptoms in both acutely ill and chronically stable patients, and that sarcosine can be used as monotherapy in acute psychosis. Sarcosine also improves life quality and functioning. Our study also showed that sarcosine was more efficacious than a commonly used anti-depressant, citalopram (a selective serotonin reuptake inhibitor), in the treatment of major depressive disorder. The sarcosine-treated patients improved more in global functioning and were more likely to be remitters. Sarcosine monotherapy also benefited drug-naive patients with obsessive compulsive disorder. In a double-blind, placebo-controlled trial, 1-g/day sodium benzoate adjunctive therapy significantly and safely improved positive, negative, general, and cognitive symptoms in patients with chronic schizophrenia.

**Conclusion:** These findings indicate that enhancing NDMA function via inhibiting GlyT-1 or DAAO can improve symptoms of schizophrenia or other mental disorders and can be a novel mechanism for drug development.

**S-32-004** D-Serine, glia-synapse interaction and schizophrenia

T. Nishikawa, Tokyo Medical and Dental University, Japan

**Objective:** An endogenous coagonist for the N-methyl-D-aspartate (NDMA) type glutamate receptor (NDMA receptor), D-serine, and its metabolic precursor glycine participate in glia-glutamate synapse communication linked with the glutamate-GABA interaction, which could malfunction in a group of glutamate-GABA co-agonists. The molecules composing these systems might be the new candidate targets for the D-serine modulating anti-schizophrenic agents.

**Conclusion:** The rodent brains, the selective destruction or activity manipulations of the neurons and glia resulted in the changes in the tissue and extracellular contents of D-serine in different ways from those observed in classical neurotransmitters, and a local application of agents acting at the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate type glutamate receptor and the GABAA receptor. Moreover, we have isolated a gene, D-serine-modulator-1, which encodes the protein influencing the intra- and extracellular D-serine contents when expressed in the Xenopus oocytes and its association studies are in progress.

**Results:** In the rodent brains, the selective destruction or activity manipulations of the neurons and glia resulted in the changes in the tissue and extracellular contents of D-serine in different ways from those observed in classical neurotransmitters, and a local application of agents acting at the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionate type glutamate receptor and the GABAA receptor. Moreover, we have isolated a gene, D-serine-modulator-1, which encodes the protein influencing the intra- and extracellular D-serine contents when expressed in the Xenopus oocytes and its association studies are in progress.

**Conclusion:** These findings suggest that brain D-serine might participate in glia-glutamate synapse communication linked with the glutamate-GABA interaction, which could malfunction in a group of schizophrenia. The molecules composing these systems might be the new candidate targets for the D-serine modulating anti-schizophrenic agents.

**Thursday 7 June 2012**

**S-33** Do psychotropics affect brain structure? Linking animal models, imaging and clinical studies

**S-33-001** Contrasting effects of antipsychotics and lithium on the brain: In-vivo MRI and ex-vivo confirmation

S. Kapur, Institute of Psychiatry, London, United Kingdom

It has long been a matter of controversy whether psychotropic drugs, particularly antipsychotics and lithium, have an effect on ‘brain structure’. To address this issue, we implemented a model in rats combining serial in vivo MRI, ex vivo MRI and post-mortem analysis with clinically relevant drug doses. Haloperidol (HAL, 2 mg/kg/d), olanzapine (OLZ, 10 mg/kg/d) or vehicle (β-hydroxypropylcyclodextrin,
20% w/v, acidified by ascorbic acid, to pH 6) was continuously administered to rats for 8 weeks (wks). In a second group, HAL (0.5, 2 mg/kg/d) or lithium chloride (LiCl, 2 mMeq./kg/d) was administered for 8 wks followed by an equivalent wash out period (16 wks total). Drugs were given subcutaneously via osmotic mini-pumps. Serial MRI scans were obtained, and after the terminal scan the animals were perfused, ex vivo MRI scans acquired and brain tissue processed for post-mortem analysis. Region of interest (ROI) volume analyses were performed on MR images and post-mortem brain tissue by 2 independent raters blinded to treatment group. Chronic (8 wks) HAL and OLZ treatment resulted in decreased whole brain and cortical volume, the magnitude of this effect being smaller in OLZ-treated animals. Chronic HAL, but not OLZ, increased striatal volume in vivo. In contrast, chronic LiCl (8 wks) increased whole brain and cortical volume in vivo. The drug effects tended to reverse with the washout, with the exception that LiCl-treated animals retained greater whole brain volume. These data were confirmed by ex vivo MRI and all MRI data were confirmed post-mortem using unbiased stereology. Thus, chronic treatment with APD and LiCl has contrasting effects on rat brain structure, though some of these effects appear to be reversible. The cellular basis of these changes is currently under investigation. The findings provide the first systematic MRI post-mortem study of these drugs and provide a basis for understanding some of the clinical studies with MRI.

Policy of full disclosure: • There is no ex vivo MRI data for animals who were ON then OFF drug for 8 weeks. We only confirmed the data post-mortem • We have no data on drug withdrawal for Olanzapine.

S-33-002 Antipsychotic medications and progressive brain tissue loss in schizophrenia

N. Andersen. University of Iowa, Department of Psychiatry, Iowa City, USA

Objective: Studies comparing brain volume measurements in patients at the time of onset with healthy normal volunteers have indicated that the patients have smaller mean volumes in many regions, particularly frontal cortex. Furthermore, longitudinal studies have shown that the mean differences in brain volumes continue to progress over time and that these differences have functional significance, in that they are related to cognitive impairments. The focus of scientific attention is now on determining why the tissue loss occurs and why it continues to progress. The loss is very likely due to multiple factors: genes and their expression, environmental factors such as substance abuse, effects of treatment, and effects of the course of the disease. This presentation examines two of these factors: treatment effects and disease progression as measured by number and duration of relapse.

Methods: We studied 202 patients drawn from the Iowa Longitudinal Study of First Episode Schizophrenia (ILS) for whom we have adequate sMR data (N=661 scans, an average of 3/subj) obtained at regular intervals over an average time period of seven years. Because we obtained clinical follow-up data at six-month intervals, we were able to obtain measures of treatment intensity using dose-years and of relapse number and duration and relate them to sMR measures.

Results: Both antipsychotic treatment intensity and relapse duration were independently and significantly related to progressive brain tissue loss. However, the tissue types and regions affected were somewhat different.

Conclusion: Thus, paradoxically, two factors appear to account for the brain changes that occur after the onset of schizophrenia: relapse duration and intensity of antipsychotic treatment. Determining how to balance the impact of these factors poses a major clinical and scientific challenge.

Policy of full disclosure: Funding sources: research grants from NIMH and Janssen Scientific Affairs.

S-33-003 Drugs, stress and inflammation: Explaining progressive brain changes in schizophrenia

C. Pantelis. University of Melbourne, Australia

Objective: In schizophrenia the view since the 1980’s was that brain pathology begins during foetal development and is static. This suggested that identification of abnormalities in patients with established disorder would provide markers relevant to early identification of at-risk individuals. However, the available neuroimaging evidence in early illness stages does not support such a notion. Rather, the evidence indicates that there is neuroprogression in psychotic disorders (Pantelis et al., 2005). Some progressive change is also consistent with the clinical picture of psychosis. Thus, clinical deterioration is often observed after the first few years of the illness. While progressive brain changes over the initial phase of illness are consistent with the clinical deterioration, there is a continuing debate about their validity, and the nature of the underlying neuropathology. Criticism has been levelled at the methods, the possibility of artefact, the impact of therapeutic as well as illicit drugs, diagnostic heterogeneity, and the influence of factors such as stress and the HPA-axis function.

Recent evidence has investigated these factors.

Methods: Our group has undertaken a series of longitudinal imaging studies across the stages of illness from pre-psychosis onset and has examined some of these potential confounds.

Results: 1 will present the findings from our series of studies investigating progressive brain changes in psychosis from before illness onset and examine confounds that may explain these changes (esp. cannabis, stress and the effects of medication).

Conclusion: Progressive brain changes begin from before illness onset and are most apparent over the first few years of illness. Factors such as drug use, the impact of stress and medication need to be taken into account in understanding these changes. I will also discuss the possible role of neuroinflammation and how this may be examined.

Policy of full disclosure: The studies were funded by National Health and Medical Research Council (NHMRC) of Australia and Australian Research Council (ARC). Additional support was provided by University of Melbourne, Melbourne Health, Jack Brockhoff Foundation, Ian Porter Foundation, AE Rowden White Foundation, Ramaciotti Foundation, Pratt Foundation, Woods Family Trust, Rebecca L Cooper Medical Research Foundation, Australian Computing & Communications Institute, Wellcome Trust, NARSAD, Stanley Foundation. The PET study was funded by Janssen-Cilag.

S-33-004 Lithium effects on brain gray matter volumes

P.F. Renshaw, T.-S. Kim. University of Utah, Salt Lake City, UT, USA

Objective: The monovalent cation lithium remains one of the first-line mood stabilizing agents for the treatment of bipolar disorder (BD) in both the acute and maintenance phases. A substantial amount of preclinical and clinical evidence suggests that lithium may exert neuroprotective and/or neurotrophic effects in response to a range of insults. This presentation will provide an overview of the evidence in support of neuroprotective and/or neurotrophic effects of lithium on the brain and suggest clinically related research directions for future studies.

Methods: The authors review animal and cellular studies that explore the effects of lithium on neurons and structural neuroimaging studies that investigate the relationship between lithium use and brain gray matter (GM) volume in BD patients.

Results: A number of preclinical studies have demonstrated that lithium increases the neuroprotective proteins, bcl-2 and brain-derived neurotrophic factor; inhibits glycogen synthase kinase 3β activity to regulate phosphorylated tau and β-catenin; and protects brain cells from glutamate-induced, N-methyl-D-aspartate receptor-mediated apoptosis. Several structural neuroimaging studies have supported the neuroprotective and potentially neuroregenerative effects of lithium in BD patients. Recent meta-analyses have also suggested that lithium use in BD patients may be associated with volume increments not only in total GM but also in hippocampus and amygdala. Longitudinal neuroimaging studies have corroborated the lithium-induced increase in GM volume of BD, especially in the prefrontal cortex. Interestingly, these neurotrophic effects have also been associated with positive clinical response to treatment in BD.

Conclusion: Preclinical and clinical studies suggest that lithium may have neuroprotective and/or neurotrophic effects and its use in BD patients may be related to volumetric increase of GM. Future studies will be needed to investigate possible lithium effects on the GM volume of specific brain regions related to cognitive and emotional symptoms in BD patients.
S-34. Molecular imaging biomarkers in major CNS diseases and drug development

S-34-001 Translational prediction and validation of imaging biomarkers

T. Suhara, National Institute of Japan, Radiological Sciences, Chiba, Japan

Alzheimer’s disease is featured at a molecular level by depositions of amyloid-β peptides (Aβ) and tau proteins. Mutagenesis and multiplication of the genes encoding these compounds will certainly contribute to further drug development. Aβ deposition is treated as a hallmark of Alzheimer’s disease. PET imaging of amyloid plaques will be discussed. Pet imaging studies show that amyloid PET tracers preferentially bind to an N-terminally truncated, modified Aβ subspecies dubbed Aβ(1-40). A genetic deficiency of an Aβ-degrading enzyme, neprilysin, has given rise to selective overproduction of Aβ(1-40), enhanced amyloid PET signals and augmented cognitive deterioration in APP transgenic mice. The notion that Aβ(1-40) is a major constituent of binding sites for radioligands and disrupts neuronal integrity. Multi-tracer, multi-receptor PET imaging is also of pivotal importance using PET ligand for translocator protein (TSPO) for capturing glial activation. Neuroimaging biomarkers with amyloid imaging will also promote bidirectional translational research between clinical and preclinical levels, since they serve as common indices shared by humans and animals and thus ease extrapolation of pathological information in a reciprocal manner.

S-34-002 Amyloid imaging: A boost for drug development

K. van Laere, Leuven, Belgium

Since the first human imaging trials with 11C-PIB less than a decade ago, large efforts by industry and academia have resulted in a boost of specific and clinically applicable 18F-labeled radiotracers for beta-amyloid. This was led both by clinical demand for early and differential diagnostic tools for in vivo assessment of amyloidosis in Alzheimer’s disease and other forms of dementia, as well as the commercial drive for a biomarker for objective quantitative assessment of disease burden in anti-amyloid trials. Early 2012, at least five 18F-labeled amyloid ligands are in phase II or III clinical trials, and three are expected to obtain FDA approval in the course of 2012-2013: 18F-flutemetamol, 18F-florbetaben and 18F-florbetapir. 18F-AZD4694 and 18F-MK3328 are two more recent compounds, currently in phase II trials. Despite some differences in dynamic range, all these ligands allow excellent separation of amyloid positive scans versus controls. Neuroanatomical correlations have shown the robustness of in vivo amyloid imaging. Whereas aspecific uptake in white matter is seen for Aβ(1-40), specific uptake in white matter is seen for Aβ(1-42). "Amyloid PET imaging of the brain shows amyloid deposits in the normal elderly, a small proportion of elderly healthy individuals have positive amyloid imaging. Asymmetric uptake in white matter is seen for Aβ(1-42), specific uptake in white matter is seen for Aβ(1-40)." Neuroanatomical correlations have shown the robustness of in vivo amyloid imaging.

S-34-003 Imaging biomarkers in substance abuse

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Objective: Functional imaging has been increasingly used in the past decade for the characterization of patients with substance abuse disorders in order to gain insight in the neurobiology of these diseases and to enhance the development of drugs to treat them. Here we will review the current knowledge.

Methods: The available PET studies especially on the function dopamine systems in substance abuse will be reviewed, with a focus on alcohol and nicotine dependence and special emphasis on own studies in those patient groups. FMRI studies will be discussed where relevant for the interpretation and understanding of the PET studies.

Results: Irrespective of the abused drug, dopamine D2 receptors seem to be down-regulated and pre-synaptic dopamine function is apparently reduced in substance abuse disorders. Furthermore, the interaction between dopamine and other neurotransmitter systems, such as the opioidergic, seems to be dysregulated in a specific manner. FMRI studies demonstrate that the response of the reward system to drug-related cues is increased, while processing of cues not related to drug-use is diminished.

Conclusion: Substance abuse disorders irrespective of the abused drug share in common similar molecular imaging biomarkers, which can be used both for characterization of these disorders and for evaluation of antithrombic drugs. Furthermore, functional magnetic resonance imaging can complement PET imaging, thereby providing information a single modality is unable to deliver.

Policy of full disclosure: Dr. Gründer has served as a consultant for Astra Zeneca, Bristol-Myers Squibb, Chelapharm, Eli Lilly, Johnson & Johnson, Lundbeck, Otsuka, and Servier. He has served on the speakers’ bureau of Astra Zeneca, Bristol-Myers Squibb, Eli Lilly, Janssen Cilag, Otsuka, Pfizer, Servier, and Wyeth. He has received grant support from Alkermes, Bristol-Myers Squibb, Eli Lilly, and Johnson & Johnson. He is co-founder of Pharma-Image – Molecular Imaging Technologies GmbH, Düsseldorf, Germany. Dr. Vernaleten has served on the speakers’ bureau of Bristol-Myers Squibb, Eli Lilly, and GlaxoSmithKline. The other authors declare no conflicts of interest.

S-34-004 Novel PET biomarkers for dementia and psychosis and target engagement: Cannabinoids, metabotropic glutamate, glycine and beyond

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Objective: There are challenges associated with the development of new drugs, especially in neuropsychiatry, particularly in industry sponsored research. This is despite the continuing morbidity and challenges in treatment of schizophrenia and the exponential increase expected in dementia related disorders. There clearly is a need to meet these increasing public health needs. It has been suggested by some leaders in the drug development field that much of the effort should be placed on early human development (such as Phase I equivalent) and late preclinical discovery to try to select the most viable candidates early. Thus, the increasingly limited resources for CNS drug development should be focused with the greatest efficiency. Fortunately, several areas continue to appear to be great opportunities for therapeutic target methods.

Methods: In this presentation, we will present a number of novel potential biomarkers, both in imaging and related CSF and plasma levels, to aid in such drug development. Specific topics will include successful non-human primate and human target engagement dosing and mechanism of action studies for CB1 and CB2 cannabinoïds, and metabotropic glutamate (mGluR5, mGluR2/3, Gly/1, PDE4, PDE10) and others. In the last few years, through successful collaborations between academia and industry, several new PET radioligands have been developed from novel structures and rapidly accelerated for dose ranging occupancy and correlation with early efficacy studies.

Results: Studies from our preclinical human research in glutamate mGluR5, glycine, two [18F] amyloid radioligands and CB1 and CB2 cannabinoids will be presented.

Conclusion: The focus of this presentation will concentrate on this novel information.

S-35. Advances in understanding the causes and treatment of major depressive disorders

**S-35-001** The role of tumour necrosis factor in the pathophysiology of major depressive disorder, bipolar disorder and schizophrenia

A. Gibbons, Mental Health Research Inst, Parkville, Australia

**Objective:** Altered plasma levels of pro-inflammatory cytokines have been reported in individuals with mood disorders and schizophrenia. Elevated protein levels of the transmembrane form of the pro-inflammatory cytokine tumour necrosis factor (tmTNF) were recently reported in the dorsolateral prefrontal cortex (DLPFC) but not the anterior cingulate (ACC) from subjects with major depressive disorder (MDD). By contrast, levels of the soluble form of TNF (sTNF) were not changed in either region. These findings have been extended by measuring cortical tmTNF and sTNF levels in bipolar disorder (BPD) and schizophrenia.

**Methods:** Experiments were performed on DLPFC and ACC obtained post-mortem from 10 subjects with BPD, 10 subjects with MDD and 10 matched controls and from 19 subjects with schizophrenia and 20 matched controls. Western blotting was used to measure the protein levels of tmTNF and sTNF in BPD and schizophrenia. TNF mRNA levels were measured using qPCR. Surrogate protein markers of glial (GFAP), microglial (CD11b) and pre- and post-synaptic neuronal (synaptophysin and PSD-95) cell type and IL-1B protein were measured using western blotting.

**Results:** tmTNF protein levels were increased in the ACC but not the DLPFC in BPD (p<0.05). sTNF levels were unchanged in both regions compared to controls and TNF mRNA levels were also unaltered. There was no evidence of gliosis or apoptosis or of a broader cytokine response, indicated by unaltered cell-type marker and IL1B protein levels respectively, to suggest the increase in tmTNF is reflective of a pro-inflammatory response. Levels of tmTNF and sTNF protein or TNF mRNA were not significantly altered in schizophrenia.

**Conclusion:** Regionally specific increases in cortical tmTNF levels contribute to the pathophysiology of BPD and MDD but not schizophrenia. These elevated tmTNF levels are not consistent with a pro-inflammatory response, suggesting TNF’s non-inflammatory signalling pathways are likely to be affected in the CNS of individuals with mood disorders.

**S-35-002** The neuroanatomy of melancholy: An update circa 2012

J. Soares, University of Texas-Houston, Department of Psychiatry, USA

Mood disorders such as unipolar depression and bipolar disorder present brain abnormalities in key fronto-limbic brain circuits involved in emotional modulation. Over the past two decades a substantial number of neuroimaging studies have been completed and despite sometimes conflicting results, there is considerable evidence to support the fronto-limbic dysregulation hypothesis. Our presentation will review the anatomical and functional studies that focused on patients with major depression to summarize the status of knowledge in this maturing field. We will discuss a model where key abnormalities in the anterior cingulate, amygdala and hippocampus, as well as circuits that interconnect these regions, may be key steps involved in pathophysiology of these serious mental illnesses.

**Policy of full disclosure:** None.

**S-35-003** Animal models of depression: Relevance to drug discovery

T. Norman, University of Melbourne, Department of Psychiatry, Heidelberg, Australia

**Objective:** This paper reviews some traditional as well as innovative approaches to the use of pre-clinical models for drug discovery.

**Conclusion:** Major depressive disorder is a complex, genetically inherited set of conditions, the underlying causes of which are far from completely delineated. Consequently development of pre-clinical models is doomed to fall far short of the goal of a complete analogy. Clearly some symptoms of depression cannot be modelled in animals. Nevertheless, despite these limitations, numerous “so-called” animal models of depression have been developed in the past. Traditional models have proven useful for the discovery of newer agents, but there have been some notable (and costly) failures. More recent approaches to the development of animal models have taken discoveries from the clinic and using various genetic strategies have attempted to develop models based on incorporating these findings. The utility of this approach for the discovery of truly novel agents awaits further studies.

**S-35-004** How to improve treatment strategies in depression

P. Bleie, P. McGrath, R. Bergeron, J. Stewart, Ottawa, Canada; New York State Psychiatric Inst, New York, USA; University of Ottawa, Canada; New York State Psychiatric Inst, USA

**Objective:** Two prior double-blind studies using mirtazapine combinations from treatment initiation produced greater responses than antidepressants used in monotherapy, but not in a single-blind trial using low and/or conventional doses. High doses of escitalopram and bupropion were investigated based on their synergy between the serotonin and noradrenergic systems.

**Methods:** Patients with MDD (n=241; minimum MADRS: 22) in 3 centers were randomized to escalating doses at weekly intervals of escitalopram (10–40 mg/day), bupropion (150–450 mg/day), or their combination, according to tolerability and/or achievement of remission status. Patients were assessed using the HAMD, the MADRS, and the CGI-severity and -improvement scales. Assessments were done weekly for the first 4 weeks and at weeks 6, 8, 10, and 12.

**Results:** The sample did not differ at baseline on the demographics between the 3 groups, although there were differences between sites. The overall dropout rates at week 12 were not statistically different: escitalopram-25%, bupropion-35%, and combination-30%. There were significantly more remitters at week 2 in the combination group vs. both monotherapies based on the HAMD, the MADRS, and the CGI at week 12. There were more remitters on escitalopram (54%) than on bupropion (33%), but not on the combination (42%); X^2=7.67, df=2, P=0.02.

**Conclusion:** Early remission was hastened by the combination. High doses of escitalopram outperformed optimal doses of bupropion. The combination was not the most effective treatment at study end in the overall analysis, although further analyses remain to be carried out to determine the influence of demographics and dropout rates.

**Policy of full disclosure:** Astra Zeneca, Bristol Myers Squibb, Euthymics, Janssen, Lundbeck, Merck, Pfizer, Servier, Takeda, Valiant.

S-36. Drug targets and novel treatment strategies in alcohol and drug addiction

**S-36-001** Development of new medications for the treatment of alcoholism

C. O’Brien. University of Pennsylvania, Department of Psychiatry, USA

**Objective:** Translate findings from animal models of alcohol use disorder to the improved clinical treatment of alcoholism. Develop personalized treatment by studying genotypes relevant to the endogenous opioid system of alcoholism. Use human lab studies of drinking behavior, check family histories of successful patients, analyze DNA, search for genetic variants in the endogenous opioid system of successful v. unsuccessful patients.

**Methods:** A novel model of alcohol drinking in monkeys showed that blocking opioid receptors blocked alcohol self-administration. Translate to human alcoholics in double blind clinical trial. Study successful patients using human lab studies of drinking behavior, check family histories of successful patients, analyze DNA, search for genetic variants in the endogenous opioid system of successful v. unsuccessful patients.

**Results:** Patients randomized to naltrexone reported less craving for alcohol and less pleasure if they did drink. Successful patients had strongly positive family history of alcoholism & more pre-treatment craving. Those with an allele variant of the gene for the µ opioid receptor had a high probability of success if randomized to naltrexone. Another opioid receptor antagonist, nalinephene, was...
also found to reduce heavy drinking in clinical trials in the U.S. and Europe.

Conclusion: Alcohol produces reward via several mechanisms and one important mechanism involves activation of endogenous opioids. Blocking this effect with an opioid antagonist reduces the reward from alcohol and makes the patient more responsive to counseling. Unfortunately, in the U.S., anti-medicine philosophy dominates and few patients receive the benefits of this treatment.

A recent advance is the introduction of a slow release depot product that improves compliance and thus improves the success rate of naltrexone treatment.

Policy of full disclosure: Consultant to Alkermes, producer of Vivitrol, slow release naltrexone.

S-36-002 The role of the GABAB receptor system in alcoholism and stress: The role of the GABAB receptor agonist baclofen
G. Addolorato, Catholic University of Rome, Depert. of Internal Medicine, Italy
Alcoholism and stress share some common neurobiological circuits, including the GABAergic system. In particular, the GABAB receptor seems to play an important role. The GABAB receptor agonist baclofen has been studied as a treatment for alcohol-dependent subjects. Baclofen administration in alcohol-dependent patients was able to promote abstinence, reducing the remission of withdrawal symptoms, reducing alcohol craving, and reducing alcohol intake. Baclofen also reduced anxiety in alcohol-dependent subjects, probably acting on brain stress circuitry and/or on other neuroendocrine systems. Baclofen also showed excellent safety and tolerability, even in alcohol-dependent patients with advanced liver disease (i.e., cirrhosis). Future studies should investigate which alcoholic subtype may better benefit from the administration of baclofen in the treatment of alcohol dependence.

S-36-003 Impact of the stress hormone system as a pharmacotherapeutic target in the treatment of alcohol and drug addiction
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The ability of most drugs to enhance dopamine neurotransmission particularly within the mesocorticolimbic dopamine (“reward”) system was demonstrated repeatedly. However, the past decade has placed the dopamine system within a broader context of neuronal circuitry involved in drug seeking, drug taking, and recovery. Specific effects on other receptors symptoms provide particular challenges given the almost ubiquitous expression of these receptors throughout the CNS. Additionally, new emphasis on various neuropeptide systems has re-emerged, including opioid peptides and the stress-related peptides of the hypothalamic-pituitary-adrenal axis. The stress hormone system serves as a pharmacotherapeutic target in the treatment of alcohol and drug addiction; new data based on a GWAS on alcohol dependence and a pharmacogenomic follow-up study point towards an involvement of neuroendocrine pathways in relapse-related behavior. Continued research is warranted on the various neurobiological based components that underlie the transition from drug intake to addiction to define drug targets for innovative pharmacological treatment options.

S-36-004 ADHD in drug addiction: A RCT on the feasibility of methylphenidate treatment in criminal amphetamine users
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Objective: The present clinical trial was designed to evaluate the feasibility and efficacy of methylphenidate (MPH) for the treatment of ADHD in patients with amphetamine dependence and comorbid ADHD, using relapse to drug use as the primary outcome variable.
Methods: The study was a double-blind, placebo-controlled trial with parallel groups design. Participants were recruited and assessed while serving a short (<1.5 yrs) prison sentence in a medium security prison. The efficacy of ORGN MPH (max dose 180 mg/day) was compared with identical placebo (PL) in currently abstinent adult males. Fifty-four treatment-seeking patients fulfilling DSM-IV criteria for amphetamine dependence and ADHD were randomized to MPH/PL. The medication started 14 days before release from prison and continued at an outpatient facility with twice weekly visits and supervised urine drug screening. ADHD-symptoms, other psychiatric symptoms and relapse to criminality were also monitored. All patients participated in a relapse prevention training programme on a weekly basis.

Results: The mean age was 42.3 years (SD 10.5). All had i.v. amphetamine use and the mean debut age was 18 years, mean length of use 19.6 years (SD 11). The participants had been incarcerated on 11.3 occasions (SD 8.2). The most frequent axis-II diagnoses were antisocial (50%), obsessive-compulsive (23%) and borderline personality disorder (18%). Forty-four percent had prior alcohol dependence, 19% other substance use disorders and 13% anxiety syndromes. The average retention in treatment was 11.3 weeks (CI 8.7-13.8). Twenty-four percent (n = 12) of the participants completed all 24 weeks of treatment. Retention in treatment was significantly higher in the MPH group. No unexpected adverse events were detected using the maximum dose of MPH.

Conclusion: This clinical trial demonstrates the feasibility and safety of studying long-acting MPH in convicted patients with ADHD and comorbid amphetamine dependence.

Policy of full disclosure: The study was supported by grants from the Stockholm County Council and the Swedish Research Council.

S-37. Stress and vulnerability – antecedents to psychopathology and implications for effective treatment

S-37-001 Early life adverse experience, 5-HT2 receptors and long-term epigenetic modifications: Implications for affective vulnerability
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Objective: Prefrontal serotonin 5-HT2 receptors have been linked to the pathogenesis and treatment of affective disorders, yet their function in psychiatric vulnerability is not known. We examined the effects of 5-HT2 receptors in a rat model of early life stress, and addressed whether postnatal 5-HT2 receptor blockade would prevent the consequences of early stress on anxiety, hippocampal neurogenesis and dysregulated gene expression.

Methods: Control and maternally separated animals received treatment with the 5-HT2 receptor antagonist, ketanserin, and were examined for effects on adult anxiety, stress-induced gene expression responses, transcriptional changes and hippocampal neurogenesis.

Results: Stimulation of 5-HT2 receptors potentiated head shake behavior and heightened transcriptional changes in maternally separated animals, indicating enhanced 5-HT2 receptor responses. Treatment with ketanserin during postnatal life blocked the effects of maternal separation on anxiety, perturbed gene expression and hippocampal neurogenesis. Ketanserin treatment also normalized the changes in serotonin type 2A receptor messenger RNA expression during postnatal life and in genes associated with G-protein signaling in adulthood

Conclusion: Animals with an early stress history of maternal separation exhibited exaggerated 5-HT2 receptor mediated responses. Postnatal treatment with the 5-HT2 receptor antagonist, ketanserin, blocked specific consequences of maternal separation, including anxiety behavior, changes in hippocampal neurogenesis and dysregulated gene expression in the prefrontal cortex and hippocampus. Our results suggest that enhanced 5-HT2 receptor function may contribute to the emergence of anxiety behavior and perturbed stress responses following early life stress.
Thus, we present findings that are likely to be important for the pro-
levels of glutamate receptors and transporters after physical activity.

Methods: The single housed male FSL rats, runners, were allowed free access to a running wheel during 5 weeks whereas controls, non-runners, had no access. We analyzed effects of running on hippocampal size using volumetric 3-D in vivo Magnetic Resonance Imaging, 9.4 Tesla, long-term potentiation (LTP) induction in CA1 in hippocampal slices, and spine density in dentate gyrus. Levels of glutamate receptor and transporters were analyzed in hippocampus from rats with or without access to running wheels.

Results: Wheel running increased the size of hippocampus and number of spines in dentate gyrus compared to the non-running controls. Moreover, levels of the AMPA receptor subunit GluK2 and the glutamate transporter GLAST were increased in hippocampus after running. LTP, could not be induced in non-running FSL rats but was induced in the group of runners.

Conclusion: Physical activity can induce both structural and func-
tional plasticity. In the FSL model of depression with social isolation we find an enlarged total hippocampal volume, increased dendritic spine numbers, increased sensitivity to LTP induction, and increased levels of glutamate receptors and transporters after physical activity. Thus, we present findings that are likely to be important for the pro-
tective effects of physical activity on depression.

S-37-003 Rodent models of vulnerability to emotional trauma: Neural correlates and novel treatment options

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Objective: There are individual differences in coping with emotional trauma, including the ability to extinguish learned fear responses, which is suggested as a biomarker predicting the vulnerability to de-
velop specific anxiety disorders. Animal models of deficient extinction could be particularly useful to study underlying mechanisms and identify novel targets to inhibit pathological fear persistently.

Methods: Different pharmacological and non-pharmacological treatments were investigated for their fear extinction-promoting effects using classical conditioning/extinction paradigms in rodent models of impaired extinction, the Wistar rat line selectively bred for high anxiety-related behavior. Forced and indib. 129/SvJl (129Si) mice. Associated brain neuronal activity changes were assessed by quantification of immediate-early-gene expression.

Results: show that rescue of impaired extinction in HAB rats and 129Si mice was achieved by neuropeptide S or α-2 adrenergic antagonist treatments. Further testing in 129Si revealed that SSRIs and in particular novel treatments targeting the zinc system, histone acetylation, mGluR7-mediated transmission or deep brain stimulation rescued the highly impaired fear extinction in this model. Con-
siderable differences in the efficacy of these treatments to inhibit re-
turn of fear persistently were evident. In particular we observed that targeting histone acetylation and zinc systems very efficiently pro-
tected against spontaneous recovery and fear renewal in a novel context. Rescue of impaired extinction was associated with normalis-
ation of aberrant functional brain activity in 129Si. This normalisation

was observed in key regions of fear/extinction circuitries including the prefrontal cortex, intercalated cell masses of the amygdala and culminated in attenuation of hyperactivity of the medial subunit of the central amygdala, the main amygdala output region controlling fear behaviour.

Conclusion: These studies in psychopathologically relevant animal models identified extinction-enhancing treatments that promoted sustained inhibition of fear and furthermore, revealed important neural target correlates of such interventions. These findings should provide a basis for the development of novel therapeutic adjuncts in extinction-driven therapy.

Policy of full disclosure: Supported by the Austrian Science Fund (FWF) SFB-F410 (NS).

S-37-004 Chronic stress, dysregulation of prefrontal cognitive function and mechanisms underlying the response to effective antidepressant treatment

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Objective: Cognitive flexibility, the ability to modify established thoughts and behaviors based on changes in the environment, de-
pends upon prefrontal cortical function, and is compromised in many stress-related psychiatric disorders, e.g., depression. Using rat mod-
els, we address mechanisms by which chronic stress impairs cognitive flexibility, and by which therapeutic approaches exert beneficial effects.

Methods: The rat attentional set-shifting test was used as a measure of prefrontal cognitive flexibility. Prefrontal function was assessed by loss of activation during reversal learning. These deficits were reversed or prevented by chronic treatment with selective NE or 5-HT reuptake blockers, respectively. Alpha1 adrenergic receptors in mPFC facilitate set-shifting, and 5-HT2A receptors in OFC facilitate reversal learning. These mechanisms contribute to effective anti-
depressant response. However, noradrenergic facilitation in mPFC also contributes to the detrimental effects, as antagonist treatment during chronic stress protects against the cognitive deficit. Thus a paradox – how can elevating NE by chronic stress be bad, but elevating NE by chronic reuptake blockade is good? We hypothesize that noradrenergic facilitation interacts with other convergent stress-
evoked signaling pathways in PFC, including cytokines, contributing to the detrimental effect. Finally, preliminary results indicate that a rat model of CBT has antidepressant efficacy.

Conclusion: Monoaminergic modulation in PFC enhances cogni-
tive flexibility, and contributes to effective antidepressant response. Approaches that target other convergent pathways to improve treatment response. Further, behavioral or other strategies that engage the prefrontal circuitry compromised in depression can induce direct improvement, or provide an active substrate for monoaminergic fa-
cilitation.

Policy of full disclosure: This work was supported by research grants from NIH and the Department of Defense (USA). The author has received funds in the past year from Forest Laboratories for re-
search on a product unrelated to any of the material or data presented in this talk.
hypothesis-guided treatment approaches – concentrated for a long
time on alterations on monoaminergic or endocrine systems. A more
comprehensive and appropriate treatment might arise from modeling
depression as a dysfunction of specific brain networks mediating
mood and reward signals. DBS is currently being researched actively
for its putative application in treatment resistant major depression
(TRD). While first studies on three different targets in TRD (Brodmans
Area cg25, anterior limb of the capsula interna and Nucleus
Accumbens) showed promising effects in comparable patient popu-
lations, only 50–60% of patients responded at a clinically significant
level. Furthermore, stimulation intensities ranging from 4–10V and
large electrodes geometries were used; somewhat undermining target
specificity.

**Methods:** Seven patients suffering from extremely treatment re-
sistant depression (TRD, mean lengths of current episode 7.6 years)
underwent bilateral DBS electrode implantation in the supero-lateral
medial forebrain bundle slMFB) after Diffusion Tensor Imaging (DTI)
based personalized target site definition.

**Results:** Montgomery Åsberg Rating Scale for Depression
(MADRS) scores decreased from a mean of 29.9 (SD 8.0) at baseline
to 12.4 (SD 10.2) after 11 weeks of stimulation, onset of efficacy
was typically observed within two days of start of stimulation and
6 patients reached the response criterion within 7 days. Stimulation
intensity ranged from 1.5 to 2.5V.

**Conclusion:** These pilot data support the notion that slMFB DBS
might be associated with more rapidly developing and significantly
stronger antidepressant effects in patients with TRD.

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**S-38-003 Deep Brain Stimulation to the subcallosal cingulate
gyrus for treatment resistant depression: An update**

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**Objective:** Antidepressant treatments, including pharmacotherapy
and psychotherapy, do not result in remission for the majority of
patients with Major Depressive Disorder. Consequently, the high
prevalence of treatment resistant depression (TRD) results in a high
social and economic burden.

**Methods:** The emergence of neurostimulation therapies, including
Deep Brain Stimulation (DBS) for TRD is a promising development
that involves the bilateral implantation of electrodes to a neuroana-
tomical site, which receives remote electrical stimulation via a sub-
clavicularly implanted pacemaker. Through the use of neuroimaging,
and other biomarker testing, there is an opportunity to elucidate both
the underlying circuitry of TRD and the mechanism of action of DBS.
Studies on the neurocircuitry of depression support hyperactivity in
the subcallosal cingulate gyrus-Area 25 (SCg25), which is ameliorated
by neuromodulation treatments.

**Results:** The Neurostimulation team at University Health Network,
University of Toronto has a seven-year experience involving over 30
patients who have received SCg25 DBS, and have been followed up to
6 years. These data support the long-term effectiveness of DBS for
TRD, while highlighting the mortality rate associated with treatment
resistance. Beyond the initial DBS trial to the SCg25, additional
neuroanatomical targets are being explored, including the nucleus
accumbens and internal capsule/ventral striatum, lateral habenula,
and inferior thalamic peduncle.

**Conclusion:** To date, there are open-label reports on over 100 sub-
jects, demonstrating acute and sustained effectiveness and safety.
However, until published randomized controlled trials establish
efficacy for this invasive treatment, the medical community and the
media need to exercise caution in their enthusiastic endorsement of
this appealing advance in psychiatry.
RA-01. Rafaelsen Award Posters

**RA-01-001**

**Regulation of inflammation and T cells by glycogen synthase kinase-3 (GSK3) and association with depression**

E. Beurel, Dept of Psychiatry, Miami, USA

**Objective:** Accumulating evidence shows that inflammation strongly influences the development and treatment of depression. Inflammatory molecules are elevated in many patients with depression, and inflammation in rodents causes depressive-like behaviors and impairs antidepressant therapeutic effects. Glycogen synthase kinase-3 (GSK3) is a critical regulator of the immune system, which may contribute to its action in increasing susceptibility to mood dysregulation. Previously, GSK3 was shown to have important influences in mood disorders: (a) GSK3 is inhibited by mood stabilizers and antidepressants, (b) pharmacological or genetic reduction of GSK3 activity reduces depression-like behaviors in rodents, (c) GSK3 is activated when serotonergic signaling is deficient, (d) brain-derived neurotrophic factor, that may be deficient in depression, normally inhibits GSK3, and (e) studies of human blood cells, postmortem brain, and polymorphisms implicate GSK3 in mood disorders.

**Methods:** GSK3 activity was increased by using GSK3α/β/21A/21A/9A/9A knockin mice with serine-to-alanine mutations to block inhibitor serine-phosphorylation of GSK3 or decreased by administration of GSK3 inhibitors (liothion, CHIR99021 and TDI-D-9). Cytokines were measured by ELISA. Activation of the transcription factor signal transducer and activator of transcription-3 (STAT3) was assessed by immunoblotting. The learned helplessness paradigm of depression-like behavior was evaluated in adult male mice.

**Results:** Inhibition of GSK3 or knockdown of GSK3 inhibited inflammatory cytokine production by astrocytes and microglia and blocked the inflammatory activation of the transcription factor STAT3. Blocking cytokine production and downregulation of STAT3 by GSK3 inhibition diminished T cell differentiation towards pathogenic Th17 cells, whereas active GSK3 promoted depressive-like behavior in mice and increased Th17 cells in mouse brain.

**Conclusion:** Altogether, these findings indicate that GSK3 promotes inflammatory immune system activation and depression-like behavior. Activation by dysregulated GSK3 of these immune system actions may contribute to susceptibility to mood disorders and be controlled by mood stabilizers.

RA-01-002

**Association of nicotine dependence susceptibility gene, CHRNA5, with Parkinson’s disease age at onset: Gene and smoking status interaction**

L. Greenbaum, A. Right, L. Nutter, R. Cilia, S. Tesei, R. Asselta, R. Djaldetti, S. Goldwurm, B. Lerer, 1 2 3 4 3 4

**Objective:** Smoking is a well documented environmental factor that reduces susceptibility to Parkinson’s disease (PD). Several genetic variants within the nicotinic cholinergic receptor gene cluster, CHRNA5-CHRNA3-CHRNB4 have been reported to be associated with nicotine dependence (ND), and this association has been validated in multiple studies. Due to the inverse correlation between smoking and PD susceptibility, we investigated whether ND-related genetic variants are associated with age at onset (AAO) of PD among smokers.

**Methods:** We performed a genetic association study in a sample of 667 Italian PD patients, ages 34–76. 438 had never smoked (NS), and 239 were current or past smokers (ever smokers, ES). Three independent SNPs within the CHRNA5-CHRNA3-CHRNB4 gene cluster (rs588765, rs16969968, rs578776) were analyzed for association with AAO.

**Results:** We demonstrated an interaction between the rs588765 SNP and smoking status (NS vs. ES) that was nominally significant in its effect on PD AAO (p = 0.04). The rs588765 ND risk allele, C, was associated with delayed AAO among ES, but had no significant effect among NS. In the ES group, a dominant model of inheritance was observed: carriers of the CC genotype presented delayed AAO compared to carriers of the CT or TT genotypes.

**Conclusion:** Our preliminary results suggest that the ND risk variant, rs588765, has a protective effect in PD, and is associated with later AAO, but only when the individual was previously exposed to nicotine. This may be explained by modulation of dopamine transmission by nicotinic cholinergic receptors expressed on dopaminergic neurons in PD relevant brain regions.

RA-01-003

**Opioid receptors and reward: An fMRI study with naltrexone**

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**Objective:** Opiates are known to be involved in facilitating consummatory behaviour in animals and humans. Opioid receptors are highly expressed in neural ‘reward’ areas such as orbitofrontal cortex, ventral tegmental area and nucleus accumbens. Naltrexone, an opioid antagonist, can decrease the behaviour-reinforcing effects of primary rewards and increase the effect of negative experience, such as pain. The aim of the current experiment was to examine the effects of the opioid antagonist naltrexone on rewarding and aversive taste processing in the human brain.

**Methods:** We used functional magnetic resonance imaging (fMRI) to examine the effects of naltrexone on the neural responses to pleasant chocolate and aversive tastes and sights of mouldy strawberry in a within-subjects double-blind crossover design (n = 20).

**Results:** Relative to placebo, naltrexone decreased the neural activation to the rewarding chocolate stimulus in the vmPFC but increased activation to the aversive strawberry stimulus in the same region. Results are consistent with studies showing opiates reduce reward but also how opioid antagonists may enhance the unpleasantness of aversive stimuli.

**Conclusion:** These findings provide novel insight into the mechanism by which opioid antagonists may reduce food intake not only through effects on reward but also effects on unpleasant food stimuli. These results have implications for the use of opioids as possible treatments for disorders of compulsion such as obesity.

RA-01-004

**BDNF-TrkB signaling is involved in the antidepressant-like effect induced by genetic deletion of iNOS**

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**Objective:** We have recently shown that the pharmacological or genetic inhibition of the inducible nitric oxide (NO) synthase (iNOS) isoform evokes antidepressant-like effects. However, the molecular mechanism underlying this effect is still unknown. Brain derived neurotrophic factor (BDNF) is a neurotrophin implicated in the antidepressant effect and it can be modulated by NO in hippocampus (HPC) and pre-frontal cortex (PFC). Therefore, the aim of this study was to investigate the hypothesis that inhibition of iNOS induces...
antidepressant-like effects associated to increased BDNF signaling in hippocampus and PFC.

Methods: Male iNOS deficient (KO) and C57BL/6 wild-type (WT) control mice were submitted to forced swimming test (FST) and their hippocampus and PFC were dissected. BDNF and its receptor, TrkB, as well as NOx levels were measured. Independent groups of KO and WT mice were treated with K252a, a Trk antagonist, and submitted to FST or to the open field test (OFT).

Results: iNOS KO animals presented a decreased immobility time in the FST compared to WT controls ($t_{14}=3.18; p<0.01$). KO animals had increased levels of BDNF in HPC and PFC (genotype x stress: HPC; $F_{1,32}=5.41; p<0.05$; PFC; $F_{1,28}=4.48; p<0.05$), which was not influenced by FST. iNOS KO mice also had increased levels of TrkB ($t_{13}=3.29; p<0.05$) and NOx ($t_{6}=2.526; p<0.05$) in PFC. In the HPC, only TrkB levels were increased ($t_{13}=2.182; p<0.05$). Systemic injection of K252a reversed the behavioral phenotype of iNOS KO mice, without changing the behavior of WT mice (drug x genotype: $F_{1,32}=13.21; p<0.01$). No effects were observed in the OFT.

Conclusion: Our results indicate that there is a differential interaction between NO and BDNF-TrkB signaling in HPC and PFC. This interaction may be involved in the antidepressant-like phenotype of iNOS KO mice.

RA-01-006 Impact of the genome-wide supported NRGN gene on anterior cingulate morphology in schizophrenia

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Objective: The rs12807809 single-nucleotide polymorphism in NRGN is a genetic risk variant with genome-wide significance for schizophrenia. The frequency of the T allele of rs12807809 is higher in individuals with schizophrenia than in those without the disorder. Reduced immunoreactivity of NRGN, which is expressed exclusively in the brain, has been observed in Brodmann areas (BA) 9 and 32 of the prefrontal cortex in postmortem brains from patients with schizophrenia compared with those in controls.

Methods: Genotype effects of rs12807809 were investigated on gray matter (GM) and white matter (WM) volumes using magnetic resonance imaging (MRI) with a voxel-based morphometry (VBM) technique in a sample of 99 Japanese patients with schizophrenia and 263 healthy controls.

Results: Although significant genotype-diagnosis interaction either on GM or WM volume was not observed, there was a trend of genotype-diagnosis interaction on GM volume in the left anterior cingulate cortex (ACC). Thus, the effects of NRGN genotype on GM volume of patients with schizophrenia and healthy controls were separately investigated. In patients with schizophrenia, carriers of the risk T allele had a smaller GM volume in the left ACC (BA32) than did carriers of the non-risk C allele. Significant genotype effect on other regions of the GM or WM was not observed for either the patients or controls.

Conclusion: Our findings suggest that the genome-wide associated genetic risk variant in the NRGN gene may be related to a small GM volume in the ACC in the left hemisphere in patients with schizophrenia.
RA-01-007 Circuit-wide effects of deep brain stimulation for neurological and psychiatric disorders: A comparison
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Objective: High-frequency electrical stimulation of specific brain structures, commonly known as deep-brain stimulation (DBS), has attracted substantial attention for treatment of neurological and psychiatric disorders that fail to respond to standard therapies. Here, we compare and contrast the circuit-level effects of DBS applied to either the nucleus accumbens (NAC), an effective target for treating OCD and depression, or the entopeduncular nucleus (EP), the rat homolog of the internal globus pallidus and a target for treatment of dystonia and Parkinson’s disease.
Methods: We used simultaneous multi-site local field potential (LFP) recordings in urethane-anesthetized rats to assess the effects of high-frequency (HF, 130 Hz; clinically effective), low-frequency (LF, 10–15 Hz; clinically ineffective) and sham DBS delivered to either NAC or EP. For NAC DBS, LFP activity was recorded from the orbital and medial prefrontal cortices, mediodorsal thalami, and the stimulation site. For EP DBS, we recorded from dorsal striatum, ventroanterior thalamus, primary motor cortex, and the stimulation site. Spontaneous and acute stimulus-induced LFP oscillation power and coherence were assessed at baseline, and after 30, 60, and 90 minutes of stimulation.
Results: Compared to LF and sham, HF NAC DBS was associated with widespread, time-dependent increases in fast (beta/gamma) oscillation power, whereas HF EP DBS produced no specific changes in spontaneous fast oscillation power. LF NAC DBS produced region-specific increases in theta band power, and reduced induced gamma coherence between regions; LF EP DBS produced no significant changes. Notably, HF DBS of both EP and NAC DBS produced time-dependent increases in spontaneous and induced beta and gamma coherence between regions.
Conclusion: These data suggest that enhanced coherent activity in the beta and gamma bands along cortico-basal-ganglia-thalamic circuits may represent a common mechanism of action of DBS for different indications. Future studies will continue to dissect generalized and disease-specific therapeutic mechanisms to better optimize this technology.

RA-01-008 Psychopharmacological effect of naringin in unpredictable chronic mild stress model of depression: Behavioral, biochemical & neurochemical evidences
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Objective: A complex relationship exists among stressful situations, body’s reaction to stress, and the onset of clinical depression. Chronic unpredictable stressors can produce a situation similar to clinical depression and such animal models can be used for the pre-clinical evaluation of antidepressants. Clinical studies reported neurotransmitter alterations, increased MAO activity, nitroative stress and inflammation in patients with depression. The present study was designed to investigate the effect of naringin on unpredictable chronic stress-induced behavioral, biochemical and neurochemical alterations in mice.
Methods: Animals were subjected to different stress paradigms daily for a period of 21 days to induce depressive-like behavior. The sucrose preference, immobility period, locomotor activity, memory acquisition and retention were significantly altered in stressed mice. These behavioral deficits were integrated with decreased biogenic amine (dopamine, norepinephrine and serotonin) levels, increased nitroative stress (increased lipid peroxidation & nitrite levels; decreased glutathione levels, superoxide dismutase & catalase activities), enhanced MAO and inflammatory cytokine (TNF-α & IL-1β) activities.
Results: Chronic treatment with naringin significantly and dose-dependently restored the unpredictable chronic stress-induced behavioral (increased immobility period, reduced sucrose preference), biochemical (decreased nitroative stress, MAO and inflammatory cytokine activity), and neurochemical (dopamine, norepinephrine and serotonin levels) deficits induced by chronic unpredictable stress.
Conclusion: The study revealed that naringin exerted antidepressant-like effects in behavioral despair paradigm in chronically stressed mice, specifically by modulating biogenic amines, MAO, nitroative stress and inflammation. Thus, naringin may find clinical application in therapeutic armamentarium of stress induced depression.

RA-01-009 Estrogen affects neural processing in empathy task in women. An ultra-highfield 7 tesla functional MRI study
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Objective: Neural mechanisms of empathy, defined as a psychologcal construct of understanding and responding to other peoples’ affective experiences, have gained focus in neuropsychological research. Studies revealed higher empathy scores in females and suggested that neural empathy networks are differentially modulated by gender. Furthermore, estrogen has been shown to influence brain activation in memory as well as emotional tasks in women. Following that, this study with functional magnetic resonance imaging (fMRI) aims to investigate the relation between estrogen plasma levels and brain activation during an empathy task.
Methods: 17 healthy female volunteers (26.4±5.8 years) were analysed in this 7 Tesla ultra-highfield (Magnetom T7, Siemens Medical) fMRI study undergoing an fMRI scan (245 whole brain volumes, matrix size 128×128×2×32, TR=1.4 s, TE=22 ms, FoV=192×192×2 mm3, 2 mm slice thickness). All subjects performed an empathy-related task, previously described by Lamm et al., Participants were watching video clips of actors who were instructed to emphasize a painful response to an auditory stimulation, whereas the participants where informed that they would see patients with a psychological construct of understanding and responding to other peoples’ affective experiences, have gained focus in neuropsychological research. Studies revealed higher empathy scores in females and suggested that neural empathy networks are differentially modulated by gender. Furthermore, estrogen has been shown to influence brain activation in memory as well as emotional tasks in women. Following that, this study with functional magnetic resonance imaging (fMRI) aims to investigate the relation between estrogen plasma levels and brain activation during an empathy task.
Results: Compared to LF and sham, HF NAC DBS was associated with widespread, time-dependent increases in fast (beta/gamma) oscillation power, whereas HF EP DBS produced no specific changes in spontaneous fast oscillation power. LF NAC DBS produced region-specific increases in theta band power, and reduced induced gamma coherence between regions; LF EP DBS produced no significant changes. Notably, HF DBS of both EP and NAC DBS produced time-dependent increases in spontaneous and induced beta and gamma coherence between regions.
Conclusion: These data suggest that enhanced coherent activity in the beta and gamma bands along cortico-basal-ganglia-thalamic circuits may represent a common mechanism of action of DBS for different indications. Future studies will continue to dissect generalized and disease-specific therapeutic mechanisms to better optimize this technology.
P-01. Antipsychotics

**P-01-001** Treatment adherence pattern in patients affected by schizophrenia or bipolar disorder that switched from quetiapine IR to quetiapine XR

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**Objective:** In patients with schizophrenia and bipolar disorder (BD), non-adherence to medication can increase the risk of relapse. The Italian Burden of Illness on Schizophrenia and BD (IBIS) study aimed to describe pharmacological utilisation of antipsychotic treatment in schizophrenia and BD patients. A secondary study objective was to assess differences in medication adherence for patients switching from quetiapine immediate release (QTP-IR) to quetiapine extended release (QTP-XR). Here we present interim adherence results collected from administrative databases in 6 of 20 Italian Local Health Units included in the study.

**Methods:** Multicentre, retrospective, observational cohort study (NCT01392482). Data were collected between 1 January 2008 and 31 December 2010. Patients were included for analysis when they switched from the antipsychotic medication QTP-IR to QTP-XR. Data were collected 6 months before and 6 months after the switch. A control group that received QTP-IR was matched to the switching group based on diagnosis, gender and age, for analysis. Adherence ±SD was estimated using the Catalan method.

**Results:** Of 6,817 patients in the study population, 213 switched medication from QTP-IR to QTP-XR (with schizophrenia, 127 with BD). Overall, there was an increase in adherence to medication after switching (from 44.2 ±24.7 % to 62.6 ±26.5 %; p = 0.009). For patients with schizophrenia adherence increased from 48.3 ±23.5 % to 56.5 ±27.0 %: p = 0.125, and for patients with BD adherence increased from 41.3 ±25.3 % to 66.7 ±25.4 %: p = 0.036. In the matched control group smaller increases in adherence were observed in the overall interim population, and stratified by disease: 51.8 ±22.5 % to 53.4 ±26.4 %: p = 0.493 in total; 55.7 ±22.2 % to 56.6 ±25.7 %: p = 0.816 in patients with schizophrenia; 49.2 ±22.4 % to 51.3 ±26.8 %: p = 0.479 in patients with BD.

**Conclusion:** These interim results suggest that adherence improved in patients with schizophrenia and BD after switching from QTP-IR to QTP-XR.

**Policy of full disclosure:** The IBIS study was funded by AstraZeneca and the presenting author received a grant from AstraZeneca.

**P-01-002** Variability of treatment patterns for patients affected by schizophrenia and bipolar disorder

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**Objective:** Schizophrenia and bipolar disorder (BD) are psychiatric disorders commonly treated with antipsychotic medications. Little is known about which combinations of antipsychotics are frequently used in clinical practice. The Italian Burden of Illness on Schizophrenia and BD (IBIS) study aims to describe the pharmacological utilisation of antipsychotic and concomitant medications in patients with schizophrenia and BD.

**Methods:** Multicentre, retrospective, observational cohort study (NCT01392482). Interim data are shown from administrative databases of 6 of 20 Italian Local Health Units included in the study, collected between 1 January 2008 and 31 December 2010. Patients were retrospectively followed for one year from index date (first prescription of antipsychotics).

**Results:** In total, 6,817 patients were included in the study population (4,097 with schizophrenia, 2,720 with BD). In patients with schizophrenia, 65.5 % were treated with a single antipsychotic, and 34.5 % were prescribed more than one antipsychotic during the study period. A notable number of schizophrenic patients receiving either one or multiple antipsychotics, respectively, also received mood stabilisers (13.5 %, 21.3 %), antidepressants (15.9 %, 17.5 %) or both (5.5 %, 15.2 %). In patients with BD, 66.7 % were prescribed a single antipsychotic and 33.3 % multiple antipsychotics. Concomitant medications were more frequently prescribed in patients with BD than with schizophrenia; BD patients receiving single and multiple antipsychotics, respectively, also received mood stabilisers (31.0 %, 27.0 %), antidepressants (14.8 %, 13.6 %) or both (34.9 %, 48.5 %). Overall, in patients receiving multiple antipsychotics, up to 333 different combinations were used. Of the antipsychotic combinations reported in the study, 22.7 % of schizophrenia patients received the 5 most frequently used combinations for schizophrenia, and 23.4 % of BD patients received the 5 most common combinations for BD.

**Conclusion:** These interim results show a high level of treatment variability in schizophrenia and BD patients. Most were treated with a single antipsychotic, and concomitant treatment with mood stabilizers and antidepressants was common.

**Policy of full disclosure:** The IBIS study was funded by AstraZeneca and the presenting author received a grant from AstraZeneca.

**P-01-003** Interactions between adenosine-A2A and alpha2 adrenergic receptors and their potential role in antipsychotic drug response

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**Objective:** The aim of the current study was to investigate potential interactions between A2A and alpha2A adrenergic receptors and their putative role in antipsychotic drug response.

**Methods:** Male Wistar rats (300–350 g) were used in the experiments. In-vivo electrophysiology, under propofol (1.2 mg/kg/min, i.v.) anesthesia, was used to assess the firing activity of norepinephrine neurons in the locus coeruleus (LC). In-vivo microdialysis (in freely-moving rats) was used to assess dopamine and norepinephrine levels in the nucleus accumbens (NAcc) and prefrontal cortex (PFC). Microdialysis probes were implanted under isoflurane anesthesia, 24 hours prior to the experiment. The levels of catecholamines in dialysates were assessed using the high-performance liquid chromatography (HPLC) and electrochemical detection.

**Results:** The mean basal firing rate of norepinephrine neurons was 2.87 ±1.54 Hz. Selective agonist of A2A receptors, CGS 21680 (0.05–0.5 mg/kg, i.v.), significantly and dose-dependently decreased the firing rate of norepinephrine neurons (to 25 % of baseline). Subsequent administration of the selective antagonist of A2A receptors, ZM 241385, partially recovered the firing rate to 50 % of baseline. Finally, injection of clonidine (0.02 mg/kg) almost completely (>90 %) inhibited norepinephrine neurons in the LC. Haloperidol (1 mg/kg, s.c.) significantly increased dopamine levels in NAcc and PFC; norepinephrine levels were not altered. Pre-treatment with ZM 241385 (0.5 mg/kg, i.p., 40 min prior to haloperidol administration) resulted in significant increase in norepinephrine levels in the PFC and in potentiation of haloperidol-induced elevation of dopamine levels in the NAcc (Figure 1).

**Conclusion:** CGS 21680 inhibits the firing rate of norepinephrine neurons; this inhibition is reversed by ZM 241385. ZM 241385 potentiates the effect of haloperidol on dopamine levels in the NAcc.
and norepinephrine levels in the PFC. Antagonists of A2A receptors may be thus beneficial as adjuncts to antipsychotic drugs.

**P-01-004** Metabolic syndrome in a sample of drug-naive Egyptian patients with psychotic disorders

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**Objective:** The main objective of this study is to determine the rate of occurrence of metabolic syndrome (MetS) in a sample of drug-naive patients with psychotic disorders compared with a matched control group and to identify the significant criteria for this diagnosis.

**Methods:** This study is designed as a preliminary cross-sectional case–control study. Twenty patients were selected from inpatient psychiatric units at the Institute of Psychiatry, Ain Shams University, Cairo, Egypt, with an established diagnosis of acute psychosis or first episode schizophrenia according to ICD-10 classification during a period of 6 months and matched with 20 controls. The case group was assessed by a semistructured psychiatric interview sheet of the Institute of Psychiatry, Ain Shams University, and both the groups were subjected to measurements of (a) waist circumference (WC) and BMI and (b) laboratory investigations including an oral glucose tolerance test (OGTT), HDL and triglycerides, and (c) blood pressure measurements.

**Results:** MetS was detected in seven (63.6%) patients with schizophrenia, one (33.3%) patient had acute psychosis, four patients had unipolar depression, and only one had bipolar affective disorder compared with seven (35%) participants in the control group. In addition, WC, BMI, and OGTT were found to be significantly correlated to development of MetS among patients with psychotic disorders even before starting their antipsychotic medications.

**P-01-005** High doses of long acting atypical antipsychotics: Role in a severe mentally illness treatment retention

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**Objective:** To know the retention in treatment of severe mentally ill patients and the role of long acting atypical antipsychotics, taking into account high doses tolerability.

**Methods:** 3-year prospective, observational study of patients undergoing specific severe mental illness programme (September 2007 to September 2011). (N = 319; 44.2% of them with schizophrenia). Assessment included the Clinical Global Impression (CGI) severity scale, the WHO Disability Assessment Schedule (WHO/DAS), the Camberwell Assessment of Need (CAN), laboratory tests and weight, at the beginning and after three years of follow-up. Time in treatment, reasons of discharge, medications used and hospital admissions were registered.

**Results:** CGI at baseline was 5.72 ± 0.8; After three years 35.7% of patients continued under treatment (CGI = 4.11 ± 0.9; p < 0.01); 40.4% were medical discharged (CGI = 5.14 ± 1.3; p < 0.001); DAS also decreased in the four areas (self-care and employment p < 0.01; family and social p < 0.005) and also CAN (p < 0.01); 8.5% had moved to other places; 14.1% were voluntary discharges. There were significant less hospital admissions than during the 18 months previous treatment (p < 0.001). Four patients dead. Time in the Programme was 23 ± 7.1 months. 43% of patients received risperidone longacting injectable (RLAI) (109.7 ± 19 mg/14 day). Tolerability was good and there were almost no discharges (4.2%) due to side effects or to relevant biological parameters alterations or weight gain.
Conclusion: Retention of patients with severe mental illness in a specific programme was high. And the use of long acting atypical antipsychotics in patients who had needed high doses (over 75mg/14 day of RLAI) to get clinical stabilization and better functioning seemed to be useful in improving treatment adherence, due to their high tolerability.

P-01-006 The effect of clozapine on white matter in schizophrenia: A diffusion imaging and tractography study

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Objective: The pathophysiology of schizophrenia has been associated with structural brain changes and clozapine, an effective antipsychotic medication has been suggested to have neuroprotective effects in preclinical studies. However in vivo imaging studies report a decline in brain volume as a result of long-term clozapine use. Herein we explicitly test the effect of 6 months of treatment with clozapine on white matter organization quantified as fractional anisotropy (FA).

Methods: Twenty-one chronic treatment-resistant individuals with schizophrenia (SZ, 16 male, mean-age=35.9 ± 9) and twenty-one age- and gender-matched controls (HC, 12 male, mean-age=39.1 ± 10) underwent psychiatric clinical assessment and diffusion-MR scanning before and after either six months of treatment with the atypical antipsychotic clozapine or no treatment, respectively. Analysis of FA included voxel-based (TBSS) and tractography (ExplorDTI).

Results: The SZ-group improved clinically by an average of 21-points (± 13.53 %) on the positive and negative syndrome scale (PANSS) from baseline (48 ± 14) to follow up (24 ± 16). Compared with baseline, patients treated with clozapine displayed reduced FA in the genu and body of the corpus callosum, the cingulum bundle, and anterior superior longitudinal fasciculus (SLF). There were no significant FA changes in the HC group. Tractography detected reduced mean tract FA in the genu following treatment with clozapine (DTI: 1.49 %, t(19)=2.58, p = 0.018; CSD:3.13 %, t(20)=2.40, p = 0.026) but not in the HC group (DTI: 0.20 %, t(19)=0.51, p = 0.62; CSD: 0.72 %, t(20)=0.27, p = 0.45).

Conclusion: Patients treated with clozapine for 6 months display reduced microstructural organization of the commissural fibers, cingulum bundle and SLF. It remains unclear whether this represents a side-effect or mechanistic element of clozapine treatment or a manifestation of illness progression, in which case clozapine does not reverse or halt microstructural disorganization in schizophrenia. CSD-based proved more sensitive than did tensor-based tractography in detecting these changes.

P-01-007 Involvement of 5-HT2A receptor and a2-adrenoceptor blockade in the asenapine-induced elevation of prefrontal cortical monoamine outflow

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Objective: The psychotrophic drug asenapine is approved for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. Asenapine exhibits higher affinity for several 5-HT and a2-adrenergic receptors than for D2 receptors. Noteworthy, both blockade of 5-HT2A and a2-adrenergic receptors has been shown to enhance prefrontal dopamine release induced by D2 receptor antagonists. Previous results show that asenapine, both systemically and locally, increases dopamine, noradrenaline and serotonin release in the medial prefrontal cortex (mPFC), and that the increased dopamine release largely depends on an intracartical action.

Methods: Using reverse microdialysis in freely moving rats, we here assessed the potency of low concentrations of asenapine to cause a pharmacologically significant blockage in vivo of 5-HT2A/2C receptors and a2-adrenoceptors within the mPFC, and thus its ability to affect cortical monoamine release by these receptors.

Results: Intracartical administration of DOI, a 5-HT2A/2C receptor agonist, increased cortical monoamine release, effects that were antagonized both by asenapine and the selective 5-HT2A antagonist M100907. Application of clonidine, an a2-adrenoceptor agonist, significantly reduced monoamine release in the mPFC. The selective a2-adrenoceptor antagonist idazoxan blocked, whereas asenapine partially blocked clonidine-induced cortical dopamine and noradrenaline decrease. The effects of asenapine and idazoxan on clonidine-induced serotonin decrease were less pronounced.

Conclusion: Our results propose that low concentrations of asenapine in the mPFC exhibit a pharmacologically significant 5-HT2A and, to a weaker extent, a2 receptor antagonistic activity, which may contribute to enhance prefrontal monoamine release in vivo and, secondarily, its clinical effects in schizophrenia and bipolar disorder.

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P-01-008 Defined daily dose system as a tool for standardizing antipsychotic dosages. Reliability in high dose users

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Objective: There is a report that found the Defined Daily Doses (DDD) system as a reliable tool for standardizing antipsychotic dosages in drug utilization research (Nose et al., 2008). However, this study was based upon a population receiving a wide range of antipsychotic doses, with few of them being prescribed high doses defined as 1000 mg or more chlorpromazine equivalents (CPZEs) thus limiting the results. The aim of this study was to establish whether the DDDS system could be reliably applied to standardize antipsychotic dosages, focusing in high dose antipsychotic users.

Methods: The study was done in the Neuropsychiatric Hospital Dr. Alejandro Kom, Argentina. Data was extracted from clinical records on a census day 14th december 2009. The relationship between antipsychotic doses expressed as DDDs, CPZEs and percentages of the British National Formulary (BNF) maximum recommended daily dose investigated by calculating Spearman’s rank correlation coefficients. It was approved by an Independent Ethic Committee.

Results: The study sample were all of the 167 inpatients with schizophrenia receiving > 1000 mg CPZEs. Relationship between antipsychotic daily doses expressed as multiples of DDDs and CPZEs revealed a significant correlation (Spearman’s r = 0.983, P < 0.001). Similarly, the relationship between antipsychotic daily doses expressed as multiples of DDDs and percentages of the BNF maximum recommended daily dose revealed a significant correlation (Spearman’s r = 0.920, P < 0.001). We also analyzed both relationships in the 239 schizophrenic inpatients with low and medium antipsychotic doses showing similar significant positive correlations.

Conclusion: In conclusion, this study found that the DDD system is a reliable tool to standardize antipsychotic dosages even in the sub-population on high dose regimens.


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Objective: The aim was to identify changes in prescription patterns for patients with chronic hospitalization between two different periods in terms of availability of psychotropics, 1995 when clozapine was only available in Argentina and 2009 when clozapine was available in the wider range of these drugs.

Methods: The study was performed at the Alejandro Kom Hospital, Argentina. All inpatients in the chronic rehabilitation wards were included on both census days 13–06–1995 and 14–12–2009. Data was extracted from clinical records. The study was approved by an Independent Ethics Committee.

Results: The total number of inpatients dropped from 1048 to 648 between 1995 and 2009. Mean age increased from de 52.9 to 58 years
and male population grew up from 44.2% to 57.2%. The most prevalent diagnoses were Schizophrenia and Mental Retardation with 45% and 28% respectively in 1995, and 40% and 31% in 2009. The length of hospital stay was above 20 years in almost 30% of the patients in both census. The mean antipsychotic dose was similar in both periods, 600 mg chlorpromazine equivalents. The proportion in each census of schizophrenic (89% and 93%) and mental retardation patients (79% and 80%) receiving antipsychotic agents, was preserved. The rate of antipsychotic polypharmacy dropped. However, in both periods 53% of the patients with schizophrenia were prescribed 3 or 4 psychotropic agents simultaneously. Haloperidol was the most frequently antipsychotic used in both samples, and was prescribed to over 30% of the inpatients. The rate of patients with general clinical medications was higher in 2009 than 1995 (37.1% and 27.1% respectively).

Conclusion: In conclusion, there is an aging of the population of inpatients and a reversion in the gender distribution with a greater proportion of males in 2009. There are no significant changes in the overall prescription patterns despite the availability of different atypical antipsychotics in 2009 census.

Epidemiology of antipsychotic-induced hyperpolactinemia in psychiatric in-patients

Objective: To evaluate prevalence of antipsychotic-induced hyperpolactinemia (AHP) in psychiatric in-patients.

Methods: Cross-sectional study in 143 psychiatric in-patients (F/M = 65:78) treated with antipsychotics, mostly for schizophrenia (93%). The patients were screened for serum prolactin and macroprolactin levels as shown by median [1, 3 quartile]. Odds ratios (OR) for AHP with various antipsychotics were calculated, compared to AHP with haloperidol.

Results: Overall AHP prevalence was 57.0% (F: 72.0%; M: 43.6%). Macroprolactin was found in one patient only (2.0%). Prolactin levels inversely correlated with duration of mental disorder in women (r = -0.3, p = 0.02), but not in men. AHP prevalence in women with disease duration of <9 yrs was higher (85%) than in women with disease duration of >9 yrs (60%, p = 0.02). AHP prevalence in men of 19–34 yrs was higher (57%) than in men of 35–45 yrs (28%, p = 0.01). In order of OR for AHP, antipsychotics ranged as follows: 1, risperidone (OR = 12.5); 2, amisulpride (OR = 1.2); 3, olanzapine (OR = 2.2); 4, thioridazine (OR = 1.4); 5, chlorpromazine (OR = 1.2); 6, clozapine (OR = 1.1); 7, trifluoperazine (OR = 1.0); 8, fluphenazine, zuclopenthixol, perizacine (OR = 0.9 each); 9, chloroprothixene (OR = 0.8); 10, perphenazine (OR = 0.6); 11, quetiapine and aripiprazole (OR = 0.5 each). With risperidone, AHP was most probable both in men and women (OR = 10.3 and 3, respectively). Besides, in men, AHP was predominantly associated with olanzapine and olanzapine (OR = 5.7 each), in women, with sertraline and sulpiride (OR = 1.4 each). Conclusions: AHP in psychiatric in-patients is more than 1.5-fold prevalent than that diagnosed by referral (39%). In patients with AHP, measurement of macroprolactin is unnecessary. Men at risk for AHP belong to a younger age group, women at risk have shorter duration of mental disorder. The results cannot be fully explained by preferential use of atypical antipsychotics in the respective age and/or disease duration groups.

Thyrotoxicosis presenting with capgras delusion-a case report

Objective: Psychiatric manifestations of hyperthyroidism are usually anxiety and depression. Psychosis is rare and affects around 1%. Methods: Single case report.

Results: We present a 54 year old lady with hyperthyroidism who presented with psychosis as well as Capgras delusions. The symptoms resolved with correction of her hyperthyroid status and low 

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P-01-010

P-01-013

Cost minimization analysis comparing paliperidone palmitate with risperidone long-acting injectable in Spain

Objective: Estimate the savings produced by the use of Paliperidone Palmitate (PP) instead of Risperidone Long-Acting Injectable (RLAI) when treating schizophrenia patients, from the perspective of the Spanish National Health System.

Methods: The cost-minimization analysis used in the SMC (Scottish Medicine Consortium) evaluation was adapted for the treatment of patients with schizophrenia in Spain. Only direct costs were included: (1) medication costs (including oral antipsychotic drug supplementation cost) and (2) cost of administration in the community. Two different time horizons were used: 1 year (to compare initiation treatment) and 2 years (to compare maintenance treatment). The following assumptions were used for the base-case: (1) 50% of the patients initiate treatment in hospital and 50% in community; (2) 50% of patients initiate treatment from a long-acting injectable and 50% from an oral antipsychotic; (3) no reduction in the length of stay.

Results: PP use could save €648 per patient during the first year of treatment compared to RLAI. From the second year the saving could be €606 per patient/year also in favour of PP. These savings are mainly due to (1) lower drug cost of PP vs. RLAI in the community setting, (2) fewer visits to Community nurses for drug administration. Sensitivity analyses were done for the main parameters of the model and confirmed the robustness of the results, even in the most unfavourable scenarios: if 100% of the patients (1) initiate treatment in hospital the savings could be €628 per patient/year, (2) initiate treatment from an oral antipsychotic the savings could be €418 per patient/year. If PP could reduce the length of stay by approximately one third, as some studies indicate (SMC, Crivera), the savings could be €1,707 per patient/year.

Conclusion: To treat patients with PP instead of RLAI could be a cost-saving strategy for the Spanish National Health System.

Policy of full disclosure: This study was supported by Janssen.

Incidence and time course of extrapyramidal symptoms: A comparison of oral and long-acting injectable paliperidone randomized controlled studies

Objective: To compare incidence and time course of extrapyramidal symptoms-related (EPS) adverse events (AEs) between oral and long-acting injectable (LAI) paliperidone palmitate.

Methods: Analysis included pooled data (safety analysis set; n = 2256 for non-placebo treated patients) from randomized, double-blind and controlled paliperidone studies (3 oral [6-wks each]; 4 LAI [13-wks each]), and assessed comparable doses (oral: 3–15 mg; LAI: 25–150 mg eq [US doses 39–234 mg] intramuscularly). We summarized incidence rates and time of onset for EPS-related AEs, categorized by MedDRA EPS group terms as tremor, dystonia, hyperkinesia, parkinsonism, and dyskinesia. Mean values over time for AIMS (Abnormal Involuntary Movement Scale; dyskinesia), BARS (Barnes Akathisia Rating Scale; akathisia) and SAS (Simpson Angus Rating Scale; parkinsonism) were graphed.

Results: Mean reductions (SD) from baseline to endpoint in EPS scores were larger for LAI (AIMS: –0.10 [0.27]; BARS: –0.09 [0.16]; SAS: –0.04 [0.20] vs. oral studies (AIMS: –0.09 [0.32]; BARS: –0.03 [0.24]; SAS: 0.0 [0.23]). These differences favored LAI for BARS (P = 0.023) and SAS (P < 0.0001) but not AIMS (P = 0.49). Anti-cholinergic use (to treat EPS) was lower in LAI (12%) vs. oral studies (17%). Incidence for all categories of spontaneously reported EPS-related AEs was highest in the first 8 treatment days though generally lower for LAI than oral. Mean values for EPS scale scores were comparable (LAI and oral) without evidence of a dose response; scores increased between days 8–15 in LAI, but not oral studies.
P-01. Antipsychotics

Conclusion: Incidence of spontaneously reported EPS-related AEs was similar following approximately 90 days exposure with LAI and 40 days of oral paliperidone, at comparable doses.

Policy of full disclosure: All authors are full-time employees of Johnson & Johnson.

P-01-014 Clinical and sociodemographic characteristics of 140 male patients treated with long-acting risperidone during period of 4 years

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Objective: Risperidone long-acting injection is momentarily only long-acting second generation antipsychotic reimbursed in Croatia and it is registered for treatment of positive and negative symptoms of schizophrenia. Risperidone long-acting injection (RLAI) has been shown to improve clinical parameters, to decrease relapse rate and increase adherence in patients suffering from psychotic disorders.

Objective of this poster is to describe demographic and clinical features of acute psychiatric ward male patients, who were in everyday practice clinically estimated as suitable for risperidone long-acting injection treatment.

Methods: Research included all patients treated with risperidone long-acting injection, in inpatient and outpatient setting of acute male ward of Psychiatric Hospital “Sveti Ivan” in Zagreb, Croatia, over time period of 4 years. Patients have been diagnosed by criteria of International Classification of Diseases (ICD), 10th revision. Data were collected by computerized search of digitalized medical records of Psychiatric Hospital “Sveti Ivan”.

Results: Research sample included 140 male patients, in age range from 21 to 70 years. Results will be available next month and they will describe and show patients family status, education, place and conditions of living. They also show diagnoses, earlier antipsychotic treatment clinically estimated as suitable for risperidone long-acting injection treatment.

Conclusion: Poster data represent overview of our clinical experience with risperidone long-acting injection in naturalistic setting of an acute male ward in psychiatric hospital, over period of 4 years. Presented data describe demographic and clinical features of patients who were considered to be suitable for risperidone long-acting injection treatment and who were expected to gain benefit from it.

P-01-015 Effective pharmaceutical care by pharmacists in psychiatric medication therapy

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Objective: Evaluation in the pharmaceutical care by pharmacists on physician’s prescriptions for mental illness.

Methods: Design- Seventeen inpatients with schizophrenia who are given polypharmacy and/or excessive dose of antipsychotics are described. Interventions to correct medication-related problems in these patients are described. -Setting: Inpatients psychiatry service in Sawa hospital in Japan.-Patients: Subjects are inpatients with chronic antipsychotics therapy. Average age is 49.2 years (SD = 15.0), n = 17 and duration of schizophrenia is 26.3 years (SD = 13.5, n = 17).

Pharmacists monitored the prescriptions and the patient’s outcomes. If the results end up failing, pharmacists intervene in them actively.

-Interventions: We performed to optimize and/or simplify a formula in subjects who take polypharmacy and/or excessive dose of antipsychotics and to monitor side effects.

Results: Of the 14 patients, the number of antipsychotics (from 3.1 (SD = 1.2) to 1.2 (SD = 0.4) medications) and dose (from 1775.8 mg (SD = 744.8) to 594.8 mg (SD = 320.4) as chlorpromazine equivalent), were reduced and led to monotherapy in 12 patients. Reducing the dose of antipsychotics is attributed to decreasing the side effects as well as improving psychotic symptoms.

Conclusion: In the pharmaceutical care, medication-related problems are prevalent in psychiatric patient, contributing to polypharmacy and/or excessive dose. In this clinical practice, interventions by pharmacists on physician’s prescriptions are performed. Thereby reducing polypharmacy can lead to decreasing the side effects as well as improving psychotic symptoms.

P-01-016 Psychopharmacology and psychopathology of dopaminergic system

Y. Hayashi. University of Kochi, Kochi City, Japan

Objective: It is well known that psychotrophic agents, which block the dopaminergic system, show remarkable effects in schizophrenia especially in those cases with positive symptom. Moreover, the equivalent amount of psychotropic agents actually works extremely well in dissociative identity disorder (multiple personality disorder) as well. There is also a certain amount of medical literature stating that anti-dopaminergic psychotropic agents are effective in the treatment of pathological gambling (compulsive gambling).

Methods: I experienced two cases of dissociative (conversion) disorders treated with haloperidol effectively. I introduce it in detail and consider their pharmacological/biologic bases and psychopathological bases as well as schizophrenia.

Results: They can be said that the development of schizophrenia, dissociative identity disorder (multiple personality disorder), and pathological gambling (compulsive gambling) somehow involves the dopaminergic system.

Conclusion: If so, what is the psychopathological feature common to these pathologies which involve the dopaminergic system in their development? The objective of this article is to start discussion of the psychopharmacology (psychobiology) of the dopaminergic system from this point. Schizophrenia.

P-01-017 Dose of atypical antipsychotic drugs and cognitive impairments in schizophrenia patients: Aripiprazole has different cognitive profile from other atypical antipsychotics?

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Objective: We investigated the effects of the atypical antipsychotics risperidone, olanzapine, and aripiprazole on cognitive functions in Japanese patients with schizophrenia from the view point of dosing schedule.

Methods: We performed a cross-sectional survey. Neurocognitive functions were evaluated using the Brief Assessment of Cognition in Schizophrenia, Japaneselanguage version (BACS-J) in 101 schizophrenia patients who were maintained with the same dose of one of the three above-named antipsychotics for at least 3 months.

Results: The BACS-J composite score was significantly correlated with the dosage of risperidone and olanzapine. On the other hand, no correlation was found between the BACS-J composite score and the dosage of aripiprazole. Moreover, the primary scores of verbal learning, motor function and attention and processing speed were significantly negative correlated with the dose of risperidone. The scores of verbal learning and motor function were also significantly negative correlated with the dose of olanzapine. No correlation was found between any scores of the BACS-J and the dose of aripiprazole.

Conclusion: Aripiprazole had a different pattern of relationship between doses and cognitive impairments, which might be due to its unique pharmacological profile.

P-01-018 Dopamine D2 receptor occupancy with risperidone long-acting injectable during maintenance treatment in schizophrenia: A cross-sectional study

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Objective: While 65~80% occupancy of dopamine D2 receptors with antipsychotics has been proposed to achieve optimal therapeutic response during acute treatment of schizophrenia, it remains unclear as to whether it is also necessary to maintain D2 receptor occupancy within this “safe” window for ongoing maintenance treatment. The data are especially scarce for long-acting antipsychotic formulations.

Methods: Clinically stable patients with schizophrenia (DSM-IV) receiving a stable dose of Risperidone Long-acting Injectable (RLAI)
as antipsychotic monotherapy for at least three months and free of any psychiatric hospitalization over the past six months were included. Dopamine D2 receptor occupancy levels at trough were estimated from plasma concentrations of risperidone plus 9-hydroxyrisperidone immediately before the intramuscular injection of RLAI, using a one-site binding model derived from our previous positron emission tomography data.

**Results:** 36 patients were included in this study (mean ± SD age, 49.3 ± 14.0 years; mean ± SD dose and interval of injections, 38.2 ± 11.6 mg and 16.3 ± 14.0 days, respectively). Mean ± SD D2 receptor occupancy was 62.1 ± 13.4%; 52.8% of the subjects (N = 19) did not demonstrate an occupancy of ≥ 65%. On the other hand, 13.9% (N = 5) showed a D2 occupancy as high as over 80% at the estimated trough.

**Conclusion:** More than half of patients on RLAI maintained clinical stability without achieving continuous blockade of dopamine D2 receptors > 65% in real-world clinical settings. Results suggest that sustained dopamine D2 receptor occupancy levels of ≥ 65% may not be necessary for maintenance treatment with RLAI in schizophrenia.

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**P-01-019** Paliperidone in the treatment of hebephrenic type of schizophrenia

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**Objective:** Hebephrenic Schizophrenia is the type of the schizophrenia disorders range with the worst prognosis, given that it is related to disorganized behavior and residual symptoms, despite the relative absence of delirious ideas and delusions. Paliperidone (9-OH Risperidone), a metabolite of risperidone, blocks D2 Dopamine-receptors and 5HT-2A Serotonin receptors. The aim of the study is to elevate the effectiveness of Paliperidone for the treatment of Hebephrenia.

**Methods:** 20 patients (n = 20), 12 male and 8 female were studied in the inpatient facility and the outpatient setting of the Psychiatric Department of “Konstantopouleio” General Hospital, Nea Ionia, during the years 2009 and 2011. All patients received Paliperidone, in monotherapy, at a dose of 9–12 mg. The above patients were given the PANSS (Positive and Negative Symptoms in Schizophrenia), CGI-S (Clinical Global Impression of Severity), and QOL (Quality of Life) Scales before commencing treatment with Paliperidone, and again after 30 and 45 days of Paliperidone reception commencement. The age range of the patient sample was 18–31 years.

**Results:** 16 patients (85%) out of 20 patients (n = 20), PANSS scoring reduced. 10 out of 16 patients (n = 16) were male and 6 female. On the remaining 4 patients (15%), PANSS scores remained unchanged after 30 and 45 days of treatment. This effect urged the change of medication, or the addition of different antipsychotic medication. On the 16 patients above, CGI-S was reduced from 5 to 3.1, while Qol Scale scores also improved. Of those patients that interrupted treatment and showed adverse effects, 2 women showed gatalthorrougha with an increase of prolactin, and 2 men showed severe insomnia and EPS. None of the 20 patients given Paliperidone treatment showed any cognitive deficits.

**Conclusion:** Paliperidone is known to be a safe and effective medication for the treatment of Hebephrenia. The release of long-action Paliperidone may also prove an effective treatment for this resistive form of schizophrenia.

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**P-01-020** Psychopharmacological treatment of cycloid psychosis

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**Objective:** INTRODUCTION: The concept of cycloid psychosis, pertains to particular types of acute, episodic, polymorphic psychotic disorders, which are, frequently, diagnosed by the formal diagnostic systems as either brief psychotic disorder, schizophreniform disorder or psychotic disorder not otherwise specified. Three overlapping cycloid subtypes (anxiety-happiness psychosis, confusion psychosis, and motility psychosis) have been described, representing a valid clinical construct that can be easily differentiated from the boundary disorders on clinical grounds. The favourable prognosis of this acute psychotic disorder in the long-term, makes it necessary to emphasize in the importance of the accurate diagnosis and the appropriate therapeutic approach. **OBJECTIVES:** To review in the bibliographic literature the psychopharmacological treatment of the cycloid psychosis and present a case report that exemplifies its clinical features.

**Methods:** A bibliographic search is made in PUBMED and CSIC database including the terms cycloid psychosis, looking for all the literature that contains scientific evidence about its pharmacological treatment. A case report is attached.

**Results:** No controlled studies of cycloid psychosis treatment have been conducted to date; this being mainly due to the fact that the disorder remains largely unrecognized in the formal diagnostic systems. Data on treatment is based on clinical experience, uncontrolled studies, and anecdotal case reports. – Controversy in the use of pharmacological treatment in the acute episode and as a maintenance therapy. – Antipsychotics seem to be effective in aborting the episode, as we could see in the case report presented, but their potential to reduce relapse rates remains unclear. – Other treatments described: Electroconvulsive therapy, benzodiazepines, lithium and estradiol substitution.

**Conclusion:** The treatment with low-doses of atypical antipsychotics is a good alternative in the acute treatment of cycloid psychosis. – Future studies on the psychopharmacological treatment of this specific group of patients would be useful to ensure the appropriate therapeutic approach.

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**P-01-021** Simulation of dopamine D2 receptor occupancy by aripiprazole in steady state: Based on PK-PD modeling

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**Objective:** Receptor occupancy study has been performed to evaluate pharmacokinetic profiles in antipsychotic drug development. In particular, dopamine D2 receptor occupancy is a meaningful biomarker in that it reflects the antipsychotic action at the target site in the brain and predicts both the clinical response to antipsychotic drugs and the emergence of drug side effects. The importance of measuring dopamine D2 receptor occupancy by a novel antipsychotic drug is further emphasized by studies showing wide discrepancy between the time courses of drug concentration in plasma and receptor occupancy in the brain. While these findings highlight the value of measuring receptor occupancy in dose-finding study, a challenge is the impossibility of obtaining as many receptor occupancy data as would be necessary to design clinical trials with various dosing strategies. This raises the necessity of in-silico simulation of dopamine receptor occupancy by antipsychotic drugs.

**Methods:** We previously reported a novel methodology using pharmacokinetic-pharmacodynamic (PK-PD) modeling for the concentration-occupancy relationship analysis and estimated parameters for the PK-PD model after single administration of aripiprazole (J Cereb Blood Flow Metab. 2011 Dec 21. doi: 10.1038/jcbfm.2011.180). Based on the parameter estimates from the PK-PD model, we simulated dopamine D2 receptor occupancy by aripiprazole in steady state.

**Results:** In the case of once-a-day dosing schedule, the simulation shows that dopamine D2 receptors would be almost fully occupied in steady state even with 10mg of aripiprazole. In addition, the fluctuation index (=(maximal level-tough level)/trough level) in steady state was lower than 5% in occupancy while higher than 100% in plasma concentration. These findings suggest that aripiprazole is likely to be given with higher dose and shorter interval than is required for the treatment of schizophrenia in terms of receptor occupancy.

**Conclusion:** This study shows in-silico simulation based on the PK-PD modeling can be useful for exploring appropriate doses for antipsychotic drugs.
P-01. Antipsychotics

**P-01-022** Association of antipsychotic-induced akathisia with dopamine D2/3 receptor occupancy in ventral striatum: A high-resolution PET study with [11C]raclopride

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**Objective:** The neurobiological basis of akathisia is not well understood, although the strong affective component suggests that it is of a central origin. The authors examined the relationship between antipsychotic-induced akathisia and dopamine D2/3 receptor occupancy in striatal subdivisions using high-resolution positron emission tomography (HRRT) with [11C]raclopride to better understand its underlying neurochemical mechanism.

**Methods:** Twenty-one schizophrenia patients receiving stable doses of antipsychotics and 24 age- and gender-matched normal controls completed 3-Tesla magnetic resonance imaging and HRRT scans with [11C]raclopride in order to measure D2/3 receptor binding potential (BPND) in the striatum. The D2/3 receptor BPND was obtained using Logan graphical analysis with reference region input and receptor occupancy was calculated as the percentage reduction of receptor BPND with drug treatment relative to baseline. The data obtained from age- and gender-matched normal controls were used as an estimate of the patients’ baseline, as previously proposed. Antipsychotic-induced akathisia was measured with the Liverpool University Neuroleptic Side-Effect Rating Scale. The striatum was divided into 5 anatomic regions of interests (ROIs), including the ventral striatum (VST), the pre-commissural dorsal caudate (preDCA), the pre-commissural dorsal putamen (preDPU), the post-commissural caudate (postCA), and the post-commissural putamen (postPU). Pearson’s bivariate product-moment correlations were calculated between akathisia score and D2/3 receptor occupancy in subregions of the striatum. The strict level of significance for the analysis of 5 ROIs was adjusted as p < 0.009 using Bonferroni correction.

**Results:** The analysis revealed that akathisia score had significant positive associations with D2/3 occupancy only in the VST (r = 0.56, p = 0.009).

**Conclusion:** These results suggest that akathisia is significantly associated with D2/3 receptor blockade in the limbic subdivision of the striatum, i.e., VST, which plays a crucial role in the regulation of affect and motivation.

**Policy of full disclosure:** This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant (No. 2010-0022796).

**P-01-023** Paliperidone ER versus risperidone for neurocognitive function in patients with schizophrenia: A randomized, open-label, controlled trial

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**Objective:** The neurobiological basis of akathisia is not well understood, although the strong affective component suggests that it is of a central origin. The authors examined the relationship between antipsychotic-induced akathisia and dopamine D2/3 receptor occupancy in striatal subdivisions using high-resolution positron emission tomography (HRRT) with [11C]raclopride to better understand its underlying neurochemical mechanism.

**Methods:** Twenty-one schizophrenia patients receiving stable doses of antipsychotics and 24 age- and gender-matched normal controls completed 3-Tesla magnetic resonance imaging and HRRT scans with [11C]raclopride in order to measure D2/3 receptor binding potential (BPND) in the striatum. The D2/3 receptor BPND was obtained using Logan graphical analysis with reference region input and receptor occupancy was calculated as the percentage reduction of receptor BPND with drug treatment relative to baseline. The data obtained from age- and gender-matched normal controls were used as an estimate of the patients’ baseline, as previously proposed. Antipsychotic-induced akathisia was measured with the Liverpool University Neuroleptic Side-Effect Rating Scale. The striatum was divided into 5 anatomic regions of interests (ROIs), including the ventral striatum (VST), the pre-commissural dorsal caudate (preDCA), the pre-commissural dorsal putamen (preDPU), the post-commissural caudate (postCA), and the post-commissural putamen (postPU). Pearson’s bivariate product-moment correlations were calculated between akathisia score and D2/3 receptor occupancy in subregions of the striatum. The strict level of significance for the analysis of 5 ROIs was adjusted as p < 0.009 using Bonferroni correction.

**Results:** The analysis revealed that akathisia score had significant positive associations with D2/3 occupancy only in the VST (r = 0.56, p = 0.009).

**Conclusion:** These results suggest that akathisia score had significant positive associations with D2/3 occupancy only in the VST (r = 0.56, p = 0.009).

**Policy of full disclosure:** This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant (No. 2010-0022796).

**P-01-024** The effect of paliperidone ER on subjective well-being and attitudes toward medication among patients with schizophrenia

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**Objective:** This study aims to evaluate the subjective well-being and attitudes toward antipsychotic medication of patients with schizophrenia who had switched to paliperidone extended release (ER).

**Methods:** A total of 291 patients with schizophrenia treated with antipsychotics participated in this open-label, 24-week switching study. The primary outcome measures were the Subjective Well-Being Under Neuroleptic Treatment Scale-short version (SWN-K) and the Drug Attitude Inventory (DAI).

**Results:** Data from a total of 243 subjects who received the study medication and had at least one follow-up assessment without a major protocol violation were analyzed. Scores on the DAI and SWN-K showed significant improvement between baseline and end-point measurements beginning during the second week. Scores on the Kraviecka scale, all five subscales of the Clinical Global Impression-Schizophrenia scale, and the Personal and Social Performance scale were also significantly improved at the end point compared with the baseline. Scores on the DAI and total SWN-K scores were significantly improved in subjects who were previously treated with risperidone but not in those who were previously treated with other antipsychotics.

**Conclusion:** Paliperidone ER was effective for improving the subjective well-being and attitudes toward antipsychotic medication of patients with schizophrenia, particularly those who had been previously treated with risperidone.

**Policy of full disclosure:** This study was supported in part by an investigator-initiated grant from Janssen Korea Co. Ltd. Representatives of the company were allowed to comment on the report, but the final approval of content was retained by the investigators exclusively.

**P-01-025** Effectiveness of long-acting risperidone for patients with treatment refractory schizophrenia

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**Objective:** Up to 30-60% of patients with schizophrenia do not respond sufficiently to antipsychotics. Treatment-resistant Schizophrenia (TRS) can have several reasons, including early onset, nonadherence to oral medication regimens, and persistent negative symptoms known as deficit syndrome. Recently, dopamine supersensitivity psychosis (DSP) and tardive dyskinesia (TD), both of which
could be caused by inappropriate pharmacotherapy, as typified by excessive dosages of antipsychotics, have also been presumed relevant to TRS. Several lines of evidence suggest that both DSP and TD are closely linked to the supersensitivity of dopamine D2 receptors; this could be caused by a potent blockade of the receptors by antipsychotics. Several studies have reported that risperidone long-acting injection (RLAI) successfully reduced antipsychotic dosage and extrapyramidal symptoms, as well as relapse rate. Furthermore, some reports suggested greater improvement in the psychotic symptoms in RLAI compared to oral medication. We have therefore hypothesized that RLAI with narrower blood kinetics than oral medication could provide a continuous optimal blockade of dopamine D2 receptors, leading to the prevention and/or improvement of the supersensitivity state of the receptors.

Methods: Here we try to verify RLAI’s effectiveness in a TRS group, including patients with a background of DSP. This study, which is in progress as of January 2012, is a naturalistic, one-arm design with a 12-month observation period of a moderate sample size (N = 150).

Results: Of the 43 TRS patients with 6 months observational period following RLAI initiation, 25 (58%) were diagnosed as DSP following 6 months of RLAI treatment, 17 of these 25 DSP patients (68%) had responded to RLAI, whereas the 18 patients without a history of DSP showed insufficient responses, indicating that RLAI is exceedingly effective in patients with DSP.

Conclusion: Although this is only a progress report, the present results strongly suggest that RLAI could become an effective treatment strategy for TRS with DSP.

P-01-026 These data support results from recent studies that paliperidone ER is well tolerated and effective in patients previously unsuccessfully treated with other antipsychotics

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Objective: Paliperidone is a second generation antipsychotic medication approved for the treatment of schizophrenia. It is a useful option in the treatment of the acute symptoms of schizophrenia and may also be used in patients previously unsuccessfully treated with other antipsychotics. The aim of this work was to explore tolerability and treatment response of flexible doses of paliperidone ER (3, 6, 9, 12 mg/day) in adults suffering from resistant paranoid schizophrenia.

Methods: Four patients with resistant paranoid schizophrenia were included in this study. The patients were male, on the average 39.8 years old, diagnosed according to DSM-IV with schizophrenia from 12 mg/day to 5 mg and with the introduction of anticholinergic agents.

Results: Three patients completed the four month trial of paliperidone ER and one of them interrupted the medication (3mg/day) after one month because of the noncompliance. One patient started and finished the treatment with paliperidone XR 6mg/day, two patients started the treatment with 9mg/day, but during the last month they received 12mg/day for better improvement. The PANSS, CGI-S, AEs and PSP scales indicated that the treatment with paliperidone XR of three schizophrenic patients was effective and paliperidone did not produce adverse events. The treatment with this medication was noneffective only for one patient.

Conclusion: These data support results from recent studies that paliperidone ER is well tolerated and effective in patients previously unsuccessfully treated with other antipsychotics.

P-01-027 Novel D2/5-HT6/5-HT7 receptor antagonist with a broad antipsychotic activity

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Objective: 5-HT6 and 5-HT7 receptor antagonism has been associated with potential proconvulsive as well as antidepressant and anxiolytic activity. Therefore, introduction of strong functional antagonism of these receptors is considered beneficial for the profile of a modern antipsychotic drug. We designed and synthesized a novel series of aryssulfanamide derivatives being strong D2,5-HT6,5-HT7 receptor antagonists, without significant anticholinergic and antihistaminergic effects or hERG channel blockade and tested them in a series of in vivo models.

Methods: The following animal models were used: ● apomorphine (0.6 mg/kg) and dizocilpine (1.2 mg/kg) induced hyperlocomotion in mice ● DOI (2.5 mg/kg) induced head twitches in rats ● Conditioned avoidance response and passive avoidance in rats ● Prepulse inhibition deficit induced by amphetamine (6.0 mg/kg) ● Tail suspension test in mice ● Porsolt’s forced swim test in rats ● Four-plate test in mice ● Vogel’s conflict drinking test and elevated plus maze test in rats.

Results: Minimal effective doses of the best compound (in mg/kg) are as follows: apomorphine and dizocilpine induced hyperlocomotion – 2.5 and 1.25, apomorphine and dizocilpine induced stereotypies – 10 and 3, DOI induced head twitches – 1, conditioned avoidance response – 3, prepulse inhibition deficit induced by amphetamine – 30, tail suspension test – 0.156, Porsolt’s forced swim test – 0.3, four-plate test – 0.32, Vogel’s conflict drinking test and elevated plus maze test – 3 and 0.3. Not active in passive avoidance test up to 30 mg/g.

Conclusion: The most interesting compound displayed a wide antipsychotic activity in a broad range of mice and rat models. At the same time it proved to have no detrimental effect on cognition as well as to possess potentially beneficial influence on affective dimension of schizophrenia.

Policy of full disclosure: The studies were co-financed by Adamed Pharmaceuticals, Pienkow, Poland and National Centre for Research and Development, Warsaw, Poland grant no. KB/88/12655/IT1-C/ U/08.

P-01-028 Rabbit syndrome due to olanzapine

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Objective: There are very few case reports in the literature on rabbit syndrome due to olanzapine and other atypical antipsychotic agents. We describe a patient who developed this syndrome with olanzapine and it improved with reduction of dose and with introduction of anticholinergics (benzhexol).

Methods: 32 year old lady with learning disability and bipolar depression (Severe Depressive disorder with psychotic symptoms). She developed rabbit syndrome after the dose of olanzapine was increased to 15 mg. Symptoms improved after the reduction of dosage to 5 mg and with the introduction of anticholinergic agents.

Results: Patient is currently receiving Olanzapine 5 mg/day and Mirtazapine 30 mg/day and the extrapyramidal symptoms have abated.

Conclusion: This case adds on to the existing literature of rabbit syndrome secondary to use of atypical antipsychotic drugs.
P-01-029 Antipsychotic preferences for psychiatrists and their family members

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Objective: We aimed to evaluate which antipsychotic drugs psychiatrists would prefer for themselves, their partners and children in case of a mental illness.

Methods: The study was conducted among psychiatrists in Serbia and we have assessed 90 participants: 68 (75.6 %) psychiatrists and 22 (24.4 %) psychiatric trainees who were asked to complete the questionnaire about their drug selection in hypothetical situations of becoming ill with schizophrenia or these conditions occurring in their partners and children.

Results: In case of schizophrenia, majority of participants reported that they would take atypical antipsychotic and risperidone was the first choice made by most psychiatrists for themselves (51.1 %), their partners (55.8 %) or children (43.3 %), followed by clozapine (12.2 %), haloperidol (10.0 %) and olanzapine (10.0 %). The preferred doses were slightly lower than the recommended ones (Risperidone 2.8 mg, Clozapine 181.8 mg, Haloperidol 5 mg, Olanzapine 11.7 mg). All the preferences were similar, regardless the respondent was specialists in psychiatry or psychiatric trainee.

Conclusion: Most psychiatrists would take or administer atypical antipsychotics as the first choice for themselves, their partners or children. These preferences are mostly in accordance with current treatment guidelines, but there is still room to narrow the gap between guideline recommendations and psychiatrists’ medication choices in personally meaningful situations.

P-01-031 Dopamine D2 antagonist-induced striatal gene expression requires activation of mGlu5 receptors by cortical afferents

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Objective: Antipsychotic drugs are used to alleviate schizophrenia symptoms. Despite the fact that all antipsychotic drugs interact with dopamine D2 receptors, the exact mechanism that explains their activity still remains elusive. Here we explored the relationship between glutamate, adenosine and dopamine receptors in the modulation of the transcription factor Nur77 (NGF-B, NR4A1) in the striatum, an important brain structure involved in antipsychotic drug effects.

Methods: We performed eticlopride (ETI; D2 antagonist) treatments in transgenic mice with a genetic deletion of the postsynaptic dopamine D2L receptor isoform, as well as in rats bearing an isotonic acid-induced cortical lesion. Additionally, groups of mice receiving an acute treatment with MPEP (mGluR5 antagonist), SCH58261 (A2A antagonist), ETI or compound combinations have been investigated. Organotypic cultures of striatal slices exposed to these drugs were also performed.

Results: ETI was still able to strongly induced Nur77 mRNA levels in the striatum of D2L receptor knockout mice, while cortical lesions strongly attenuated ETI-induced Nur77 expression in the striatum. Systemic blockade of mGluR5 and A2A receptors strongly reduced ETI-induced Nur77 mRNA levels in the striatum, whereas MPEP or SCH58261 alone remained inactive. On the other hand, mGluR5 agonists can directly modulate Nur77 expression in striatal organotypic cultures. Furthermore, blockade of glutamate reuptake in organotypic striatal slices strongly activated Nur77 transcription that can be abolished by an mGluR5 antagonist. Interestingly, D2 agonists or antagonist cannot modulate Nur77 expression by themselves in the striatal slices.

Conclusion: These observations indicate that modulation of the transcription factor Nur77 in striatal cells following dopamine D2L antagonists (antipsychotic drugs) is mediated, at least in part, by an interaction of the drug with presynaptic dopamine D2S receptors located on corticostriatal afferents and subsequent activation of postsynaptic mGluR5/A2A receptors in striatal cells. JM holds a studentship from the Canadian Institute for Health Research (CIHR).

P-01-032 Role of the transcription factor NUR77 in haloperidol-induced hyperprolactinemia

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Objective: Antipsychotic drugs are used to treat schizophrenia symptoms. But, they are known to cause various motor and endocrine side effects and have a limited effectiveness. The main characteristic of antipsychotic drugs is to interact, and act as antagonists, with the dopamine D2 receptors. In lactotrope cells of the anterior pituitary, activation of D2 receptors inhibits prolactin (PRL) secretion and synthesis. Accordingly, antipsychotic drugs increase PRL transcription and induce hyperprolactinemia. However, the molecular mechanism leading to the hyperprolactinemia remains elusive. Previous works from our laboratory suggest that the transcription factor Nur77 (Nr4a1) is associated with motor side effects induced by antipsychotic drugs (Levesque and Rouillard, TINS, 2007).

Methods: In the present study, we measured pituitary Nur77 and PRL mRNA levels using quantitative RT-PCR assays, and serum PRL levels were evaluated by ELISA in wild type FHH and Nur77 knockout (-/-) rats (FHH-Nr4a1m1Mcwi, nonsense mutation Y130stop) treated with vehicle or haloperidol. Electrophoretic gel mobility shift assays (EMSA) were performed to identify transcription factor binding to the PRL promoter.

Results: We report that Nur77 is expressed in basal conditions in the anterior pituitary and that Nur77 mRNA levels are significantly up-regulated by haloperidol. Interestingly, in Nur77 knockout (-/-) rats, basal pituitary PRL mRNA levels are elevated, but haloperidol is unable to increase PRL transcription, as compared to their littermates. Consequently, haloperidol-induced serum PRL levels are strongly reduced in Nur77 (-/-) rats. In silico analysis reveals numerous putative Nur77 responsive elements (NBRE) in the PRL promoter and electrophoretic gel mobility shift assays (EMSA) indicate that Nur77 can bind to the PRL promoter.

Conclusion: Taken together, these results indicate that Nur77 regulates PRL transcription and secretion following the administration of a typical antipsychotic drug.

P-01-033 Regulating oligodendrocyte regeneration and development in vitro: A new feature of atypical antipsychotic drugs?

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Objective: Neuroimaging and microarray studies have indicated that oligodendrocyte and myelin abnormalities are important pathological changes of schizophrenia. Antipsychotic drugs (APDs) are effective in treatment of schizophrenia; but the underlying mechanism remains unknown. Our previous studies suggested that quetiapine, an atypical antipsychotic drug, promoted neural progenitor cells to differentiate into oligodendrocyte lineage cells and alleviated CPZ-induced demyelinating pathology. In this project, we further investigated the effect of different antipsychotic drugs on the oligodendrocyte in vitro.

Methods: A well established oligodendrocyte-lineage cell line, CG4 cells were used to test the effect of three antipsychotic drugs: haloperidol, quetiapine and olanzapine. Antipsychotics showed no effects on proliferation of CG4 cells evaluated by CCK-8 proliferation assay. However, all of the drugs promoted differentiation of CG4 cells into mature oligodendrocytes when it was evaluated by the expression of CNPase, a maker of mature oligodendrocyte. Further to investigate the mechanism of antipsychotic drugs, we found the expression of oligodendrocyte transcription factor 1 (olig1) and 2 (olig2) were distinctly regulated by the drugs.

Results: The expression of olig2 was up-regulated by the all the drugs tested and olig1 was only increased by quetiapine and olanzapine, but not by haloperidol. These data suggested that olig1 and olig2 may play a key role in the regulation process of APDs on oligoden- drocyte development and there may be some differences between the action of typical and atypical antipsychotics.

Conclusion: Our results indicate APDs have effects to promote the differentiation of CG4 oligodendrocyte cell line in vitro and oligoden- drocyte/myelin may be a novel target for APDs.
Policy of full disclosure: Dr. Xin-Min Li accepted research grant from AstraZeneca Canada and Pfizer Canada.

P-01-034 Preventing and treating olanzapine-induced obesity with betahistine: A chronic animal model study

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Objective: Olanzapine, an atypical antipsychotic drug, is widely prescribed to treat schizophrenia, but induces serious weight gain/obesity side-effects. Antipsychotic drugs antagonist affinity for histamine H1 receptors is the main indicator of weight gain side-effects. This study aimed to investigate whether chronic treatment with betahistine (H1 receptor agonist/H3 receptor antagonist) could prevent/treat olanzapine-induced weight gain at different stages of treatment.

Methods: Female Sprague-Dawley rats were administered under 5 conditions (n = 12): (1) Rats were treated with vehicle (control) during whole experimental period; (2) “Obesity treatment group”: 5 weeks olanzapine treatment (1 mg/kg, i.d.), followed by 6 weeks co-administration of olanzapine with betahistine (0.6 mg/kg, i.d.); (3) “Obesity prevention group”: 3.5 weeks olanzapine treatment, followed by 2.5 weeks withdrawn, then co-administration of olanzapine and betahistine (4.8 mg/kg, i.d.) was introduced; (4) Solitary olanzapine treatment following the same time course as Group 3; (5) Rats were treated solely with betahistine (4.8 mg/kg, i.d.) during weeks 7–11.

Results: Compared to controls, olanzapine treatment increased body weight (p < 0.001), food intake (p < 0.01), inguinal fat mass (p < 0.01) and liver weight (p < 0.01). On the other hand, the "obesity treatment group" had lower weight gain (p < 0.001), food intake and inguinal fat (p < 0.05) than the solitary olanzapine treatment group. The "Obesity prevention group" also showed significantly decreased weight gain (p < 0.05), compared to the olanzapine group.

Conclusion: This study revealed that chronic co-administration of olanzapine and betahistine is effective at reducing olanzapine-induced obesity side-effects. These results provide support for further clinical trials to improve the olanzapine-induced obesity side-effects using betahistine co-treatment.

P-01-035 Insulin resistance, obesity and metabolic syndrome in psychiatric patients

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Objective: The treatment with certain antipsychotics, antidepressants, stabilizers of mood, in patients with schizophrenia, unipolar or bipolar disorder, can contribute to produce dismetabolism and to configure a metabolic syndrome with a coronary and brain vascular risk. Nutritional, carbohydrate metabolic disorders such as functional hypoglycemia, resistance to insulin, hyperinsulinism, diabetes, obesity can accompany, induce, aggravate the development of neuropsychiatric alterations. The objective is to prevent obesity, insulin resistance, that are determinant factors in metabolic syndrome, therefore the goal of recovery needs to combine the concept of general medical health with that of the healthy mind. When there is hyper-insulinism it creates insulin resistance, obesity, there are more adipocytes, liberation of free fatty acids, adipokines, inflammatory cytokines, and these intervene in the metabolic disbalance producing a pro-atherogenic, prothrombotic state, endothelial disfunction, which are all present in the metabolic syndrome. Obesity is also associated with a state of inflammation and immune response characterized with elevation of reactive protein C, adipokines TNF alpha a mediator to insulin resistance.

Methods: We implemented a program with aerobic exercise, restriction of calories, refined sugars, flour, and a balanced diet with the addition of nutritional supplements, because food controls insulin, it can reduce oxidative stress, inflammation and prevent development of metabolic syndrome.

Results: We obtained a regulation in all parameters that were altered in the metabolic syndrome in the psychiatric patients and in ratio TGL/HDL, that is an indirect marker of the levels of inflammation and insulin.

Conclusion: We give importance to exercise and the nutritional factors that regulate insulin/glucagon axis, to prevent functional hypoglycemia, hyperinsulinism, insulin resistance obesity, diabetes, inflammation which conduce to metabolic syndrome. In patients with mental illness that are taking antipsychotics, antidepressants and stabilizers of mood it is necessary to elevate the metabolic monitoring in the care and in the management of cardiac and brain risk factors to prevent premature death.

P-01-036 Clozapine induces differentiation of human preadipocytes via the aryl hydrocarbon receptor

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Objective: Among the pleiotropic pharmacology of clozapine is the undesirable effect of preadipocyte differentiation, which can be antagonized by green tea extract (EGCG) in vitro. As this drug effect differs from fat cell hypertrophic changes seen under olanzapine, we hypothesize that an unshared molecular mechanism of clozapine should be responsible. The chemical structure of clozapine resembling a chlorinated polycyclic aromatic hydrocarbon led us to study the involvement of the aryl hydrocarbon receptor (AhR).

Methods: Human preadipocytes obtained as a by-product of abdominal plastic surgery were isolated and cultured in vitro. Cell differentiation was studied by histochemistry 14 days after the addition of hormones and clozapine vs. hormones and other neuroleptic compounds. EGCG and alpha-naphthoflavine (alpha-NF) were used as antagonists. AhR activity was studied by luciferase reporter gene assay and by RT-PCR of target gene CYPIA1.

Results: Unlike olanzapine and other atypical neuroleptics, clozapine addition significantly increased preadipocyte differentiation by up to 60%. This effect was fully antagonized by either EGCG or alpha-NF. Clozapine specifically increased both AhR promoter activity and transcription of target gene CYPIA1.

Conclusion: Our study indicates that clozapine induced preadipocyte differentiation is mediated by AhR activation. This mechanism may be unique to clozapine, as it differs from fat cell hypertrophy effected by olanzapine and other neuroleptic compounds. AhR mediated effects by clozapine may have further relevance at the CNS and stem cell level, and could possibly account for some components of its complex pharmacology.

P-01-037 Use off label of antipsychotic medication – a 6 month descriptive study of the antipsychotic use in the first visits in our center for mental health

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Objective: To evaluate the characteristics of the first 100 new patients and to determine the use of antipsychotic in our Center for Mental Health between July and December 2011 and to determine the characteristics of the patients that were prescribed the use of anti-psychotic.

Methods: Subjects: The population study were a hundred patients that were first time visited in the Center for Mental Health between July and December 2011. Procedure: This is a cross-sectional study – Independent variable were sex and age. Patients were diagnosed according to DSM-IV criteria of Unipolar disorder, Bipolar affective disorder /Psychotic disorders /Substance use disorder / or comorbidity among axis II.

Results: From the selected sample of 100 patients 40 were male and 60 were female. The 24 % were treated with antipsychotic in the first visit. The 86 % of the selected sample were diagnosed Unipolar Depression or/and Anxiety disorders and only 8 % of Psychotic disorder and 7 % of substances abuse disorder. The range of age in which more patients were treated with neuroleptics was between 17th and 35th years old (27.6 % of patient between these ages were treated with antipsychotic). The 37.5 % of the patients that were treated with
Antipsychotic had diagnosis of personality disorders. To be men aged between 17th–35th years old were the main variables associated to be prescribed the use of antipsychotic [IC95 % (24.8–55.2) p-value 0.002].

Conclusion: From our selected hundred patients visited from the first time in our Adults Center for Mental Health 24 were treated with antipsychotic in spite of the fact that only 6% of these patients were diagnosed of Psychotic disorder. The use of low-dose of typical anti-psychotics in the treatment of personality disorders are useful not only to improve symptoms of psychotic type (cognitive dysfunction, perceptual, anxiety and paranoid ideation) but also the depressive spirt, the impulsiveness and the anger.

P-01. Antipsychotics

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Objective: To analyse the prescription of clozapine in a sample of 37 patients admitted to the mental health rehabilitation unit.

Methods: This is a transversal study. All patients admitted for psychiatric rehabilitation treatment from the 01/01/2010 to the 31/12/2011 were included. Data about socio-demographical status, information about the admission and clinical situation were obtained. We then compared the patients who received treatment with clozapine with the ones who did not.

Results: The sample was composed by 37 patients (78.4% men; mean age: 36 + 10 years). The majority of them were single (89.2%). All of them were Spanish. Only the 5.4% of them were working and the most represented group (75%) were receiving a disability allowance. In the 70.27% of the cases schizophrenia was the diagnose motivating the admission. The 378% of all patients had a comorded substance use disorder. Within the 26 patients with the diagnose of schizophrenia, 9 (34.61%) did receive clozapine during the admission. We compared the two groups (clozapine group vs. non-clozapine group) and obtained the following results: there were no significant differences between the groups in terms of sex, civil state or working state. Instead, it seemed that in the clozapine group the patients were older, had a major number of previous hospital admissions, had a larger trajectory of their disease and had more often committed suicide attempts.

Conclusion: Patients requiring treatment with clozapine had a major number of hospital admissions and had more often committed suicide attempts, suggesting a more severe course of the disorder. They were older as the non-clozapine group. This last may be related with the fact that clozapine is delayed in its use among treatment-resistant patients [2]. It’s worth highlighting that only 3461% of the schizophrenic patients in the rehabilitation unit received clozapine. This could mean that clozapine is underprescribed.

P-01-039 How to conduct clinical bioequivalence trials with higher-dose quetiapine fumarate or pramipexole hydrochloride hydrate safely in healthy subjects

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Objective: The aims were (1) to determine the maximum tolerated doses (MTD) of quetiapine and pramipexole when given to healthy Japanese male subjects in gradually increasing single doses and (2) to evaluate the availability of this exploratory method for further bioequivalence trials.

Methods: This study was approved by Kyushu Clinical Pharmacology Research Clinic Institutional Review Board, and all subjects gave their written informed consent. In the quetiapine group, 18 participants received 25 mg in the first stage. In the second stage, they were divided into three groups of six subjects each and designated to receive either 50 mg, 75 mg or 100 mg depending on the severity of the symptoms in the first stage. In the pramipexole group, 18 participants received 0.125 mg and then received either 0.25 mg, 0.375 mg, or 0.5 mg in the same manner as the quetiapine group.

Results: In the group receiving 75 mg of quetiapine, three mild adverse events (AEs) and seven moderate AEs (e.g., nightmare and syncope) were reported from all six subjects. In the group receiving 0.5 mg of pramipexole, three mild and five moderate AEs were reported from five subjects. In both groups, although no severe or serious AEs were reported, we judged that doses equal to or greater than 75 mg and 0.5 mg of quetiapine and pramipexole, respectively, were not tolerated well in healthy subjects. The maximum concentration of the drug in each subject was not always correlated with severity of the AEs.

Conclusion: Doses of quetiapine 75 mg and higher and doses of pramipexole 0.5 mg and higher were not tolerated well in healthy subjects. Determining the MTD of psychotropic agents in bioequivalence trials was safely achieved by giving the agents gradually increasing doses based on severity of symptoms in the first stage and by carefully observing subjects in small groups (n = 6).

P-01-040 Antipsychotic-like properties of zolpidem in the rat

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Objective: Preclinical and clinical studies support the assumption that positive GABA-A receptor modulators may possess antipsychotic properties. Our preliminary research showed that selective alpha1 GABA-A receptor agonist, zolpidem, but not benzodiazepines, can produce neuroleptic-like cataleptic-like responses in the rat. The aim of the present study was to investigate a potential antipsychotic profile of zolpidem in a series of preclinical models of psychosis.

Methods: All experiments were conducted on drug-naïve male Wistar rats. Zolpidem and comparator drugs (diazepam, midazolam, zaleplone, haloperidol, olanzapine) were tested in several preclinical models: hyperlocomotion induced by amphetamine (1.0 mg/kg) and dizocline (0.3 mg/kg), apomorphine (0.6 mg/kg)-induced stereotypes, dioxcline (1.2 mg/kg)-induced stereotypes, DOI (2.5 mg/kg)-induced head twitches, pre-pulse inhibition (PPI) deficits induced by amphetamine (6.0 mg/kg) or dizocline (0.6 mg/kg), conditioned avoidance response (CAR).

Results: Low doses of zolpidem (0.3–3.0 mg/kg, i.p.) inhibited hyperlocomotion induced by amphetamine or dizocline. Higher doses of the drug (3.0–10.0 mg/kg) reversed apomorphine- and dizocline-induced stereotypes as well as DOI-induced head twitches. Zolpidem (3.0–10.0 mg/kg) also reversed PPI deficits produced by amphetamine and inhibited CAR.

Conclusion: Zolpidem produced dose-dependent antipsychotic effects in several preclinical models of psychosis. Its efficacy was comparable to haloperidol and olanzapine and was superior to less selective GABA-A positive modulators (diazepam, midazolam, zaleplone).

P-01-041 One-year open-label study of the cognitive efficacy of blonanserin in antipsychotic-naive first-episode schizophrenia

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Objective: Cognitive impairment, a core feature of schizophrenia, has been established as an important symptom domain associated with long-term outcome. The purpose of this study was to evaluate the long-term effects of blonanserin, a novel second-generation antipsychotic drug developed in Japan in 2008, on cognitive function in first-episode schizophrenia.

Methods: Twenty-four antipsychotic-naive patients with first-episode schizophrenia participated in the study. Blonanserin (2–24 mg/day) was given in an open label design for one year. The Brief Assessment of Cognition in Schizophrenia (BACS-J) was administered as the primary outcome measure at baseline, 24, and 52 weeks. Clinical evaluation included the Positive and Negative Syndrome Scale (PANSS), the Schizophrenia Quality of Life Scale (S-QLS-J), and the Clinical Global Impression-Severity of Illness Scale (CGI-S). This study protocol was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.
Results: Thirty patients (6 males and 7 females; mean age, 28.2 ± 5.6 years) completed the study. The mean daily dose of bionanserin was 4.2 ± 3.0 mg/day at 52 weeks. One patient used anticholinergics (biperiden dose: 2 mg/day) at endpoint. At the 52-week endpoint, significant improvements were shown in letter fluency, executive function, and composite score, as measured by the BACS-I compared with baseline (p < 0.05). In addition, the psychosocial condition score (p < 0.01) and motivation/energy score (p < 0.05) on the SQUI-S, and all items on the PANS-S (p < 0.01) and CGI-I (p < 0.01) significantly improved after 52 weeks treatment.

Conclusion: These results suggest that bionanserin has a beneficial effect on some types of cognitive function associated with prefrontal cortical function in patients with antipsychotic-naïve first-episode schizophrenia. However, the conclusions that can be drawn are limited by the small sample size and the lack of control groups to exclude the possibility of retest effects.

Policy of full disclosure: Dr. Miyamoto has served as a consultant for Dainippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with this study.

P-01-042 Caregiver burden of patients with psychotic disorders
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Objective: To evaluate the prevalence of caregiver burden in psychotic outpatients who are treated in Mental Health Clinics and to know clinical features associated with the presence of burden.

Methods: Cross-sectional study conducted in naturalistic type of Mental Health Outpatient Clinics in Balearic Islands (Spain) belong to hospitals in Majorca (Hospital de Manacor and Hospital son Llatter) and Menorca (Hospital Mateu Orfila). We used the Zarit Scale for assessing caregiver burden.

Results: We obtained a final sample of 77 caregivers. The mean score on the Zarit scale was 39 (+17.11) Patients with psychotic disorders assessed were male (62%) with a mean age of 43 years (+14.4) with a diagnosis of more than 5 years evolution (72.7%) schizophrenia was the most frequent diagnosis (55%) and risperidone long-acting injection (RLAI) the most widely used antipsychotic (55.8%).

Conclusion: 1. The patients on maintenance monotherapy with RLAI showed better adherence rates and more insight, evaluated by their psychiatrists. 2. 78% of patients receiving antipsychotics mediation injections were satisfied with the treatment. 3. Patients with RLAI given in deltoid were satisfied in 65.7%.

P-01-043 Dopamine D2 receptor occupancy and remission in schizophrenia: Analysis of the catie data
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Objective: In treating schizophrenia, it has been established that 65–80% occupancy of dopamine D2 receptors optimizes therapeutic efficacy while minimizing risks of extrapyramidal symptoms and cognitive impairment. However, it is unclear as to whether it is necessary to keep D2 receptor occupancy within this therapeutic window to maintain clinical response.

Methods: The dataset from phase 1 of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial was used. Patients receiving risperidone, olanzapine, or ziprasidone were included in the present analysis if they fulfilled the following definition of remission: a score of <3 on 8 specific Positive and Negative Syndrome Scale (PANSS) items (i.e. P1, P2, P3, N1, N4, N6, G5, and G9) at baseline and months 1, 2, and 6. These criteria follow the definition proposed by Andreasen et al., (2005). Peak and trough D2 receptor occupancy levels at month 6 and endpoint were estimated from plasma antipsychotic concentrations using population pharmacokinetic analysis and our D2 prediction model.

Results: 30 subjects (15 men; mean ± SD age = 41.5 ± 11.8 years; risperidone, N = 12, olanzapine, N = 12, and ziprasidone N = 6; mean ± SD duration of follow-up 495.5 ± 78.1 days) fulfilled inclusion criteria. Peak and trough D2 receptor occupancy levels at month 6 were 70.3 ± 9.8% and 60.5 ± 20.2% (mean ± SD, respectively); among these individuals, 46.7% (N = 14) did not achieve continuous blockade of ≥65% (i.e. trough D2 occupancy of <65%). 25 of these subjects completed phase 1 with improvement; of these, 52.0% (N = 14) did not achieve continuous blockade of ≥65% at endpoint. No significant difference was found in peak or trough D2 occupancy between those who successfully completed phase 1 and those who did not.

Conclusion: Approximately half of patients who maintained remission did not achieve continuous blockade of D2 receptor occupancy ≥65%. Results suggest that sustained D2 receptor occupancy over 65% is not always necessary for the maintenance treatment of schizophrenia.

Policy of full disclosure: Data used in the preparation of this article were obtained from the limited access datasets distributed from the NIH-supported “Clinical Antipsychotic Trials of Intervention Effectiveness in Schizophrenia” (CATIE-S2). This is a multisite, clinical trial of persons with schizophrenia comparing the effectiveness of randomly assigned medication treatment. The study was supported by NIMH Contract #N01MH90001 to the University of North Carolina at Chapel Hill. The ClinicalTrials.gov identifier is NCT00014001. The version of the dataset used was 1.0. This study was also supported by grant R01MH084173 from the National Institute of Mental Health and was ancillary to Clinical Antipsychotic Trials of Intervention Effectiveness, N01MH90001, from the National Institute of Mental Health.

P-01-044 A comparison of the pharmacotherapy of japanese mental disorders between inpatients and outpatients receiving home visit nursing service
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Objective: Japan’s rapidly aging population has become a top medical issue. Similarly, Japanese mental disorders face the problem of aging. In contrast, the Ministry of Health, Labor and Welfare plan to reduce long hospitalization of Japanese mental disorders to improve their quality of life and restrain increases in medical expenses. One of the plans is home visit nursing service. The purpose of this study was to examine the pharmacotherapy of Japanese mental disorders between inpatients and outpatients receiving home visit nursing service.

Methods: We conduct a survey of prescription and demographics from inpatient’s medical records dated 30th September 2009 and outpatient’s dated 31st May 2011 at Showa University Karasuyama Hospital. This study was approved by the Medical Ethics Committee of Showa University School of Medicine.

Results: As a result, one hundred fifty-seven inpatients and sixty-eight outpatients (almost chronic schizophrenia) had similar outcomes and demographics. As they grew older, they had more physical diseases (r = 0.43, p < 0.0001) and took lower amount of antipsychotics (r = −0.34, p < 0.0001) (Pearson product-moment correlation coefficient). Outpatients had more physical diseases for their age than inpatients because outpatient’s illnesses were more out of control. Both patients had diabetes mellitus, hyperlipidemia, bone fracture, difficulty swallowing and others, that could have influenced the pharmacotherapy for rapidly aging mental disorders.

Conclusion: In conclusion, these results indicate that aging outpatients were not healthier than inpatients. Various physical diseases they had will affect selection of drug by psychiatrists materially. Psychiatrists in an aging society, like Japan, should realize the necessity of managerial support for their illness and be more careful when prescribe for aging outpatients.
Objective: The use of long acting injectables (LAI) antipsychotics is mainly reserved as the second line treatment when all efforts to ensure patients’ adherence to regular oral medication failed. We aim to describe the common clinical features of patients with schizophrenia who benefited from the use of LAI early in the course of illness.

Methods: We report four patients with first presentation of schizophrenia, all of whom were started with atypical antipsychotic LAI without prior history of oral antipsychotic. In all of the cases, the treating doctors independently did not use short acting major tranquilizers in the acute phase of psychosis because the patients were not agitated but remained adamant in refusing oral medications.

Results: We observed the four patients shared common clinical features of prominent delusion rather than hallucination amidst other psychotic symptoms, obstinate refusal of oral medication but without agitation, with good pre-morbid functioning and very poor insight. Interestingly, following the remission of the acute psychotic phase, all showed marked improvement in their insight and had better than expected therapeutic alliance.

Conclusion: We conclude that LAI may be used as the first line antipsychotic treatment in the acute psychotic phase in patients who are non-agitated but have prominent symptom of delusions with poor insight. LAI may improve the doctor-patient therapeutic alliance due to its minimal side effects and by ways of increasing the patients’ sense of control and allowing psychoeducation to take place when the patient is ready.

Objective: This study looked into the usefulness of switching to aripiprazole in schizophrenic patients who experienced sexual dysfunction with antipsychotic treatment. In addition, changes in the levels of satisfaction with medication were also examined.

Methods: Patients with schizophrenia receiving treatment at our hospital and taking an antipsychotic drug were surveyed about their subjective perception of frequency and severity of side effects on a self-completed questionnaire, and the level of satisfaction with their medication, using the DAI-10 (Drug Attitude Inventory-10). Of them, patients who checked one of the items concerning sexual dysfunction, attending physicians engaged in SDM (shared decision making), and those for whom it was judged reasonable for patients to switch to aripiprazole and who agreed to switch became the subjects of this study. Prolactin levels were measured upon switch to aripiprazole. As a result of this switch, they showed resolution or improvement in sexual dysfunction.

Results: Seven patients had their medication switched to aripiprazole. As a result of this switch, they showed resolution or improvement in sexual dysfunction. This in turn was considered to improve the level of patient satisfaction with medication. These findings suggested that a switch to aripiprazole may be useful in patients who experience sexual dysfunction with antipsychotic treatment.

Objective: Previous studies on the prescription patterns of psychotropic medications have highlighted the use of Clozapine in the treatment of persons with Schizophrenia. Little is known about the prescription pattern of Clozapine in Nigeria. This study examined the prescription pattern of Clozapine in a Nigerian Neuropsychiatric Hospital.

Methods: A complete list of patients that had been on Clozapine in the past year was retrieved from the pharmacy register of a Nigerian Hospital. Information on pattern of Clozapine use was obtained from Casenotes using a standardized data collection form.

Results: A total of 39 patients had received Clozapine in the past year. Mean age was 43.3 years (SD = 13). Majority were males (51.3%), unmarried (66.7%) and unemployed (64.1%). About 8 (20.5%) had comorbid substance use disorder. Most (81.2%) reported side effects related to clozapine use. Hyperbiseivation (46.2%) was the commonest reported side effect followed by drowsiness (41%), urinary problems (17.8) and constipation (12.8%). Clozapine discontinuation occurred among 64.8% of the subjects. Reasons for discontinuing included financial constraints (36.4%) and low White Blood Cell count (22.7%).

Conclusion: This study highlighted the pattern of Clozapine prescription in an understudied population. Further research on factors influencing its prescription is required.
patients with NMS secondary to both typical and atypical antipsychotic agents as well as the description of 3 cases of catatonia with different patterns of outcome.

Methods: Case Series and Literature Review.

Results: We have recently diagnosed 5 cases of NMS in the psychiatric hospital and 3 cases of catatonia in the context of affective and psychotic disorders. A retrospective medical chart review of the cases was made along with the literature review. We found a positive response to a benzodiazepine trial in half of the cases.

Conclusion: The pathophysiology of Neuroleptic Malignant Syndrome (NMS) and Catatonia remains enigmatic due to its unpredictable and the absence of established vulnerability markers. In both conditions a variety of mechanisms have been proposed to account for the clinical characteristics including reduced dopamine transmission, sympathetic nervous system dysregulation, disordered muscle metabolism, adrenal gland secondary dysfunction and altered central GABAergic function. Since its initial description by Kalbhaub over a century ago, catatonia has been associated with psychiatric, neurologic, and medical disorders.

Contemporary authors view catatonia as a syndrome of motor signs in association with disorders of mood, behavior or thought.

P-01-050 Differential effects of aripiprazole and haloperidol on dopamine markers in the arcuate nucleus and prolactin levels in male rats

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Objective: Aripiprazole is a new antipsychotic drug with a high affinity for dopamine D2 receptors but reduced risks for inducing extrapyramidal (EPS) and hyperprolactinaemia (HPL) side-effects. Our previous study (Han et al., 2009, International Journal of Neuropsychopharmacology 12: 941–952) showed that aripiprazole selectively reduced the expression of tyrosine hydroxylase (TH; a rate-limiting enzyme for the synthesis of dopamine) in the ventral rat midbrain, which strongly reduced central dopamine transmission. Conversely, haloperidol increased plasma prolactin levels in male rats. This study investigated the effects of haloperidol and aripiprazole on the expression of dopamine markers in the Arc and plasma prolactin levels following short and long-term treatment. As a comparison, the effects of haloperidol on these measurements were also examined.

Methods: Male Sprague Dawley rats were treated with aripiprazole (0.75mg/kg, t.i.d.), haloperidol (0.1mg/kg, t.i.d) or control (vehicle) for 1-week or 10-weeks (n=6/group). Protein levels of TH, phospho-TH (pTH) and dopamine transporter (DAT) in the Arc, as well as prolactin levels, were examined.

Results: Compared to controls, haloperidol significantly increased TH levels (p<0.01) after both short- and long-term treatment, and pTH and DAT after long-term treatment (p<0.05); however, aripiprazole had no significant effect on these dopamine markers in the Arc. Consistently, haloperidol (p<0.01), not aripiprazole, significantly increased plasma prolactin levels.

Conclusion: Aripiprazole and haloperidol have different effects on the expressions of dopamine markers in the Arc and prolactin levels. These results support the selective effects of aripiprazole on dopamine synthesis in different dopamine pathways as a possible mechanism for the long-term efficacy of aripiprazole with low EPS and HPL side-effects liability.

P-01-051 Metabolic syndrome in patients with schizophrenia treated with antipsychotics: Attitudes from psychiatrists

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Objective: to evaluate the prevalence of metabolic syndrome in patients with schizophrenia and to investigate the consequent actions implemented in the Mental Health Services (MHS).

Methods: This was part of a longitudinal research focused in physical health of patients treated with antipsychotic medication, performed in two outpatient clinics. 147 patients (84 males) with a DSM-IV diagnosis of schizophrenia (n = 111), schizoaffective disorder (n = 18) or related psychoses (n = 18) were included. Metabolic syndrome was defined according to NCEP-III criteria. Actions implemented after the evaluation of the patients were assessed with medical records and a structured questionnaire. Associated factors and actions were included in a logistic regression model.

Results: 52.7% of the patients fulfilled metabolic syndrome criteria. BMI was associated to all the metabolic factors (p < 0.001), time of antipsychotic medication was associated with metabolic syndrome, abdominal perimeter and triglycerides. Tobacco use was associated to glycaemia and HDL and gender was related to glycaemia. The model for metabolic syndrome (N = 30.040; R²: 0.225; p < 0.001) included gender, age, BMI and tobacco. Only 23 patients (15.4%) were receiving treatment for any metabolic factor. In patients with metabolic syndrome, 50% were intensified in the monitoring, 45.5% were referred to the GP and 3.9% received pharmacological treatment. Remission to GP (N = 29.584; R²: 0.189; p < 0.001) only included glucose, triglycerides and HDL levels and polymedication as independent predictor factors. Interestingly, two fold differences between the Mental Health Services were observed in the rate of implemented actions.

Conclusion: Metabolic syndrome was highly prevalent and related to male gender, tobacco and BMI. Actions implemented appear to be conservative and unequal. Glucose, triglycerides and HDL levels were the factors implied in more actions. There is a need of implementation of standard procedures in MHS in order to reduce the impact on cardiovascular risk and the differences between services.
Responders were characterized by 20% decrease of total PANSS score at least.

Results: Fourteen patients were included in the study, average age was 24 years and average duration of schizophrenia was 4.4 months. 71% of patients were assessed as responders (N = 10) and 29% of them as nonresponders (N = 4). In the second week of therapy, responders reached higher decrease of total PANSS score (about 43%) in relation to nonresponders (about 22%).

Conclusion: First episode schizophrenia patients are characterized by the high reactivity to antipsychotic therapy. The most prominent improvement of schizophrenic symptomatology occurs during first two weeks of treatment. Early response in the second week predicts consecutive response in the fourth week of the therapy. Acknowledgement: This work was supported by the project “CEITEC – Central European Institute of Technology” (CZ.1.05/1.1.00/02.0006) from European Regional Development Fund.

P-01-053 Clozapine induced rash: Case report of successful desensitisation

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Objective: Clozapine is the drug of choice for patients with treatment-resistant schizophrenia. However a minority of them have been unable to continue with Clozapine due to side-effects, for example rash. This report looks at the use of graded desensitization in a patient who developed cutaneous reactions to Clozapine.

Methods: This report describes the management of a patient with treatment-resistant-schizophrenia, mild learning disabilities and epilepsy, following a cutaneous reaction to Clozapine. Having been maintained on Clopexol depot until 4 years ago, he required a change in antipsychotics following a relapse of psychotic symptoms. He was then put on a single case.

Results: Graded desensitization, using incremental increases in drug dose, allowed maintenance treatment with therapeutic doses of Clozapine to be achieved in the absence of cutaneous hypersensitivity reactions. The patient’s previously treatment-resistant psychotic symptoms were improved by this method.

Conclusion: We should be aware of possibilities for the management of both the common and uncommon side-effects associated with Clozapine, as the result might vastly improve the patients’ quality of life. Desensitisation regimens can be an effective means of overcoming drug hypersensitivity but should be used with great caution, especially when patients exhibit delayed-type hypersensitivity reactions (as here).

P-01-054 Psychotic episode in epilepsy-treatment modality

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Objective: The aim of this study was to compare parallel effects of risperidone and clozapine in treatment of psychotic episode in verified Grand-mall epilepsy. Due to changes in organic substrate, psychosis is not rare comorbidity in epilepsy. There were no consensus about treatment options. It is known that antipsychotics lower seizure threshold, cause EEG abnormalities and put the patients in the risk for additional seizures.

Methods: The total of 85 adult patients of both gender (39 females) with clinically and EEG confirmed Grand-mall epilepsy developed psychotic episode. The psychotic state was evaluated using BPRS scale. Subject were treated either with risperidone (n = 43) 5.7 ± 1.4 mg per day or with clozapine (n = 42) 106.2 ± 29.8 mg per day, orally. Results: The total BPRS scores in risperidone group at baseline, in 1st, 2nd and 3rd week were 134.1 ± 41.3, 98.4 ± 28.7, 88.9 ± 21.9, and 78.3 ± 14.8, respectively (p < 0.05). The total BPRS scores in clozapine group at baseline, in 1st, 2nd and 3rd week were 138.3 ± 53.7, 109.1 ± 33.1, 97.3 ± 22.8, and 90.7 ± 21.4, respectively (p < 0.05).

Conclusion: Our results showed that risperidone is more effective and comfortable drug than clozapine in the treatment of psychotic episodes in epilepsy.

P-01-055 Aripiprazole in the treatment of first episode of psychosis in a patient with hypogonadism due to hyperprolactinemia

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Objective: Aripiprazole is a new atypical antipsychotic with dopaminergic agonistic activity at a low dose. Dopamine is a prolactin-inhibiting factor and dopamine imbalance has been implicated in the pathophysiology of psychotic disorders. We investigated the probable relationship between hyperprolactinemia and the development of psychotic symptoms and the role of aripiprazole medication, in a single case.

Methods: We present the case of a patient with hypogonadism secondary to chronic, untreated hyperprolactinemia who developed acute psychotic symptoms and the beneficial role of aripiprazole mediation in an additional seizure.

Results: Psychotic symptoms resolved soon after treatment with aripiprazole in conjunction with cabbergoline, with a concomitant decrease in serum prolactin levels.

Conclusion: This is an interesting case indicating the beneficial role of aripiprazole treatment and also illustrating a complicated relationship among hypogonadism secondary to prolactinoma and dopamine and psychosis.

P-01-056 The effect of the atypical antipsychotics on cognitive deficit in schizophrenia

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Objective: While the typical antipsychotics do not improve cognition and may even alter memory due to their prevalent antimuscarinic and antidopaminergic features, recent studies show that atypical antipsychotics cause improvements in learning, processing speed, speech fluency and motor abilities. Objectives: The study aimed at defining the cognitive deficit in schizophrenia and the influence of the atypical antipsychotics on it. Another objective was to compare the neurocognitive negative effects of olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, molindone.

Methods: The study was of the observational prospective type, lasting for 52 weeks was made on 7 groups of 20 patients each, according to the type of the antipsychotic used in therapy: olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, clozapine and sertindole. The CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) and BACS (Brief Assessment of Cognition in Schizophrenia) test batteries have been applied.

Results: After 40 weeks, corresponding VI0, every antipsychotic drug improved the compound score of the CATIE and BACS neurocognitive battery comparing to the moment of the inclusion in the study (VI). There was a positive correlation: the patients who displayed a cognitive improvement at the VII moment, also displayed benefits in the social and occupational fields, which suggests a functional relevance for the improvement of cognition.

Conclusion: There is an important cognitive deficit in the majority of the schizophrenic patients. Olanzapine, quetiapine, risperidone, aripiprazole, ziprasidone, clozapine and sertindole have displayed similar results in terms of their effects on various neurocognitive deficits.
**P-01-057** Relapses in psychotic disorders treated with oral paliperidone: A 12-month follow-up

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**Objective:** Describe and compare the relapse rate at 12 months in a sample of patients with psychotic disorders treated with oral Paliperidone versus other antipsychotics.

**Methods:** Descriptive observational study comparing two historical cohorts. Patients were recruited over a period of two years. Sample of patients with psychotic disorder, mainly schizophrenia. We included patients aged ≥18 years, diagnosis of psychotic disorder and relapse situation that requires hospitalization. Subjects that in the observation period did not present psychotic symptoms are excluded.

**Results:** 200 patients were included, all the patients were hospitalized at the time of inclusion in the study. Homogeneous groups in terms of size, demographic (except for sex) and clinical characteristics. 73% had a diagnosis of schizophrenia and 7.5% had other diagnoses with transitory psychotic symptoms. 3% of patients treated with oral paliperidone relapse and were readmitted within 12 months after discharge, compared to 50% in the group of patients taking other antipsychotics (p<0.05). Both groups showed a non statistically significant difference (p=0.809) in the number of total days of hospitalization since admission: case 35.46 days (SD 31.2), controls 34.27 days (SD 37.9). There was no differences regarding the use of adjunctive BZD (cases =47%, controls =45%, p=0.77) and/or bi-periden (cases =17%, controls =27%, p=0.088). The mean dose of oral paliperidone at discharge was 10 mg/day (SD 4.41, range 3-24).

**Conclusion:** Due to the study design, no causal relationships can be established. However, data suggest that patients treated with oral paliperidone have fewer relapses and readmissions at 12 months follow-up than patients treated with other antipsychotic treatment. These results could be associated with favorable side-effect profile and a lower treatment discontinuation rate.

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**P-01-058** Switching from olanzapine to ziprasidone: A twelve-week, open-label, multicenter study evaluating the effectiveness and safety of ziprasidone in patients with schizophrenia

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**Objective:** To evaluate the effects and safety of switching from olanzapine to ziprasidone, due to inadequate response or intolerance to olanzapine.

**Methods:** Totally, 120 subjects with schizophrenia who were either suboptimal efficacy or poor tolerability to olanzapine treatment (dose range 10-20 mg/day) for ≥8 weeks were enrolled in a 12-week, open-label, flexible-dose ziprasidone trial. Olanzapine was tapered and discontinued over the course of 2 weeks, while ziprasidone was titrated up and dosed at 40-80 mg b.i.d. The primary endpoint was the improvement in Positive and Negative Syndrome Scale (PANSS) total score from baseline. The second endpoint were the change in lipid profile, fasting glucose, glycosylated hemoglobin (HbA1c) and serum prolactin level in 8 weeks of treatment from baseline.

**Results:** The intent-to-treat population was 100, and 86 patients completed 12 weeks trial. At week 12, there was a statistically significant decrease in PANSS total score, with a mean change from baseline was 65% ± 26% using the LOCt analysis. The CDSS total score and each items, except item 3, Self-depreciation, decreased significantly from baseline. There were significant decreases in levels of total cholesterol. The finding replicate the results of some earlier studies (Rossi et al., 2008; Grooters et al., 2011)[1, 2]. Adverse effect of ziprasidone is transitory and mild, including insomnia, somnolence, and nausea. There were no significant changes in the QTc interval.

**Conclusion:** Subjects switching from olanzapine to ziprasidone showed a significant improvement in clinical symptoms and quality of life, and decrease in total cholesterol levels, regardless of drug metabolic status and disease severity at baseline. Ziprasidone with a comparatively neural metabolic profile and the comparable efficacy relative to other atypical antipsychics may be an important alternative for patients experiencing no-response or lack of tolerability with olanzapine treatment.

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**P-01-059** Research of olanzapine: Comparison research of a tablet and a sustained release drug

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**Objective:** Lack of insight of the patients with bipolar disorder and/or schizophrenia is common. Therefore, maintenance management of medicinal use is important. There are many patients who do not take drugs. Changing the form of medication may make those patients feel the medicinal using easier. We aimed to evaluate the adherence at maintenance pharmacological management by changing a tablet of olanzapine into a sustained release olanzapine.

**Methods:** This is a prospective study in Japan. Subjects were the patients who had schizophrenia and/or bipolar disorder diagnosed by DSM-IV or ICD-10 who were taking olanzapine. 200 patients were included, all the patients were hospitalized. Olanzapine were changed for patients experiencing no-response or lack of tolerability with olanzapine into a sustained release olanzapine.

**Results:** Due to the study design, no causal relationships can be established. However, data suggest that patients treated with oral paliperidone have fewer relapses and readmissions at 12 months follow-up than patients treated with other antipsychotic treatment. These results could be associated with favorable side-effect profile and a lower treatment discontinuation rate.

**Conclusion:** The patients who changed from the tablet to the sustained release drug showed good adherence assessed by DAI-10. We found better adherence at two months. Conclusions: Adherence of the patient having changed into the sustained release drug from the tablet of olanzapine was quite good.

**P-01-060** Clinical interventions to counteract antipsychotic polypharmacy: A systematic review

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**Objective:** While pros and cons of antipsychotic polypharmacy have been frequently discussed, it still remains unclear as to how to counteract this common but controversial practice. The objective of this study was to synthesize the evidence on trials to reduce anti-psychotic polypharmacy in schizophrenia.

**Methods:** A PubMED search was performed to identify two types of clinical trials: studies that systematically switched antipsychotic polypharmacy to monotherapy in research settings, and studies that intervened physicians’ prescribing behaviours in clinical settings (last search: Dec 2011). The following search terms were
Antipsychotics

P-01-061 Late-onset angioedema probably induced by risperidone in an elderly woman with schizophrenia

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Objective: Angioedematous oedema is a rare adverse reaction which mainly involves oedema of the deep dermal and subcutaneous tissues. Few case reports have established its association with the use of specific antipsychotics such as risperidone, clozapine, ziprasidone, droperidol and chlorpromazine. The aim of this study is to present a case of angioedema in an elderly woman with psychosis possibly induced by risperidone.

Methods: We reviewed the patient’s case notes and the relevant literature.

Results: The patient is a 69 years old Greek woman who was hospitalized due to a psychotic relapse. Her symptoms included ideas of reference, persecutory delusions, passivity phenomena, visual and auditory hallucinations. She was diagnosed with schizophrenia of paranoid type according to DSM-IV-TR criteria. During her hospitalization she was administered antipsychotic treatment with oral risperidone which was titrated up to 3 mg daily. Psychotic symptoms improved and she was discharged from the ward. Eight months later she presented at the emergency department of the hospital suffering from oedema of face and lower extremities. These symptoms were not better accounted by any other medical condition (e.g. systemic infection, cardiovascular or respiratory disease). At that time she was not receiving any other drug treatment except risperidone and had no known history of allergy. Therefore, risperidone was considered responsible for her symptoms and was discontinued. She initially received treatment with ceftriaxone followed by low dose of hydroxyzine. The swelling subsided over a period of two weeks. Laboratory tests were within normal limits, but measurement of complement pathway activity was not performed.

Conclusion: We conclude that our patient developed late-onset risperidone-induced angioedematous oedema. To our knowledge there is no previous report in the literature about angioedematous oedema occurring within months of risperidone onset. Further studies are needed to delineate the mechanism of this kind of allergic reaction.

P-01-062 Aripiprazol (abilify) application by schizophrenia patients’ therapy and affective disorders

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Objective: 25 patients were examined stationary. According to epide- sodes clinic patients were divided into 6 groups. The 1st - of schizo- phrenia patients with affective delusive episodes included 5 people. The 2nd- with affective hallucinate episodes included 3. The 3rd- with hallucinate delusive episodes included 3. The 4th- with primary man- iacal episode included 3. The 5th- with bipolar affective disorder, current manicual episode included 7. And the 6th- with bipolar affective disorder, mixed episode included 4.

Methods: Clinic-psychopathological method.

Results: the therapy of atypical neuroleptic -abilify was being made to schizophrenia patients with productive psychotic for the 1st, 2nd and 3rd groups. The dose started from 15 mg a day with gradual dose increasing in 1-2 days to 30 mg a day intake. At the same time these patients took the dose of haloperidol – decanoate. The dose was 5 mg intramuscularly once four weeks altogether with such prepara- tion as ticlidol. Also these patients depending on emotional condition in episode took amitriptylin 50 mg a day or vellascin 50 mg a day and litiya carbonate 0,9 g a day. The improvement of these patients was noticed the 5th week therapy. “Voice” intensity and its frequency were decreased, hallucinate ideas became less actual. The expression of negative disorders of some patients was also decreased. The patients with bipolar affective disorder, current manicual episode and with primary maniacal episode took ability in dose 30 mg a day. The improvement of primary patients was the 3rd week, but the improvement of secondary patients was the 5th treatment. The mood became much better, statements and be- haviour was regulated.

Conclusion: The improvement of patients with bipolar affective disorder, current manicual episode was the 3rd week ability treatment together. The improvement of schizophrenia patients with productive psychotic symptomatology was caused by ability after 5 weeks treatment conducting with traditional neuroleptic. Abilify decreased the expression of negative symptoms of some schizo- phrenia patients.

P-01-063 Effect of chronic antipsychotic drug treatment on the rodent cerebral cortex: Linking ex vivo neuroimaging findings with post-mortem neuropathology

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Objective: To identify the locus of volume decreases in the rat neocortex due to chronic haloperidol treatment and provide preliminary evidence for the mechanisms underlying this effect. Background: Antipsychotic drugs (APD) may affect brain structure directly in Schizophrenia patients (Ho et al., 2011). Indeed, pre-clinical studies suggest chronic haloperidol treatment results in a decreased total volume of the neocortex, which is reversible upon drug withdrawal (Vernon et al., 2012). However, the location of volume changes within the neocortex and the mechanisms underlying this effect are not fully elucidated. We now report preliminary results of automated MR image analysis and post-mortem studies to address these issues.

Methods: Male Sprague-dawley rats were treated chronically (8 weeks) with placebo (n = 8) or haloperidol (2 mg/kg/day s.c. n = 8), MRI scans were acquired ex vivo after cessation of treatment. Pre-clinical treatment groups were analysed using a hypothesis-free deformation-based morphometry (DBM) analysis (Vernon et al., 2011). Volumetric differences in the neocortex identified by DBM were investigated post-mortem from nissl stained tissue sections (40 µm thick, 1/12 series) using unbiased stereology (Cavalieri probe) to validate the DBM-led approach.

Results: DBM analysis identified local tissue volume decreases in the neocortex, most prominently in the medial prefrontal cortex (mPFC) of haloperidol-treated animals (p < 0.05 uncorrected). Post- mortem analysis confirmed significant decreases in the thickness of the prelimbic (PrL) region of the mPFC and in the volume of the anterior cingulate cortex (ACC), but not in the thickness of the primary motor, sensorimotor or visual cortices. Preliminary analysis of neu- ronal number in the ACC revealed no significant differences between vehicle and haloperidol-treated groups.

Conclusion: Chronic haloperidol treatment induces volumetric decreases in the mPFC of the rat neocortex, which is potentially not explained by neuronal loss. Further detailed cell counting is now in progress.
**P-01-064** Medication adherence in schizophrenia and potential risk factors associated with non-adherence in South West Ethiopia

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**Objective:** Non-adherence behavior is a significant issue in the management of psychotic disorders, for it is major cause of psychosis relapse and is strongly influenced by many factors. Medication adherence to antipsychotic drugs is detrimental to the perceived outcome of treatment. The objective of this study is to evaluate adherence rate to antipsychotic medications and identify the potential risk factors associated with non-adherence.

**Methods:** A cross-sectional study was conducted on 336 patients using patients self-report and pharmacy refill record where by both qualitative and quantitative methods of data collection was used. The self-report involved the structured patient interview after verbal informed consent was obtained. Data were analyzed using SPSS for windows version 16.0. Chi-square test was used to observe the association of variables with adherence.

**Results:** The adherence rate of patients (n=336) is found to be 57.5% based on their refill records, compliant fill rate. On the basis of patients self-report for their pattern of drug use, 52.1% participants said that they had never missed their doses, while 32.1% participants missed daily doses sometimes, 4.7% missed only time of taking, and 5.9% missed both time of taking and missed daily dose sometimes. The most common reasons for missing dose were forgetfulness (36.2%) and being busy (21.0%). Pill burden, side effects of medications, exposure for social drugs have statistically significant negative association but, increased duration of maintenance medication is found to enhance rate of adherence.

**Conclusion:** Large proportion of the study patients failed to refill their medications properly which indicates the severity of the problem and calls due consideration in planning appropriate strategies to improve the existing conditions.

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**P-01-065** Effects of an adjunct nicotinic a7 receptor agonist to the atypical antipsychotic risperidone in animal models of antipsychotic activity and extrapyramidal side effect liability

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**Objective:** Cognitive impairment is debilitating in schizophrenia (SCH). Effects of adjunct treatment with cholinergic nicotinic a7 receptor agonists to antipsychotics (APIs) for cognitive improvement in SCH are under investigation in clinical studies with some positive reports. However, changes in retained antipsychotic efficacy of the simultaneously given API, as well as changes in extrapyramidal side effect (EPS) liability, following adjunct nicotinic a7 agonist treatment are, to the best of our knowledge, not well known. Therefore, we here investigated, experimentally, the effects of adjunct treatment with the selective nicotinic a7 receptor agonist PHA 543, 613 (1 mg/kg) to the atypical APD risperidone (0.2 or 0.8 mg/kg) in animal models of antipsychotic activity and EPS liability, in rats.

**Methods:** The conditioned avoidance response (CAR) test was used for assessment of antipsychotic activity. Assessment of EPS liability was performed using the catalepsy test. Statistical evaluation was performed by means of non-parametric statistics.

**Results:** CAR: Risperidone produced a dose-dependent, significant antipsychotic-like suppression of CAR. Compared with risperidone 0.2 mg/kg alone, pretreatment with PHA 543, 613 (1 mg/kg) showed a strong tendency to reverse risperidone 0.2 mg/kg – induced suppression of CAR that was close to statistical significance. PHA 543, 613 alone had no effects on CAR. Catalepsy: Compared with vehicle treated controls, risperidone (0.2 mg/kg) significantly increased catalepsy scores. Pretreatment with PHA 543, 613 further enhanced risperidone-induced increase in catalepsy scores. Also PHA 543, 613 alone significantly increased catalepsy scores. The difference in catalepsy scores between risperidone alone and combined PHA 543, 613/ risperidone treatment groups was close to statistical significance.

**Conclusion:** The data suggest that adjunct nicotinic a7 agonist treatment for cognitive impairment in SCH may come with a risk of reduced antipsychotic efficacy and an increase in EPS liability, at least when given with a low dose of the atypical APD risperidone.

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**P-01-066** Changes in metabolic parameters and Framingham cardiovascular risk scores after in-hospital antipsychotic treatment – preliminary results

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**Objective:** The objective of this study was to assess changes in the prevalence of metabolic syndrome (MetS) and cardiovascular risk scores after in-hospital treatment with antipsychotics.

**Methods:** 31 subjects (F 18/M 13; mean age 36.5 years) with schizophrenia were assessed on admission and at discharge. Height, weight, waist circumference, and blood pressure were measured, and lipids and glucose were measured. Smoking, illness duration, hospital stay duration, number and doses of antipsychotics, concomitant use of antihypertensives, antidiabetics or hypolipidemics were registered. International Diabetes Federation definition of MetS was used. Cardiovascular risk scores were calculated using the Framingham Heart Study algorithms.

**Results:** Mean illness duration was 126.9 months, mean hospital stay was 51.9 days. 25 patients (80.6%) were taking more than 1 antipsychotic. The majority of subjects (90.3%) were taking second generation antipsychotics. Overweight, obesity, abdominal obesity, lipid abnormalities and hypertension was found in 13 (41.9%), 14 (45.1%), 24 (77.4%), 24 (77.4%) and 16 (51.6%) patients, respectively. At discharge metabolic parameters did not improve, while triglyceride levels increased (P=0.003). MetS prevalence increased from 41.94% to 61.29% (P=0.029). Number of MetS criteria met increased (P=0.001). The rate of abdominal obesity (P=0.001), raised TGA (P=0.001), raised FPG (P=0.005) and reduced HDL (P<0.001) increased. No differences in age, sex, tobacco smoking, duration of hospital stay and schizophrenia, number and type of antipsychotics between subjects with or without MetS were found. Cardiovascular risk scores did not increase at discharge.

**Conclusion:** Between admission and discharge the prevalence of MetS, number of MetS criteria met, the rate of abdominal obesity, raised TGA, raised FPG and reduced HDL parameters did not improve during hospital stay, while triglyceride levels increased. No increase of cardiovascular risk scores was found. The majority of patients had abnormal body weight, abdominal obesity and untreated hyperlipidemia.

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**P-01-067** Animal model of treatment-resistant schizophrenia


**Objective:** Animal models are invaluable for the screening of novel compounds for mental disorders such as schizophrenia. In most of the animal models, first generation antipsychotic drugs such as haloperidol are effective in reducing spontaneous and drug-induced hyperactivity but have little effect on behavioral changes related to negative symptoms and cognitive dysfunctions. In contrast, second generation antipsychotic drugs such as clozapine are reported to be effective in ameliorating most of the behavioral abnormalities, although one-fifth to two-third of patients are considered treatment resistant and show persistent psychotic and other symptoms despite the optimal use of antipsychotic medications. To identify compounds that may be more effective than existing antipsychotic medications in ameliorating the negative symptoms and cognitive dysfunctions in schizophrenia, animal models for antipsychotic drug-resistant schizophrenia are needed.

**Methods:** Transgenic mice expressing a dominant-negative N-terminal human DISC1 under the expression control of CaMKII promoter (DN-DSCL mice) were injected with polycl.C during the neonatal stage, and their behavioral phenotypes were examined in adulthood.

**Results:** Polycl.C-treated DN-DSCL mice exhibited the deficits of short-term memory, object recognition memory, social interaction,
hippocampus-dependent fear memory, and augmentation of MK801-induced hyperactivity after puberty, although poly(I:C) treatment or DN-DISC1 expression by itself has negligible effect on wild-type mice. Cognitive impairment in this model was ameliorated by repeated administration of clozapine, but not haloperidol. Both antipsychotic drugs suppressed the enhancement of MK801-induced hyperactivity in the model but have no effects on deficits of short-term memory and hippocampus-dependent fear memory, or impairment of social interactions.

Conclusion: These results suggest that adult DN-DISC1 mice with neonatal poly(I:C) treatment may be useful for the screening of potential antipsychotic compounds that could be more effective in ameliorating social and cognitive impairments in treatment-resistant schizophrenia.

**Impact of switching to second-generation antipsychotics on the treatment of long-term inpatients with schizophrenia**

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Objective: The purpose of this study is to investigate the impact of switching from the first generation antipsychotics (FGAs) to the second generation antipsychotics (SGAs) on clinical efficacy and adverse effect in the treatment for long-term inpatients with schizophrenia.

Methods: Eighty five patients with schizophrenia diagnosed by DSM-IV were selected among inpatients hospitalized for at least 12 years. Effects on Brief Psychiatric Rating Scale (BPRS) and adverse effect on Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) have been evaluated and analyzed with these patients’ characteristics and the profiles of prescribed drugs including antipsychotics, anti-parkinsonian agents and mood stabilizer.

Results: After switching to SGAs, the scores of BPRS and DIEPSS were significantly decreased, and the number of prescribed antipsychotics and antiparkinsonian agents was significantly decreased although the total Chlorpromazine-equivalent dose of antipsychotics has been unaltered for 12 years of inpatient duration.

Conclusion: These results suggested that switching to SGAs in the treatment for long-term inpatients with schizophrenia brought a better outcome in both clinical efficacy and safety, and possible prevention of polypharmacy.

**No association between hormonal abnormality and sexual dysfunction in Japanese schizophrenia patients treated with antipsychotics**

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Objective: Although sexual dysfunction is believed to be caused by hormonal abnormalities, few reports have studied sexual dysfunction and its association with hormonal abnormalities in Asian populations with schizophrenia.

Methods: We employed a cross-sectional, case-control survey design to collect data from 191 (108 men) Japanese schizophrenia out-patients treated with antipsychotics and 182 (90 men) healthy subjets. Sexual dysfunction was evaluated using the Urdvalg for Kliniske Undersergelser (UKL) Side Effect Rating Scale. We measured plasma concentrations of prolactin in both genders and testosterone in men and estradiol in women.

Results: Multiple regression analyses revealed the following findings: the number of antipsychotics correlated with diminished sexual desire (standardized beta = 0.241, p < 0.05); the dose of antipsychotics correlated with gynecomasia (standardized beta = 0.277, p < 0.01), increased sexual desire (standardized beta = 0.229, p < 0.05), and ejaculatory dysfunction (standardized beta = 0.248, p < 0.05); and the dose of antipsychotics correlated with menorrhagia in women (standardized beta = 0.284, p < 0.05). However, neither plasma concentrations of prolactin, testosterone nor estradiol correlated with sexual dysfunction.

Conclusion: The present study demonstrated that an association between sex hormone abnormalities and sexual dysfunction is unlikely but that the dose or number of antipsychotics is associated with some sexual dysfunction.

**Effectiveness of prn medications in psychiatric patients: A systematic review**

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Objective: The use of “pro re nata (prn)” medications to manage patients’ perturbed behaviors such as agitation and aggression is widespread in psychiatric clinical practice. However, it is unclear which psychotropic drugs are more effective and tolerable than others. The aim of this study was to synthesize the evidence on prn medications in psychiatric patients.

Methods: A MEDLINE search was performed to identify studies published in English between 1966 and December 2011. The following search terms were used: (“prn” or “p.r.n” or “pro re nata” or “as needed” or “as required” or “stat med” or “as necessary”) and (psychiatr* or mental or antipsychotic or psychotropic*). Cross-referencing of the identified articles was also performed.

Results: The literature search identified 13 studies that assessed epidemiological usage of prn medications and 13 retrospective studies that evaluated the effectiveness/safety as well as reasons for prn administrations. Patients studied were all inpatients, and the reasons for prn administration were commonly acute behavioral dyscontrol. On the other hand, diagnoses and outcome measures to assess effectiveness/safety varied and inadequately described. Medications under study included antipsychotics, mood stabilizers and benzodiazepines. On the whole, most studies reported that prn medications were effective in psychiatric inpatients. However, only three prospective studies were identified to evaluate the effectiveness/safety of prn medications; furthermore, all of them included solely a child/adolescent population. One was a preliminary double-blind study of diphenhydramine in a child population (N = 21). Another was concerned about child/adolescent patients for subjective perceptions of prn medications (N = 42). The other was a post-hoc analysis of the data from clinical records of 338 child/adolescent patients.

Conclusion: Our findings indicate that there has been only equivocal evidence to guide a choice of prn medications for psychiatric patients. Further clinical trials needed to investigate the effectiveness and safety of prn medications in various psychiatric disorders.

**Not only dopamine D2 receptors involved in peony-glycyrrhiza decoction, an herbal preparation against antipsychotic-associated hyperprolactinemia**

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Objective: Hyperprolactinemia (hyperPRL) is a frequent complication of antipsychotic treatment. Clinical studies have demonstrated the effectiveness of an herbal preparation called Peony-Glycyrrhiza Decotion (PGLD) in alleviating antipsychotic-induced hyperPRL.

Methods: In the present study, we further examined the pharmacological action of PGLD on prolactin (PRL) secretion using in vitro and in vivo models, with specific attention to the role of dopaminergic mediators and other sexual hormones.

Results: Treatment with PGLD at 1 mg/ml and 5 mg/ml for 24 and 36 hrs significantly suppressed PRL secretion in MMQ cells, a model of hyperPRL derived from pituitary adenoma cells. PGLD also suppressed PRL synthesis in MMQ cells in a dose-dependent manner. These suppressive effects were completely abolished by pretreatment with 10 microM haloperidol, a dopamine D2 receptor antagonist, consistent with a D2-action, PGLD did not affect PRL secretion and...
This experimental evidence supports clinical use of PGD as an effective treatment of antipsychotic-induced hyperPRL.

Effects of chronic oral treatment with aripiprazole on the expression of NMDA receptor subunits and binding sites in rat brain

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Objective: The glutamatergic theory of schizophrenia proposes a dysfunction of ionotrope N-Methyl-D-aspartate receptors (NMDA-R). Several therapeutic strategies address NMDA-R function and effects of antipsychotic agents on NMDA-R expression have been described. Within the second generation antipsychotics, the partial dopaminergic and serotonergic agonist aripiprazole (APZ) was able to counteract behavioural effects of NMDA-R antagonists. We intended to investigate the effects of APZ on NMDA-R subunit expression and binding.

Methods: Male, wildtype Sprague-Dawley rats were treated for 4 weeks or 4 months with APZ in daily oral doses of 10 and 40 mg per kg body weight. Gene expression of the NMDA-R subunits NR1, NR2A, NR2B, NR2C and NR2D was assessed by semiquantitative radioactive in situ hybridization, and in parallel receptor binding using [3H]-MK-801 receptor autoradiography.

Results: Increased expression levels of NR1 (4 weeks), NR2A (4 weeks), NR2C (4 weeks and 4 months) and NR2D (4 months) were observed in several hippocampal and cortical brain regions. The parallel reduced expression of NR2B mRNAs (4 months) resulted in a relative increase of the NR2A/NR2B ratio. Marked differences between specific brain regions, the doses of APZ and the time points of assessment became obvious. On the receptor level, increased MK-801-binding was found after 4 weeks in the 40 mg-group and after 4 months in the 10 mg-group.

Conclusion: The effects of APZ converge in enhanced NMDA-receptor expression and a shift of subunit-composition towards adult-type receptors. Our results confirm regulatory connections between dopaminergic, serotonergic and glutamatergic neurotransmission. In consequence, APZ treatment may counteract a glutamatergic deficit state with positive consequences on cognitive and negative symptoms of schizophrenia.

New onset metabolic syndrome among patients receiving clozapine

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Objective: To study the prevalence of metabolic syndrome in patients receiving clozapine and prospectively evaluate the incidence of new onset metabolic syndrome after 3 months of therapy with clozapine.

Methods: For this study, 53 patients who were considered for clozapine therapy were evaluated for the presence of metabolic syndrome as defined by modified National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) criteria. These patients were prospectively followed after 3 months for change in metabolic syndrome status.

Results: Slightly more than one third of the patients had metabolic syndrome prior to starting clozapine. Another one sixth of the patients who did not have metabolic syndrome prior to starting clozapine developed metabolic syndrome after receiving clozapine for a duration of 3 months.

Conclusion: Clozapine contributes to the metabolic disturbances.

Course of negative symptoms in first-episode psychosis on aripiprazole vs. other antipsychotics during a two years follow-up

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Objective: Several lines of evidence indicate that early intervention with appropriate pharmacological treatment can contribute to improve the course and outcome of the illness (Linszen et al., Br J Psychiat Suppl 1998). Aripiprazole is an atypical antipsychotic that appears to be well tolerated and it has a low propensity for causing extrapyramidal symptoms which can cause secondary negative symptoms (5). The present prospective naturalistic study sets out to investigate changes in overall functionality, total symptomatology and, more specifically, negative symptomatology with aripiprazol and other second generation antipsychotics (SGA) in first episode patients during two-years of follow-up period.

Methods: Subjects with a first episode of psychosis were assessed and followed according to the first episode program of the centre (INAD). From the total sample of 130 recruited subjects, 42 completed the two years follow-up. During the follow up period, patients were clinically assessed using PANSS scale (amongst others). Antipsychotic treatment was prescribed by specialized psychiatrists according to clinical criteria. In this naturalistic study we studied the association of antipsychotic treatment (aripiprazol vs. other SGA) at 2nd year of the follow up period and change in negative symptoms during the follow-up period.

Results: Patients on aripiprazole at 2nd year in comparison to the beginning of the follow-up period had a significant higher decrease of negative symptoms: Arip: 3.09 (SD: 4.0); Others: -0.79 (SD: 5.3); p = 0.04. There were no other significant differences in changes in positive symptoms or general functioning between groups.

Conclusion: Aripiprazole seems to improve negative symptoms more than other second generation antipsychotics without significant risk of increasing positive symptoms or worsening functioning. Important limitations of this study include that patients were not randomly assigned and that aripiprazole seems to be chosen by psychiatrists for those patients showing more negative symptoms. Four patients included in another study were excluded from this analysis.

Quetiapine prevents oligodendrocyte and myelin losses and promotes maturation of oligodendrocyte progenitors in the hippocampus of global cerebral ischemia mice

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Objective: White matter impairment is the feature of vascular depression. Antipsychotic quetiapine has been shown enhancing the therapeutic effects of antidepressants on vascular depression, but the mechanism remains unknown. In this study, we will try to find the white matter protective effects of quetiapine in vascular depression mice model in order to clarify the mechanism of effects of quetiapine on vascular depression.

Methods: Mice were assigned to receive a sham or global cerebral ischemia surgery, which generated four treatment groups: Sham (sham+saline), QTP (sham +quetiapine), GCI (GCI+saline) and G+Q (GCI +quetiapine). GCI was induced by bilateral common carotid arteries occlusion (BCCA). Immunohistochemistry staining was used for pathological study. Myelin damage was observed by MBP staining. Loss and proliferation of Oligodendrocytes were observed by GST-pi, O4, NG2 and BrdU staining.

Results: We found that two weeks of treatment with quetiapine prior to bilateral carotid artery occlusion and reperfusion, an animal
model of vascular depression resulted in reduced myelin breakdown down and oligodendrocyte loss compared to placebo treated mice on postoperative day (POD) 7. For late stage of recovery (POD40), quetiapine treatment resulted in enhanced oligodendrocyte matu-
ration relative to placebo.

Conclusion: The results suggest that quetiapine is a potential intervention for oligodendrocyte damage and may contribute its antidepresant effects through white matter protection in vascular depression.

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**P-01-076** Paliperidone palmitate treatment in schizophrenia

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Objective: Treatment with Paliperidone Palmitate, see its effective-
ness, tolerability and adherence in schizophrenia, an experience with 17 patients.

Methods: In 17 schizophrenic patients (DSM-IV-TR) who were being treated with other antipsychotics, previous treatment was dis-
continued in case of intolerance or insufficient response, and changed to Paliperidone Palmitate (75-150 mg). The follow-up per-
formed was for 2 months. We used as a measure of efficacy, the PANNS and the ICG. We evaluated potential side effects reported by patients, evaluating tolerance and effectiveness of treatment. Antiparkinsonian drugs were only used in 3 patients during the first week, mainly due to presence of extrapyramidal symptomatology due to previous antipsychotic treatments.

Results: The mean baseline measurement on day 0 in the PANNS was 76 and the mean CGI was 4.5. The study is still carrying on in 17 patients. The follow-up of patients treated with Paliperidone Palmitate in the early November 2011, therefore we can not present at this time definitive data, except baseline scores. So far the improvement is good, both in efficiency and in tolerance. We will give definitive results at the end of the study.

Conclusion: If the preliminarily data obtained are confirmed at the end of the follow up period we believe that Paliperidone Palmitate should occupy a prominent place in the treatment of schizophrenia. We also believe that will facilitate treatment adherence so necessary in these patients prone to abandonment and non-compliance.

**P-01-077** Dose translation of aripiprazole between human and animal studies

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Objective: Aripiprazole is a newly developed antipsychotic which has a unique pharmacological profile of D2 receptor partial agonistic effect. As it has been approved for the treatment of schizophrenia, a growing body of studies has applied this compound to animal study in these patients prone to abandonment and non-compliance.

Methods: Plasma concentration of aripiprazole and metabolite was measures by normalizing method the oral dose for animal studies was ten times relative to placebo. We advocate that a dose translation between human and animal studies in aripiprazole should be cautious.
P-02. Addictive Disorders

P-02-001 Regulation of CB1 receptor protein and mTOR signaling in the cerebral cortex of cocaine addicts and cocaine-treated mice

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Objective: Endocannabinoids, CB1 receptors and dopamine D2 receptors interact to induce the effects of the psychostimulant cocaine. This study assessed the status of CB1 receptor protein and its downstream partner the mammalian target of rapamycin (mTOR, a serine/threonine kinase) in brains of cocaine addicts and cocaine-treated mice.

Methods: Postmortem prefrontal cortex (PFC/BA 9) was collected from cocaine addicts (5M/4F; 35±7 yr; 28±7 PMD) and healthy matched controls (5M/4F; 40±4 yr; 27±7 PMD). Toxicology at autopsy (blood and hair) revealed long-term abuse of cocaine only. CDI mice were treated (i.p.) with saline/vehicle (n=7/5), cocaine (acute: 20 mg/kg, 2 h; n=5; chronic: 20 mg/kg, 7 days, n=8) or WIN55, 212-2 (CB1 agonist; acute: 8 mg/kg, 1 h, n=5; chronic: 1–8 mg/kg, 5 days, n=5). CB1 protein (total homogenate and subcellular fractions) and p-mTOR/mTOR ratio (kinase activation in total homogenate) were quantified by Western blot analysis with specific antibodies.

Results: Cortical CB1 receptor protein was reduced in long-term cocaine addicts (44±9%, p=0.03) compared to matched controls. Chronic cocaine in mice also reduced cortical CB1 receptor protein (44±8%, p=0.01). CB1 protein (chronic cocaine; human and mouse cortex) was reduced in membranes (10–31%) and augmented in cytosol (11–23%), indicating receptor internalization. Acute WIN55, 212-2 and acute cocaine activated cortical mTOR kinase (140% and 70%, respectively). In contrast, chronic WIN55, 212-2 and chronic cocaine did not induce mTOR activation (induction of receptor tolerance). Similarly, mTOR was not significantly activated in PFC/BA 9 of long-term cocaine addicts (22±10%, p=0.05).

Conclusion: Cortical CB1 receptor protein is downregulated after chronic exposure to cocaine in humans and mice, which indicates the participation of endocannabinoids in cocaine addiction. In line with this novel finding, the signaling of CB1 receptors involving the activation of mTOR was dampened after chronic cocaine in human and mouse brains.

Policy of full disclosure: Supported by SAF2011–29918 (MEC-FEDER, Spain) and RETICS RD06/001/003 (MSC-FEDER, Spain).

P-02-002 Substance use disorders, psychiatric comorbidity, social vulnerability and long term outcome; a five year follow-up

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Objective: Although substance use disorders (SUD) among adolescents are poorly understood, it is well known that SUD in teenagers is associated with comorbid mental disorders and other adverse conditions in adult life. The aim of the study was to identify risk factors in early adolescence associated with presence of SUD five years later.

Methods: A representative sample of 180 adolescents, who had consulted a clinic for substance misuse problems, and their parents, were assessed at first contact with the clinic. The 180 adolescents and their 251 parents completed questionnaires and diagnostic interviews measuring psychopathology, substance use, maltreatment, victimization, criminality and poverty. Follow-up measurements took place five years from baseline including 147 participants from the original sample.

Results: Increased odds for presenting with SUD at five follow-up were shown for females with baseline experience of victimization by peers, sexual abuse, mothers with alcohol use disorder, fathers with drug use disorder and treatment for SUD. Male reports of baseline violent criminality and treatment for SUD elevated the odds for drug use disorder at follow up. Adjusting for baseline SUD, the odds increased among both males and females to present the same disorder five years later.

Conclusion: SUD were shown to be persistent over time. Treatment displayed no effect. Female SUD are shown to be affected largely by social context rather than individual factors. This was not shown for males.

P-02-003 Diagnosis of psychotic disorders in tirana psychiatric emergency in the context of substance use


Objective: For patients, who actively use substances and manifest psychotic symptoms, remains a challenge to define whether psychotic symptoms are due to a primary psychotic disorder or caused by substance use. Therefore it is most important the clarification of the nature of psychosis in such patients, especially during first psychotic episode. This clarification impacts the plan to their further treatment.

Methods: Patients (males and females) aged over 16 years old presenting to the Emergency of Psychiatry and hospitalized during the period January 2008–December 2011 are included, diagnosed with psychotic disorders according to DSM-IV.

Results: Data gained from this study indicate the percentage of cases diagnosed with primary psychotic disorders and how many emergency admissions are not psychotic or psychotic disorders caused by the use of substances. Diagnostic agreement was generally low (κ=0.32). Percentage of patients diagnosed with primary psychotic disorders is higher than those diagnosed with psychotic disorders caused by substances, and are treated with antipsychotics (p<0.001).

Conclusion: Clinicians in Psychiatric Urgency seem to have a tendency to attribute the psychotic symptoms rather to a primary psychotic disorder than to a concurrent substance abuse. This is a fact, which shows the importance of psychotic symptoms. The diagnosis implies with the management of psychosis significantly in the future, so it is important to improve diagnostic techniques in psychiatric emergencies.

P-02-004 Preliminary study about the vulnerability to drug consumption associated with human single nucleotide polymorphisms of CNR1, FAAH and COMT genes

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Objective: Genetic variants, such as single nucleotide polymorphisms (SNPs), influence the vulnerability to addictive behavior. SNPs present in the cannabinoid receptor 1 gene (CNR1) and the fatty acid amide hydrolase enzyme (FAAH) have been repeatedly associated with marijuana and alcohol abuse, whereas other SNPs in the dopaminergic D2 receptor D2 (DRD2) and the catechol-o-methyltransferase enzyme (COMT) have been related to cocaine and nicotine addiction. In this work we have tried to examine the association between several SNPs of the cannabinoid and catecholaminergic systems with self-reported drug consumption.

Methods: For this, DNA samples from voluntary students from the Complutense University of Madrid (Spain) were sequenced and their drug consumption habits were assessed. Moreover, participants were asked to complete valence ratings of drug-related and non-drug-related pictures.

Results: The results showed a significant association between five analyzed SNPs and drug consumption. Valence of drug-related pictures was much more positive within drug consuming participants. For example, tobacco smokers rated tobacco images significant more pleasant than ex-smoker or non-smoker.

Conclusion: Here, we provide preliminary evidences for the association of SNPs present in the cannabinoid and catecholaminergic system...
system with drug consumption. In addition, it is very robust the effect that drug consuming people show higher emotional preference for drug-related stimuli than non-drug consuming people.

**P-02-005** Patological gambling in patients under treatment for Parkinson disease

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**Objective:** The prevalence of Pathological Gambling (PG) is higher among patients with Parkinson Disease (PD) than within general population. (1) This fact could be related to the pharmacological treatments used in PD. This work aims to be a review about epidemiological, clinical and neurobiological features implied in PG in PD.

**Methods:** We looked trough Medline for articles published after 2007 regarding PG in PD. Furthermore, we will present two cases of PD in which PG is developed.

**Results:** Prevalence of Impulse Control Disorders (ICD) in PD is assessed in 4-14%, this includes compulsive shopping (5.7%), PG (5%), compulsive eating (4.3%) and hipersexuality (3.6%)(ref). The most important risk factors for the development of PG in PD are treatment with dopaminergic agonists and L-dopa used, followed by early onset of PD, long course PD and either familiar or personal history of Addictive Disorders (AD) (2). It seems that the neurobiological mechanism of PG in PD has to do with the cortico-striatal pathways, changes in the phasic secretion of dopamine and over stimulation of D2 receptor, D3 senzitancion and long-term plastic changes as a result of the former. Management of PG in PD is complex; an early diagnosis, psicoeducation and behavior measures are of great importance. As to the pharmacological strategies, lowering doses of dopa agonists with augmentation of L-Dopa, switching for another dopa agonist, treatment cessation and use of other drugs (such as antipsychotics, SSRI, mood stabilizers, amantadine, or zonisamide might be helpful (3).

**Conclusion:** 1. The relationship between PG and PD seems to be mediated by PDs pharmacological treatment rather than PD itself. 2. A subpopulation of patients with PD could have subclinical features that make them prone to the development of PG.

**P-02-007** Maladaptive schemas and coping strategies of substance dependents

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**Objective:** Substance dependence is a prevalent and chronic behavioral health problem. The aim of this study was to evaluate the substance dependents in terms of their maladaptive schemas and coping strategies.

**Methods:** Thirty one male patients (M = 24.12 ± 4.44) who were diagnosed with substance dependence according to DSM-IV criteria and hospitalized for detoxification, participated in the study. Subjects were screened for HIV, HBV and HCV markers. Schemas and coping strategies of substance dependents were evaluated using Young Schema Scale and COPE. Socio-demographic properties, kind of substance use, frequency and duration of substance use were obtained via socio-demographic information form. Moreover, each participant was evaluated through SCID-I and patients with any comorbid psychiatric disorder were excluded from the study. The control group composed of 31 male subjects (23.32 ± 2.85) without any psychiatric disorders and was evaluated through the same procedure.

**Results:** MONOVA results revealed that in terms of schemas, substance dependents scored significantly higher than control group in abandonment/installability, mistrust/abuse, defective-ness/shame, social isolation/alienation, dependence/incompetence, exhaustion/undeveloped self, failure, insufficient self-control/self-discipline, subjugation, self-sacrifice, approval-seeking/recognition-seeking, negativity/pessimism, emotional inhibition, unrelated standards/hypercriticalness, punitiveness. In terms of coping strategies, substance dependents scored significantly lower than control group in positive reinterpretation and growth, seeking social support for instrumental reasons, active coping, turning to religion, seeking social support for emotional reasons, and scored significantly higher than control group in alcohol-drug disengagement.

**Conclusion:** These findings support the importance of early maladaptive schemas which might be underlying the dependency problem and prevent the person to deal with the problem with more active and problem focused coping strategies. Therefore, in cognitive-based psychotherapeutic approaches for patients with substance dependence, it would be effective to focus on maladaptive schemas and coping strategies as part of the treatment procedure.

**P-02-008** Suppression of alcohol-dependence using high-dose baclofen: A two-year observational study of 100 patients

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**Objective:** Evaluate alcohol-dependence suppression by baclofen in a large cohort of patients.

**Methods:** Patients with treatment-resistant alcohol dependence seeking baclofen treatment were treated with escalating doses of baclofen and observed for 24 months. The baclofen treatment was evaluated after 6 months was remarkable. The average maximal dose of baclofen taken was 147 mg/day. Significant relationships were found between the amount of alcohol taken before treatment and the maximal dose of baclofen required, and between the existence of a mental disorder and a lesser effect of baclofen. Side-effects were common, but always benign.

**Conclusion:** Baclofen produces an effortless decrease or suppression of alcohol craving in almost all patients when it is prescribed with no superior limit of dose. Potential limitations in the effectiveness of baclofen include the coexistence of a mental disorder, the concomitant use of other psychotropic drugs, a lack of real motivation in patients to stop drinking, and an impossibility to reach the optimal dose of baclofen because of a limited capacity of certain patients to tolerate undesirable side-effects.

**P-02-009** The alpha-2-adrenoceptor agonist guanfacine significantly decrease voluntary ethanol intake in wistar rats

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**Objective:** Alcohol use disorder (AUD) is a chronic relapse disease. However, only three medications, with limited clinical efficacy, are available. Thus, new effective medications are needed. High rates of cravings, even after long periods of abstinence, in combination with decreased cognitive functions including impaired decision making and impulse control often lead to relapse in drinking. It has been suggested that increased release of noradrenalin during abstinence contributes to the impaired impulse control. Thus, enhancement of cognitive function through inhibition of the noradrenalin system may serve as novel treatment strategy for AUD. Recent studies show that the FDA-approved ADHD-medication guanfacine (an alpha-2-adrenoceptor agonist) attenuate reinstatement of alcohol seeking in rats. Here we evaluated the effects of guanfacine, on voluntary ethanol intake in Wistar rats following long-term voluntary ethanol consumption.

**Methods:** Wistar rats were given intrermittent-access to 20% ethanol (three 24-hour-ethanol-sessions per week; Mon, Wed and Fri) for at least three months before treatment. Acute guanfacine treatment (0.3 and 0.6 mg/kg) was given to rats voluntarily consuming low (1.9 ± 0.2 mg/kg/24 hr; n = 7) or high (4.3 ± 0.2 mg/kg/24 hr; n = 11)
amounts of ethanol. Repeated guanfacine treatment (0 and 0.6 mg/kg/day over 5 consecutive drinking sessions) were given to a group of rats consuming high amounts of ethanol (4.3 ± 0.2 mg/kg/24 hr; n = 12). All injections were given 30 minutes before the ethanol-drinking session started. Thus, the rats had undergone 23 hours of abstinence at the time of treatment.

**Results:** Acute and repeated guanfacine treatment selectively decreased ethanol intake in high, but not low, ethanol consuming rats. The repeated guanfacine treatment indicating that no tolerance to guanfacine’s ability to decrease ethanol intake develops over time. Moreover, there was no post-treatment rebound increase in ethanol consumption.

**Conclusion:** The present study gives further support for the hypothesis that the cognitive enhancer guanfacine may serve as a novel treatment for AUD.

**P-02-010** Anterior cingulate (AC) glutamate, cravings for alcohol and depressive symptoms

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**Objective:** Converging evidence indicates acute disruption in glutamatergic neurotransmission is associated with symptoms of alcohol intoxication and withdrawal. We wanted to evaluate the relationship between AC glutamate and cravings for alcohol and depressive symptoms.

**Methods:** 14 subjects (mean age = 43.0 ± 13.0; 8 females and 6 males) with alcohol dependence admitted to residential treatment have enrolled in the study. Single-voxel 2D J-resolved PRESS H-MRS of the AC was measured ~5 days from last drink and reported as Glx/creatine (Glx/Cr). Cravings for alcohol were measured by the Penn Alcohol Craving Scale (PACS) and self-report symptoms of depression were rated with the Patient Health Questionnaire (PHQ-2).

**Results:** Inverse correlations were found between Glx/Cr and PHQ-2 (r = −0.62, p ≤ 0.019) and Glx/Cr and PACS (r = −0.51, p = 0.066) indicating depressed mood, anhedonia, and alcohol craving were associated with decreased AC glutamate. When subjects were divided into both depressed (PHQ 2 ≥ 3) vs. non-depressed (PHQ 2 < 3) and high-craving (split at median) vs. low-craving groups, Glx/Cr was significantly reduced in depressed and high-craving groups.

**Conclusion:** Alcohol craving and depressive symptoms during early abstinence may be associated with a glutamate deficit in the AC. Our findings are in contrast to previous clinical studies which may be related to different methodology including the length of early abstinence period. As this sample is 5 days from last drink we conclude that the acute withdrawal period has passed and our data captures a period of relative glutamate deficit prior to normalization.

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**P-02-011** Sulforaphane as a therapeutic drug for methamphetamine abuse

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**Objective:** Accumulating evidence suggests a role of oxidative stress in the pathophysiology of substance abuse. Sulforaphane (SFN), found in cruciferous vegetables, is a potent antioxidant. It is, therefore, of interest to determine whether SFN can attenuate behavioral and neuropathological changes in mice after administration of psychostimulant methamphetamine (METH).

**Methods:** The effects of SFN on acute hyperlocomotion and the development of behavioral sensitization induced by the administration of METH were examined in male Balb/c mice. Levels of dopamine (DA) and its major metabolite 3,4-dihydroxyphenyl acetic acid (DOPAC) in the striatum were measured. In addition, immunohistochemistry for DA transporter (DAT) and MAC1 (microglia activation) was also performed.

**Results:** Pretreatment with SFN (1, 3, and 10 mg/kg) elicited a dose dependent attenuation of acute hyperlocomotion in mice after a single administration of METH (3 mg/kg). The development of behavioral sensitization after repeated administrations of METH (3 mg/kg/day, once daily for 5 days) was significantly reduced by pretreatment with SFN (10 mg/kg). In addition, the lowering of DA levels and DOPAC as well as DAT immunoreactivity in the striatum after repeated administration of METH was significantly attenuated by both pretreatment and the subsequent administration of SFN (10 mg/kg). Furthermore, SFN (10 mg/kg) significantly reduced microglial activation in the striatum after repeated exposure to METH.

**Conclusion:** These results suggest that SFN could be a potential therapeutic drug for the treatment of METH abuse since it is a safe for human consumption.

**P-02-012** A study on the effectiveness of electroacupuncture as adjunctive treatment among methadone maintenance therapy clients in University of Malaya Medical Center, Kuala Lumpur, Malaysia

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**Objective:** To investigate the role of acupuncture as an adjunct treatment for opiate dependent individuals.

**Methods:** Prospective, open-labelled, parallel, randomized-control trial will be conducted in the University of Malaya Medical Centre from Feb 2012 till December 2013. One hundred and twenty subjects who fulfilled Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for the opiate dependence receiving methadone maintenance therapy were randomly assigned into two groups. Subject will receive the methadone based on the National Guidelines of Malaysian Ministry of Health. Treatment group will receive electroacupuncture stimulation at 1.1–80 Hz while control group will receive Sham acupuncture for 30 minutes per session as followed: first week (five times per week), second week (two times per week) and third week to following weeks until one year (once a week). Outcome assessment will use structured questionnaires such as Opiate Treatment Index (OTI) to measure drug use, HIV risk-taking behaviours, social functioning, criminality, health status and psychological functioning. The World Health Organization Quality of Life–BREF (WHOQoL-BREF) will use to measure physical health, psychological health, social relationships, and environment. In addition, Clinical Opiate Withdrawal Scales (COWS) will use to measure the withdrawal syndrome in opiate dependence individuals.

**Results:** From this study, we expected to come out with acupuncture group has better results of outcomes measures as compare to control group.

**Conclusion:** The result of this study suggests that acupuncture add on treatment on top of methadone therapy potentially have additional advantage in reducing withdrawal intensity and better outcomes for overall.

**Policy of full disclosure:** This study was supported by High Impact Research Grant under The Ministry of Higher Education of Malaysia.

**P-02-013** Changes in serotonergic modulation of neuronal activity in the nucleus accumbens following repeated methamphetamine administrations in rats

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**Objective:** Electrophysiological studies were performed to determine whether or not serotonergic modulation on neuronal activities (including synapses) in the nucleus accumbens (NAcc) was affected after repeated methamphetamine (MAP) administrations.

**Methods:** Rats (age range: 5–8 weeks) were administered with either MAP (5 mg/kg; i.p.) or an equal volume of saline once daily for 5 days. Brain slices containing NAcc (thickness: 400 micro-m) were
prepared 5 days after the final injection of MAP or saline. Population spikes (PS) induced by local stimulation of NAcc were recorded with a glass microelectrode placed in the same nucleus. All agents with the same dose (10 microM) were tested via a bath perfusion system.

**Results:** Compared with the saline-treated group, PS inhibition by 5-HT was significantly attenuated in the MAP-treated group 5 days after treatment. Although administration with 8-OH-DPAT (a 5-HT1A receptor agonist) suppressed PS, the inhibition rate was not significantly affected by repeated MAP treatment. In addition, alpha-methyl-5-HT (a 5-HT2A receptor agonist)-induced inhibition was slightly reversed without significance in the MAP group. However, significant different effects on PS with m-chlorophenylbiguanide (5-HT3 receptor agonist) and 8-OH-DPAT (a 5-HT4 receptor agonist) were observed in the MAP group (vs. saline group). EMD 386088 (a 5-HT4 receptor agonist) did not affect PS in both groups. Interestingly, although slight (about 10%) enhancement effect on PS was noted in the saline group, AS 19 (a 5-HT7 receptor agonist) significantly enhanced PS in the MAP group.

**Conclusion:** In fact, 5-HT-induced inhibition of PS in NAcc was attenuated 5 days after termination of repeated MAP treatment: an effect probably due to enhancement of the excitatory modulation via the 5-HT7 receptor.

**P-02-014** Dextromethorphan induced bipolar disorder

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**Objective:** There are very few case reports in the literature linking dextromethorphan inducing bipolar disorder We describe a patient who developed recurrent episodes of mania following sustained dextromethorphan use and which resolved after cessation of its use.

**Methods:** The patient is a 42 year old male, who had a history of heroin, subutex and midazolam use in the past but completely stopped its use in 2008. He started consuming dextromethorphan tablets about 30 tablets a day (450 mg daily) since May 2011 2 to 3 times a week. He did not consume any other illicit drugs or alcohol. He started exhibiting symptoms of mania 2 to 3 weeks after starting dextromethorphan which required inpatient admission for a week. Symptoms resolved after a few days of admission. He had a second admission on 17th June 2011 after he restarted dextromethorphan use after discharge. He exhibited short lived manic symptoms which settled after 1 week of admission. This was followed again by a third episode of mania which occurred in September 2011 which lasted for 2 weeks and required inpatient admission. There was no past history of either manic or depressive episodes prior to onset of use of dextromethorphan or any significant family history.

**Results:** All these 3 episodes of mania occurred after heavy consumption of dextromethorphan use and resolved with cessation of use.

**Conclusion:** This report adds to the existing sparse literature about dextromethorphan inducing manic episodes.

**P-02-015** Sequence variation in GATA4 gene is associated with alcohol dependence

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**Objective:** Recent studies suggested that an intronic SNP (rs13273672) in the GATA4 gene encoding GATA-binding protein 4 is associated with alcohol dependence (Treutlein et al., 2010) and relapse following treatment with acamprosate (Kiefer et al., 2011). To replicate this finding and further explore potential associations between alcohol dependence and sequence variation in GATA4 gene we investigated the association of alcohol dependence with this SNP as well as 10 haplotype tagging SNPs in the GATA4 gene.

**Methods:** GATA4 SNPs were genotyped in 816 alcohol dependent cases and compared with the same SNPs 1248 controls previously genotyped as part of a genome-wide association study. When multiple SNPs in a gene are associated with a trait, a gene-level test may be a powerful approach for detecting association with variation in the gene. We therefore performed a global test for association of alcohol dependence with variation in the GATA4 gene using principle components analysis involving the 11 genotyped GATA4 SNPs.

**Results:** Our analyses did not provide significant evidence for association of alcohol dependence with SNP rs13273672. However, nominal evidence of association (p < 0.05) was obtained for five of the other ten GATA4 SNPs, including rs11012596, rs809204, rs8043283, rs6601604, and rs12550668. Significant evidence of association between GATA4 and alcohol dependence was observed at the gene level (p = 0.009).

**Conclusion:** Our findings do support potential role of GATA4 variation but not rs13273672 SNP in alcohol dependence. Further studies are needed to identify the potentially causal variant(s) and the functional mechanism contributing to this association. As part of the ongoing work of our NIAAA-funded alcoholism research center (Mayo Clinic Center for Individualized Treatment of Alcohol Dependence) we will investigate the association of these SNPs with response to acamprosate treatment.

**P-02-016** Influence of betaxolol/BTX on the methamphetamine (MAP) dependence mice

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**Objective:** We investigated the effect of BTX in MAP.

**Methods:** Animal mice were used in conditioned place preference test, Statistical analysis: one-way ANOVA/Kruskal-Wallis test.

**Results:** The repeated administration of BTX (5 mg/kg, i.p) 30 min prior to the exposure to MAP significantly reduced the development of MAP-induced CPP. When BTX was administered 24 h prior to the CPP testing session, it also significantly attenuated CPP, but not changed locomotor activity. In the drug-prime reinstatement study, the extinguished CPP was reinstated by MAP (0.125 mg/kg, s.c.) injection & this was significantly attenuated by BTX.

**Conclusion:** BTX has a therapeutic and preventive effect on the development, expression & drug-prime reinstatement of MAP induced CPP.

**P-02-017** Anxiety-like response to methamphetamine in adult mice is not altered by prenatal exposure to modafinil

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**Objective:** Methamphetamine (MET) is a commonly abused psychostimulant drug. Modafinil (MDF), a drug registered for treatment of narcolepsy, is often consumed by young fertile generation for its stimulatory properties, and thus it is important to assess its behavioural toxicity in offspring. This study investigated influence of prenatal exposure to MDF and MET on anxiety-like measures after acute and chronic administration of MET in adult mouse males using elevated plus maze.

**Methods:** Pregnant female mice were given nine daily doses of saline (SAL, 10 ml/kg/day), MET (2.5 mg/kg/day) or MDF (50 mg/kg/day). Effects of the same treatment doses were evaluated in adult male offspring in six experimental groups: SAL or MET treated offspring with prenatal exposure to SAL, MET and MDF. Anxiety was assessed as % of entries and time spent in open and closed arms in the elevated plus maze on: Day 1 – naive mice (no drug dose, baseline conditions). Day 8 – acute dose of SAL or MET. Day 15 – challenge dose after one week of repeated SAL or MET administration.

**Results:** At baseline conditions on the Day 1, prenatal treatment with MDF increased % of entries and time spent in the closed arms compared to SAL prenatal administration (but did not significantly affect behaviour in the open arms). Prenatal administration of MET did not alter anxiety-like behaviour compared to prenatally naive animals. Anxiety-like response to acute dose (Day 8) or chronic treatment (Day 15) of MET in the elevated plus maze was not altered by different prenatal exposures (SAL compared to MET and MDF).

**Conclusion:** We can conclude that prenatal treatment with MDF increases anxiety at baseline conditions. However, there were observed no differences in reactivity to postnatal administration of...
Objective: The primary aim of this study was to investigate whether daily alcohol consumption and Breath Alcohol Content (BrAC) affect the incidence of Delirium Tremens and Alcohol-related seizures in patients admitted for alcohol detoxification.

Methods: The study comprised of a cross-sectional survey in which data was collected from 100 consecutive inpatients admitted for alcohol detoxification in the unit in 2010. Data was collected from the clinical records of the patients and we looked at demographics, daily alcohol consumption, Breath Alcohol Content at admission and current episode and past history of delirium tremens and alcohol-related fits.

Results: We noticed that 14 patients experienced Delirium Tremens and 10 patients experienced alcohol-related fits during their current admission whilst 36 patients had a past history of Delirium Tremens and 40 had a past history of alcohol-related fits. 2 patients experienced both Delirium Tremens and fits. All these patients had a daily consumption of alcohol higher than 30 units of alcohol. 86 % (12/14) of the patients who developed Delirium Tremens and 90 % (9/10) of patients who had alcohol-related fits had a Breath Alcohol Content of more than 1.00 at admission.

Conclusion: Daily alcohol usage and Breath Alcohol Content at admission could be related to a risk of developing Delirium Tremens and Alcohol-related fits during the detoxification process. This can aid in identifying high risk patients and help reduce their morbidity.

Objective: The concordance of ecstasy intoxication after single doses of MDMA. The concordance of ecstasy intoxication after single doses of MDMA.

Methods: Seventeen polydrug MDMA users entered this placebo controlled within subject study with four treatment conditions. The treatments consisted of MDMA (75 mg) and Metyrapone occurred 1 h prior to MDMA or Placebo administration. Memory performance was tested at peak drug concentrations by means of several memory tests. Cortisol levels were determined in blood; this served as a control measure to see whether episodes and past history of delirium tremens and alcohol-related fits.

Results: As delerium tremens and alcohol-related seizures in inpatients admitted for alcohol detoxification related to daily alcohol consumption and breath alcohol content on admission?

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Cortisol levels and MDMA-induced memory impairment

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Objective: Ecstasy use is commonly linked with memory deficits in abstinent ecstasy users. Similar impairments are being found during ecstasy intoxication after single doses of MDMA. The concordance of memory impairments during intoxication and abstinence suggests a similar neuropharmacological mechanism underlying acute and chronic memory impairments. The mechanism underlying this impairment is to date not known. We hypothesized that cortisol might play an important role in this mechanism as cortisol, implicated in the regulation of memory performance, can be brought out of balance by stressors like MDMA. In the present study we aimed to block the MDMA-induced acute memory defect by giving participants a cortisol synthesis inhibitor (Metyrapone®) together with a single dose of MDMA.

Methods: Seventeen polydrug MDMA users entered this placebo controlled within subject study with four treatment conditions. The treatments consisted of MDMA (75 mg) and Metyrapone® (750 mg), alone and in combination, and double placebo. Pretreatment with Metyrapone or Placebo occurred 1 h prior to MDMA or Placebo administration. Memory performance was tested at peak drug concentrations by means of several memory tests. Cortisol levels were determined in blood; this served as a control measure to see whether manipulations were effective.

Results: Main findings indicated that whereas treatment with Metyrapone blocked the expected MDMA-induced increase in cortisol levels in blood, it did not prevent the MDMA-induced memory deficit from happening.

Conclusion: We therefore conclude that MDMA-induced increases in cortisol concentrations are not responsible for impairing memory performance while intoxicated with MDMA.

P-02-021 Cocaine reverses naltrexone-induced reduction in operant ethanol self-administration

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Objective: Naltrexone is a clinically approved medication for alcoholism. We aimed to investigate the efficacy of naltrexone when there is an interaction with cocaine and their associations with immediate-early gene expression in the prefrontal cortex.

Methods: Using rats, we designed the experiments to maximise their predictive validity in humans. We used chronic operant ethanol self-administration and treatments (p.o.) prescribed for alcoholism. We performed real-time PCR analysis to determine gene expression levels.

Results: Only the highest dose of naltrexone (10 mg/kg) reduced ethanol intake. Cocaine increased ethanol self-administration dose-dependently (2.5, 10, 20 mg/kg) and reverted the naltrexone-induced reduction. Naltrexone failed to prevent cocaine-induced increase in locomotor activity observed in these animals. Ethanol caused a reduction in C-fos gene expression and an overexpression of the COX-2 and Homer1a genes in the rat prefrontal cortex. Neither the suppressive effects of naltrexone nor the cocaine-induced increase of ethanol self-administration were related to the genetic changes observed.

Conclusion: Chronic ethanol self-administration is prevented by naltrexone, but cocaine fully reverses this effect. This suggests that cocaine may overcome the efficacy of naltrexone as a treatment for alcoholism. The ethanol-induced reduction in C-fos gene expression in the prefrontal cortex reveals an abnormal activity of these neurons, which may be relevant for compulsive drinking of ethanol, the regulation of behaviour and the control of reward-related areas.

P-02-022 Modification of prepulse inhibition of the startle reflex during detoxification treatment in alcohol dependent males

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Objective: Prepulse inhibition (PPI) of the startle reflex refers to the ability of innocuous sensory events to reduce startle reflex and it has been described as an operational measure of sensorimotor gating. It has been reported that alcohol withdrawing patients show a significantly decreased PPI, which reaches its lowest point on the first and third day of abstinence and increases progressively after the first week. The aim of this study was to explore modifications in PPI levels during alcohol withdrawal syndrome and detoxification treatment in alcohol dependent males.

Methods: 15 male patients, aged 18 to 55 years, who met DSM-IV criteria for alcohol dependence, were recruited through the Outpatient Alcohol Unit at the Hospital 12 de Octubre, Madrid. Patients were detoxified for a period of 10–14 days using benzodiazepines and/or anticonvulsants. They underwent testing for PPI at baseline and after detoxification had concluded.

Results: At baseline, patients exhibited remarkably low levels of PPI. After 10–14 days of detoxification treatment, PPI percentage significantly increased, specifically at both 30-ms (p<0.001) and 60-ms (p<0.05) prepulse-to-pulse interval. At 120-ms prepulse-to-pulse interval, no significant differences between baseline and post-detoxification were found.

Conclusion: These data suggest that sensory information processing could be damaged in withdrawing alcohol dependent patients, probably due to neurotoxicity of alcohol over CNS.
Objective: To describe a sample of dual diagnosed patients who were included in a methadone maintenance program at the time of discharge of a brief dual diagnosis unit. More specifically we try to find distinguishing characteristics between patients treated with standard therapeutic doses of SD (from 60 mg/day) and those treated with low doses of methadone (LD; less than 60 mg/day).

Methods: Data on demographic, family, and clinical factors were gathered among subjects admitted to our dual diagnosis unit between September 2007 and September 2011, all of them meeting DSM-IV criteria of any non-substance related Axis I or II disorder and comorbid substance use disorder (SUD). Statistical analysis was performed by using SPSS program.

Results: From the whole sample (N = 134), age 38.7 ± 7.6, most of them (68.7 %) were male. Mean length of stay were 20.8 ± 20.6. Distribution of non-SUD diagnosis was as follows: psychiatric disorders (40.3 %), personality disorders (39.5 %), depressive disorders (8.2 %), bipolar disorders (6 %) and adjustment disorders (6 %). In our sample, most common comorbid SUD (except opioid use disorder) was cocaine (64.2 %) and alcohol (32.1 %). Comparing to LD group (N = 86; 64.2 %), we found that SD group (N = 48; 35.8 %) had more prevalence of sedatives SUD, sedatives treatment both at admission and at discharge, and antipsychotic treatment at admission. In addition, we also observed an early onset of consumption of sedatives, heroin and nicotine and, in turn, an earlier onset of problematic use of alcohol, sedatives, heroine, cannabis and nicotine. It also aimed to lower consumption of cocaine and heroin in the last 30 days prior to current admission.

Conclusion: Patients treated with standard therapeutic doses of methadone showed higher prevalence of sedatives SUD and a more severe profile of substance use in respect with those patients treated with suboptimal methadone doses.

Objective: To analyze differences between patients admitted for suicidal ideation and those who join for other reasons, within the group of patients with Personality Disorders and Substance Use Disorders (SUD) comorbid admitted to a brief dual diagnosis unit.

Methods: Total of patients admitted to our dual pathology unit between September 2007 and December 2011 and who met DSM-IV criteria for diagnosis of Personality Disorder and comorbid SUD were included. Data on demographic, family, and clinical factors were collected.

Results: From the whole sample (N = 250), age 38.5 ± 8.8, most of them (64.4 %) were male. The main drugs of abuse were alcohol (47 %), cocaine (26.9 %) and cannabis (10 %). Comparing to non-suicidal ideation group (N = 163; 65.2 %), we found that suicidal ideation group (N = 87; 34.8 %) had more prevalence of females (47.1 % vs. 29.4 %; p = 0.008), higher rates of taking a drug treatment regularly during the 6 months previous to hospital admission (32.4 % vs. 18.9 %; p = 0.038), had more previous history of suicide attempts (91.2 % vs. 64 %; p < 0.001) and more prevalence of comorbid Opioids Use Disorder (37.9 % vs. 19.6 %; p = 0.002). This group received more antidepressive drugs (64.4 % vs. 41.7 %; p = 0.001). Non-suicidal ideation group had more patients admitted involuntarily (35.6 % vs. 9.2 %; p < 0.001), more previous history of physical aggression (75.3 % vs. 58 %; p = 0.038), higher prevalence of comorbid diagnosis of Psychosis (21.3 % vs. 3.4 %; p = 0.003), Antisocial Personality Disorder (22.1 % vs. 6.9 %; p = 0.002), Amphetamines Use Disorder (9.2 % vs. 0 %; p = 0.002) and Cannabis Use Disorder (36.2 % vs. 21.8 %; p = 0.02). This group showed a tendency to receive more antipsychotic drugs (70.6 % vs. 58.6 %; p = 0.068).

Conclusion: Sex, type of SUD and comorbidity with other axis I disorders, could distinguish Personality Disorders if they are or not admitted for suicidal ideation.
banned it, there is still an high number of Pro Drugs websites that actively promote to consume it. Very limited information is available on the safety of Spice ingredients in humans and the occurrence of serious health damage in abusers is highly probable, as is the likelihood of prompting the development of psychotic symptoms and full psychotic episodes.

**P-02-029** Association between the fyn kinase gene and patients with methamphetamine psychosis

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**Objective:** Dysfunction of the N-methyl-D-aspartate (NMDA) receptor has been considered to underlie the pathophysiology of psychotic disorder including schizophrenia and substance-induced psychoses. We previously reported the significant associations between methamphetamine psychosis and several genes, e.g. the dyshidrine gene, the G72 gene, the serine rasenase gene and the GRIN1 and 2B genes; those are involved in the glutamatergic signaling and NMDA receptor functions. Fyn kinase is a member of the Src family of tyrosine kinases and mediates phosphorylation of glutamatergic NMDA receptor subunits. Previous studies showed that Fyn is involved in the pathophysiology of neuropsychiatric disorders, such as schizophrenia, alcoholism, epilepsy and Alzheimer’s disease. The FYN gene is localized in the 6q21, which was found in the region linked to neuropsychiatric disorders. Therefore, we investigated the association between the FYN gene and methamphetamine psychosis.

**Methods:** Subjects were comprised of 220 patients and 293 age- and gender-matched healthy controls. We genotyped three polymorphisms, rs706895, rs3730353 and rs6916861, in the FYN gene.

**Results:** There were no significant differences in genotypic or allelic distribution of any polymorphism in the FYN gene between the two groups. Clinical phenotypes of methamphetamine dependence, e.g. age of first consumption, latency from the first consumption to onset of psychosis, complication of spontaneous relapse of psychosis, and poly-substance abuse status, did not significantly associate with any polymorphism. The three SNPs, rs706895, rs3730353 and rs6916861, showed linkage disequilibrium with each other. We then analyzed the 2- and 3-loci haplotype distribution, but no significant difference was found between patients with methamphetamine dependence and control subjects.

**Conclusion:** This study suggested that the FYN gene is unlikely to play a major role in methamphetamine dependence liability and/or the development of methamphetamine induced psychosis, at least in a Japanese population.

**P-02-028** Overexpression of Shati in the nucleus accumbens affects the abnormal behavior induced by methamphetamine in mice

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**Objective:** The abuse of methamphetamine (Meth) has significantly psychiatric and medical consequences, including dependence, psychosis and even death. A novel molecule shati has been identified from the nucleus accumbens (NAc) of mice treated with Meth using the polymerase chain reaction-select complementary DNA subtraction method. In vivo and vitro studies, shati regulates Meth-induced dopamine (DA) release. However, it is not clear which brain regions are involved with the function of shati. In this study, we overexpressed shati in the NAc or dorsal striatum (dS) of mice specifically using adeno-associated virus vectors.

**Methods:** We overexpressed shati in the NAc or dorsal striatum (dS) of mice specifically using adeno-associated virus vectors.

**Results:** Overexpression of shati only in the NAc suppressed Meth-induced hyperlocomotion, sensitization and place preference in mice. Moreover, in vivo microdialysis method revealed that overexpression of shati in the NAc inhibits Meth-induced increase of DA release.

**Conclusion:** These results indicate that shati in the NAc, but not in the dS, plays an important suppressive role in the establishment of Meth-induced dependence by mediating extracellular DA levels.

**P-02-027** Association between risk-taking behavior and voluntary alcohol intake in male outbred wistar rats

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**Objective:** Risk assessment and risk taking versus inhibitory control are evolutionary conserved behaviors of survival value implicated in the multilayered structure of impulsivity. When maladaptive, impulsivity is associated with drug-taking behavior. Previous studies have shown that locomotor activity in a novel environment is useful for identifying individuals at risk for excessive intake of drugs of abuse. In this study we focus on individual differences in risk-taking behavior in a novel environment. We hypothesize that high risk-taking (HRT) animals are prone to higher alcohol intake compared to low-risk-taking (LRT) animals.

**Methods:** Thirty adult male outbred Wistar rats were tested in the open field test. Based on the percentage duration of time spent in the central part of the open field, animals were divided into HRT or LRT. For further behavioral profiling the multivariate concentric square field (MCSF) test was used, which includes a variety of zones including sheltered, open and elevated areas, exploratory incentives, areas with different illumination, and wall-enclosed corridors. The rats then had access to 20% alcohol using a two-bottle free-choice paradigm, with intermittent 24 h access three times per week for five weeks.

**Results:** The results revealed that HRT animals displayed a higher risk-taking behavior also in the MCSF compared to the LRT animals. Moreover, HRT rats showed faster acquisition of alcohol intake, accompanied by higher alcohol preference. Furthermore, risk-taking behavior as defined in the open field test correlated with alcohol preference during the acquisition period.

**Conclusion:** While previous studies have focused on the association between locomotor activity and intake or sensitivity to drugs of abuse, we here demonstrate an association between individual differences in risk-taking behavior, of relevance for impulsivity, and voluntary alcohol intake and preference. The results demonstrate that screening of individual differences is a useful strategy in identifying subgroups of individuals at risk for excessive alcohol intake.
meets the criteria for hospitalization. Opiate dependence regarding the degree of depression best discriminate against Hamilton and Montgomery-Asberg scale.

**P-02-031** How empathetic are cocaine users? A social neuroscience approach

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**Objective:** Although it was proposed that social cognition might play a crucial role in the development and treatment of drug dependence, studies investigating social cognition in drug users are scarce. Chronic cocaine users display neurochemical and functional alterations in brain areas involved in social cognition (e.g., the medial prefrontal cortex and the ventral striatum). Therefore, we investigated mentalizing and empathy abilities in dependent and occasional cocaine users by means of video-based and photorealistic stimuli of everyday situations.

**Methods:** Seventy occasional cocaine users, 37 dependent cocaine users and 70 drug-naive control participants completed the Multifaceted Empathy Test (MET) and the Movie for the Assessment of Social Cognition (MASC). The MET assesses cognitive and emotional empathy by the judgement of emotional pictures. The MASC requires watching a short film and answering 45 questions about the actors’ mental states (Theory-of-Mind, TCM).

**Results:** Dependent cocaine users performed significantly worse on the cognitive empathy scale of the MET than occasional users and controls. In the MASC, dependent cocaine users made more mistakes than occasional users and controls primarily because of exaggerated perspective taking. Furthermore, lifetime cocaine use was significantly correlated with test performance in the MASC. No significant differences were found between control subjects and occasional cocaine users.

**Conclusion:** These results indicate that dependent cocaine users show impairments in specific mentalizing abilities. Cognitive empathy, but not the selective GluN2B antagonist, Ro04–5595; the latter rather impaired perspective taking. Furthermore, lifetime cocaine use was significantly correlated with test performance in the MASC. No significant differences were found between control subjects and occasional cocaine users.

**P-02-032** To assess prevalence of chronic pain among subjects with alcohol dependence syndrome. To study the relationship of alcohol use and its effect on pain

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**Objective:** To assess prevalence of chronic pain among subjects with alcohol dependence syndrome. To study the relationship of alcohol use and its effect on pain.

**Methods:**Patients attending outpatient services of Center for Addiction Medicine in National Institute of Mental Health and Neurosciences, Bangalore, India who fulfilled the diagnostic criteria for alcohol dependence syndrome were screened for chronic pain. Patients having chronic pain were interviewed after obtaining informed consents by following instruments – Semi structured pro-forma to collect details on demography, pain related details and formed consents by following instruments – Semi structured pro-forma to collect details on demography, pain related details and

**Results:** Chronic pain was prevalent in 18.2% of subjects with alcohol dependence syndrome with 49% of them reporting pain to be of severe intensity. Use of other substances (nicotine, benzodiazepines, opioids and inhalants) were found in 96.3% with nicotine use being most common. Use of alcohol to manage pain in last month was reported by 75% of patients while 62% reported pain as a reason to continue to use alcohol. Only 34% of patients were currently receiving treatment for chronic pain and 62% expressed interest in receiving treatment.

**Conclusion:** Chronic severe pain was prevalent in subjects with alcohol dependence syndrome attending an outpatient service. Significant number of them were using alcohol for pain relief and reporting it to be reason to continue to use alcohol. Few patients were taking treatment for pain while larger number expressed interest for effective treatment. Efforts should be made to better address the pain problems in this patient population.

**P-02-033** Blockade of ventral midbrain NMDA receptors prevents neurotensin-induced sensitization to amphetamine

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**Objective:** Previous studies have shown that neurotensin, an endogenous neuropeptide that modulates limbic neurotransmission, plays a key role in the development of sensitization to amphetamine-induced locomotor activity. In this study, we tested the hypothesis that neurotensin acts within the ventral midbrain to initiate amphetamine sensitization and that this effect is dependent upon activation of local NMDA receptors.

**Methods:** Experiments were performed on adult male Long-Evans rats implanted with bilateral cannulae above the ventral midbrain. During a first initiation period, locomotor activity (ambulatory, non-ambulatory and vertical movements) was measured in different groups of habituated rats on three occasions, every second day (day 1, 3 and 5), for two hours after bilateral ventral midbrain injections of vehicle (0.5 ul/side), D-Tyr[1]neurotensin (1.5 nmol/side), RS-CPP (40 or 120 pmol/side), Ro04–5595 (200 or 1200 pmol/side), RS-CP (40 or 120 pmol/side) + neurotensin (1.5 nmol/side) or Ro04–5595 (200 or 1200 pmol/side) + neurotensin (1.5 nmol/side). Five days after the third injection, on day 10, locomotor responses to a single injection of amphetamine sulfate (0.75 mg/kg, ip) were measured in all the animals.

**Results:** Results show that amphetamine induced significantly stronger locomotor responses (ambulatory, non-ambulatory and vertical activity) in neurotensin pre-exposed animals than in controls (vehicle pre-exposed). This amphetamine sensitization effect was prevented by the preferred GluN2A,2B subunit antagonist, RS-CP, but not the selective GluN2B antagonist, Ro04–5595; the latter rather slightly enhanced the effect of neurotensin.

**Conclusion:** These results demonstrate that i) ventral midbrain neurotensin induces glutamate release to initiate neural changes that subserve sensitization to the behavioral effects of amphetamine and ii) this sensitization effect most likely results from activation of ventral midbrain NMDA receptors that are composed of GluN2A subunits. Supported by Canadian Institutes for Health Research (CIHR, Canada).

**P-02-034** Impulsivity in Internet addiction: A comparison with pathological gambling and healthy controls

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**Objective:** be present study investigate trait impulsivity in Internet addiction compared with pathological gambling from the perspective of considering Internet addiction as an impulse control disorder.

**Methods:** Twenty-seven patients with Internet addiction (age, 24.78 ± 4.37 years), 27 patients with pathological gambling (age, 25.67 ± 3.97 years), and 27 healthy controls (age, 25.33 ± 2.79 years) were enrolled in this study. All patients were treatment-seeking, and only male subjects were enrolled. Trait impulsivity was measured by Barratt Impulsiveness Scale-11 and severities of Internet addiction and pathological gambling were Young’s Internet Addiction Test and South Oaks Gambling Screen, respectively. Beck Depression Inventory and Beck Anxiety Inventory were also administered to all subjects.

**Results:** We found that the Internet addiction group showed increased level of trait impulsivity, which was comparable to that in patients with pathological gambling. In addition, severity of Internet addiction was positively correlated with level of trait impulsivity in patients with Internet addiction.
**P-02-035**
Event-related potentials P300 in patients with alcohol dependence and pathological gambling

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**Objective:** This study was designed to evaluate the auditory and visual event-related potential P300 in the patients with alcohol dependence & pathological gambling.

**Methods:** Subjects were composed of patients with alcohol dependence (N=24), pathological gambling (N=24) and normal control (N=24). Topographic auditory & visual event-related potential P300 was measured by “Oddball paradigm”, which was known as a standard method, and was determined by a conventional method, Global Field Power method.

**Results:** In patients with alcohol dependence and pathological gambling, the amplitude of auditory & visual event-related potential P300 was significantly smaller than normal control (p<0.01). The Auditory P300 between alcohol dependence and pathological gambling had no significant differences in the amplitude and latency. In patients with pathological gambling, the latency of visual P300 was significantly later in Fz, Cz, Pz than patients with alcohol dependence (p<0.01).

**Conclusion:** It suggests that patients with alcohol dependence and pathological gambling have brain dysfunction in some neuro-physiological aspects. In patients with pathological gambling, the latency of visual P300 was significantly later in Fz, Cz, Pz than patients with alcohol dependence, and this result suggest that patients with pathological gambling may have more impairment in cognitive function than patients with alcohol dependence.

**P-02-036**
Overuse and abuse of diphenoxylate hydrochloride three case report

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**Objective:** diphenoxylate hydrochloride is an opiate derivative used for treatment of acute diarrhea to be relative safe and with low abuse potential.In last few years we have come across young adults taking heavy doses of diphenoxylate hydrochloride and physically dependent on it.

**Methods:** we report 3 cases where the subjects were taking >100 tablets of diphenoxylate hydrochloride per day.

**Results:** we report 3 cases where the subjects were taking >100 tablets of diphenoxylate hydrochloride per day.all of them started taking the drug when they were trying to stop opiates 2>100 tablets of diphenoxylate hydrochloride per day.3 patients were using multiple substance of abuse.surprisingly the withdrawal symptoms were mild in spite of heavy doses.yawning, staring, watering eyes, legs pain, sleep disturbance, none of them presented with diarrhea.

**Conclusion:** implication of the study and review of literature will be discussed in detail.

**P-02-037**
(-)-OSU6162 potentiates amphetamine-mediated effects in habituated but not in novel environments

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**Objective:** (-)-OSU6162 is a substance belonging to a new class of drugs, termed “dopamine stabilizing drugs”. (-)-OSU6162 binds with low affinity to the dopamine D2 receptor and causes different behavioral responses when administered in novel compared to habituated environments. Here we characterized the environmental impact on the interaction of (-)-OSU6162 and amphetamine.

**Methods:** The locomotor response to (+)-OSU6162 or amphetamine themselves and the combination of the two were measured in animals given the drugs in habituated or novel environments. Immunohistochemistry and in situ hybridization was used to analyze levels of protein and mRNA, respectively, of the immediate early gene c-fos in rats and mice after administration of (+)-OSU6162 and amphetamine.

**Results:** The behavioral studies showed that (+)-OSU6162 increased locomotion in animals habituated to their home cages, but not in animals given the drugs in a novel environment. (+)-OSU6162 caused a dose dependent increase of c-fos mRNA in striatum and nucleus accumbens in habituated animals, with a more homogenous induction compared to amphetamine, which was strongest in medial parts. Protein levels of c-Fos were elevated in medium spiny dopamine D1-receptor neurons of the dorsolateral striatum (+)-OSU6162 itself and even more elevated in the group receiving (+)-OSU6162 thirty minutes prior to amphetamine in their home cages.

**Conclusion:** Locomotion tests in rats given (+)-OSU6162 in combination with amphetamine show that (+)-OSU6162 attenuates amphetamine-mediated locomotion in a novel environment, but has an opposite effect in habituated animals. The c-Fos expression indicated that (+)-OSU6162 has an impact on D1-receptor medium spiny neurons in habituated animals, even though the effect is most likely not directly mediated via D1 receptors as no binding affinity has been reported for (+)-OSU6162 on D1-receptors.

**P-02-038**
The dopamine stabilizer (+)-OSU6162 attenuates voluntary ethanol intake and ethanol-induced dopamine output in the nucleus accumbens

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**Objective:** New medications for alcohol use disorder (AUD) are needed. “Dopamine stabilizers” is a new class of compounds characterized by the ability to suppress, stimulate, or show no effect on dopamine activity depending on the environmental context. Thus, they may be hypothesized to normalize dysregulated dopamine activity induced by, for example, long-term alcohol consumption.

**Methods:** The effects of acute and repeated treatment of the dopamine stabilizer (+)-OSU6162 (OSU6162) was evaluated in rats given intermittent-access to 20% ethanol for at least three months before treatment. OSU6162’s effect on ethanol seeking, using the operant self-administration paradigm, was also evaluated. Furthermore, we studied the interaction of OSU6162 with ethanol on dopamine output and metabolism in awake rats, using microdialysis.

**Results:** OSU6162-treatment selectively decreased voluntary ethanol consumption and preference without decreasing intake of water or a salicylate solution. The effect on ethanol intake was more pronounced in rats voluntarily consuming high compared to moderate amounts of ethanol. There was no tolerance development to OSU6162’s ability to decrease ethanol intake during repeated OSU6162 treatment and no rebound increase in ethanol intake after the treatment was terminated. We found that pretreatment with OSU6162 blunted the ethanol-induced dopamine output in the nucleus accumbens.

**Conclusion:** These results highlight OSU6162’s ability to stabilize dopamine activity depending on the prevailing dopaminergic tone and indicate that OSU6162 might decrease ethanol intake by attenuating the acute rewarding properties of ethanol. The present study is to our knowledge the first indicating that OSU6162 may serve as a novel medication for AUD.

**P-02-039**
Influence of GIRK channel inhibition on relapse inhibition on relapse in Japanese alcohol-dependent inpatients

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**Objective:** We examined the influence of G-protein-activated inwardly rectifying K+ (GIRK) channel inhibition on relapse risk in Japanese alcohol-dependent inpatients.
Methods: The participants included 11 patients who received GIRK inhibition treatment and 39 patients who did not receive GIRK inhibition treatment. The participants answered a questionnaire, including the Alcohol Relapse Risk Scale (ARRS) and a questionnaire about their experiences of stressful events 2 weeks after hospitalization (time 1) and completed follow-up questionnaires 45–60 days after the first rating (time 2).

Results: A significant interaction was found between group and time on positive expectancy for alcohol scores on the ARRS (F = 5.93, p = 0.02). The simple main effect test showed that the scores at time 1 in the GIRK inhibition treatment group were higher than in the non-GIRK inhibition treatment group (p = 0.03). The scores at time 1 were higher than that at time 2 only in the GIRK inhibition treatment group (p = 0.004). Significant main effects of time were found on total ARRS score (F = 7.26, p = 0.001), and these scores at time 1 were higher than at time 2. No significant interaction was found between group and time, with no main effect of either factor on the experience of stressful events.

Conclusion: The results of the present study suggest that GIRK inhibition treatment may improve the positive expectancy for alcohol, a component of relapse risk. However, the lower positive expectancy scores in patients who did not receive GIRK inhibition treatment at time 1 may be responsible for the lack of changes in positive expectancy scores. Although this result should be interpreted with caution, the present study suggests that the effects of GIRK inhibition treatment should be investigated further in future studies.

Objective: To evaluate the efficacy and tolerability of naltrexone use in patients with dual diagnosis- alcohol dependence and cluster B personality disorder.

Methods: A group of 32 patients, 19 male and 13 female, mean age 35.7, admitted in our department for alcohol dependence, were also diagnosed with cluster B personality disorders (antisocial n=9, borderline n=10, histrionic n=10, narcissistic n=3) according to the DSM IV TR criteria. Patients received naltrexone 50 mg/day, single dose daily, after the initial detoxification period (mean duration 8.5 days). Patients were monitored using every 4 weeks for 6 months Inventory of Drug Taking Situations- alcohol focused version (IDTS), Global Assessment of Functioning (GAF) and Clinical Global Impressions–Severity and Improvement (CGI-S/I).

Results: At week 24, patients had an overall improved IDTS score (−4.91 points to baseline, p < 0.01), with greater improvements observed in areas like “physical discomfort” (p = 0.022) and “testing personal control” (p = 0.0324). GAF values increased in the treatment group with 28.5 points, compared to baseline. CGI-I decreased from a mean value of 4.8 to 1.2 at week 24. A number of 7 patients discontinued treatment due to adverse events (vomiting, nausea, abdominal pains, n = 4) or non-compliance (n = 3). Mild and moderate adverse events were reported in 12 patients, especially gastrointestinal discomfort and anxiety.

Conclusion: Naltrexone is a good therapeutic option in alcohol dependent patients with cluster B personality disorder, because of its efficacy and low rate of adverse events. Naltrexone decreased significantly alcohol consumption in situations of “physical discomfort” and testing of personal control.

Methods: The research is based on the statistical method along with the analysis of data of forensic psychological – psychiatric and forensic psychiatric examinations.

Results: The research revealed the following factors leading to the consumption of alcohol, toxic and narcotic substances: group 1 (14 persons) – a one-parent family, where the child was raised by one parent who did not abuse alcohol, group 2 (14 persons) – a one-parent family in which the parent abused alcohol, group 3 (5 persons) – teenagers who do not have parents and close relatives, group 4 (4 persons) – families with both parents abusing alcohol. At the same time 12 of 50 individuals had secure families (they were brought up by both parents who did not abuse alcohol). In group 1, 4 teenagers used alcohol, 5 – inhaled vapors of toxic substances, 2 – used drugs. In group 2, 3 individuals used alcohol, 4 – inhaled vapors of toxic substances, 2 – used drugs. In group 3 all teenagers used alcohol. In group 4 one person used alcohol, 1 – used drugs. However, even among the individuals who were brought up in secure families still there were 3 inclined to alcohol abuse and 2 – to drug abuse.

Conclusion: The teenagers raised in the families with one parent no matter if he/she abused alcohol or not, are more inclined to consumption of alcohol, drugs and other toxic substances. It should also be noted that the family security is not an absolute indicator for the absence of inclination to commit criminally punishable acts and abuse alcohol and narcotic substances.
Poster Sessions, Monday 4 June 2012 – Wednesday 6 June 2012

P-02-045
Morphine excites dopamine neurons(da) in ventral tegmental area(vta): The gating role of prefrontal cortex(pfc)

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Objective: We studied the gating role of PFC in morphine-excited DA neurons in VTA.

Methods: use of in vivo single unit recording techniques and microdialysis to study how PFC regulates VTA dopamine neurons in rats in response to morphine.

Results: We found that morphine markedly increased DA cell activity. The effect of morphine can be reversed and prevented by naloxone, suggesting that the effect is associated with the activation of mu opiate receptor. Lesion of PFC by tetradotoxin produced no significant influence on basal DA cell activity in naïve rats. However, PFC lesion abolished the morphine’s effects on DA cells, accordingly, the morphine – stimulated DA content in NAc was also abolished. This indicates that the PFC is critical in mediating the morphine’s excitation on DA neurons and that the PFC might play a gating role in morphine’s effect on DA cells. Interestingly, in rats pretreated with morphine 24 hours before morphine challenge, the gating role of PFC disappeared. It thus appeared that morphine – enhanced DA neuronal firing is independent of the function of PFC in rats that previously exposed to morphine. Furthermore, we found that morphine inhibited PFC pyramidal neurons in all recorded cells in naïve rats. Whereas only 46% (7 in 15) recorded pyramidal neurons was inhibited by morphine challenge in rats that were previously exposed to morphine.

Conclusion: our data provided evidences that the PFC play a gating role in acute morphine’s effect on DA neurons, The underlying mechanism may attribute to morphine – inhibited PFC pyramidal neurons which leads to the reduced output. However, single morphine pretreatment resulted in loss of the gating effect of PFC, which may associated with the single morphine-induced disinhibition on PFC neurons.

P-03-001
Association of metabolic syndrome and clinical outcome among patients with bipolar disorder

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Objective: Bipolar disorder is with high prevalence of metabolic syndrome, ranging from 32% to 50%. However, the influence of metabolic syndrome for clinical outcome is not clear. This study evaluated the association of metabolic syndrome for clinical outcome among symptomatically stable outpatients with bipolar disorder.

Methods: The patients aged between 18 to 65 years with DSM-IV diagnosis of bipolar disorder and with clinical global severity less than 3 were enrolled. Metabolic syndrome was surveyed and clinical symptoms, side effects, insight, function, life quality, and cognitive executive function were assessed.

Results: The study enrolled 84 patients with 71.4% of female, and average age of 43.9±12.2 years old. The prevalence of metabolic syndrome was 34.5%. The patients with metabolic syndrome tended to have elder age (48.5±11.5 vs. 41.5±11.9, p = 0.084), education years less than 12 years (75.9% vs. 56.4%, p = 0.098), higher frequency of first episode with manic episode (58.6% vs. 33.3%, p = 0.092), more hospitalization times (4.2±3.8 vs. 2.8±3.5, p = 0.067) and poorer executive function of Wisconsin card sorting test percent of conceptual level response (29.0±11.3 vs. 38.2±12.6, p = 0.014).

Conclusion: The prevalence of metabolic syndrome was high to one third, and associated with poorer clinical outcomes, including more hospitalizations, more side effects, poorer insight, poorer quality of mental health and poorer cognitive executive function. Monitoring metabolic syndrome is important for patients with bipolar disorder.

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P-03-002
Correlation among impulsivity, temperament, character and neurocognitive performance in euthymic bipolar patients

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Objective: To investigate the prevalence of clinical impulsivity and its correlation with personality traits, affective temperaments and neuropsychological performance in bipolar disorder outpatients compared with healthy controls.

Methods: A sample of 63 adult (aged ≥18–65 years) outpatients who fulfilled DSM-IV-TR criteria by SCID-I interview for bipolar disorder were included. All bipolar patients fulfilled clinical criteria for euthymia [YMRS ratings <6 and HAM-D ratings <8] and also did not meet criteria for DSM-IV mood episodes for at least 8 weeks before entry to the study. Healthy controls (N=40) did not meet criteria for any axis I (SCID-I). Strict exclusion criteria were used. All subjects completed a standard neuropsychological battery and personality traits were determined by the Temperament and Character Inventory. Impulsivity was assessed using the BIS-11. Affective temperaments were evaluated using the TEMPS-A Buenos Aires.

Results: Euthymic bipolar disorders subjects demonstrate significant differences on the Barratt Impulsivity Scale (BIS-11) subsiteme and total scores compared with healthy controls. However, there were no statistical differences in impulsivity scores between both subgroups of patients (bipolar I vs. II). We found a positive correlation between impulsivity scores and sensation seeking and a negative correlation with self-directedness, measured by TCI. Euthymic bipolar disorder individuals displayed significant higher scores on cyclothymic temperament and demonstrated impaired neuropsychological functioning across almost all domains, mainly executive function, attention and memory tasks, compared with healthy controls.

Conclusion: Preliminary results show that trait-like impulsivity was substantially higher in subjects with bipolar disorder than in healthy comparison subjects, regardless of symptomatic inclusion. Within subjects with bipolar disorder during euthymia, high impulsivity scores were associated with specific personality traits, cyclothymic and anxious temperament and generalized impairment on neuropsychological functioning.

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Objective: Patients with bipolar disorder (BD) have up to a three times increased risk of type 2 diabetes mellitus (T2D). The prevalence of insulin resistance (IR) in BD, however, has not been systematically studied. The possible links between aberrant glucose metabolism and BD include treatment, lifestyle, neuroendocrine and neurotransmitter dysfunctions, and genetic predisposition. This study aims to establish the rate of IR in patients with BD and examine the correlates of abnormal glucose metabolism with the course and outcome of BD, including response to treatment and medical outcomes. We hypothesize that subjects with co-morbid T2D/IR will have a more refractory form of BD than those without T2D/IR, as well as poorer response to treatment.

Methods: Patients for this study are being recruited from The Maritime Bipolar Registry and Mood Disorders Clinic, reflecting primary and tertiary samples of BD respectively. The diagnosis of T2D is determined according to two measures of fasting plasma glucose (FPG) and OGTT if still equivocal. Fasting serum insulin and FPG is used to determine HOMA-IR to quantify insulin resistance in those with normal FPG.

Results: To date, 64 subjects have been included in the study; with a diagnosis of BD-I and BD-II and age range of 24-85 years. Only 50% of all patients had euglycemia, 29.7% have IR and 20.3% T2D. In a preliminary analysis, patients with T2D had significantly higher rates of psychosis during mood episodes than euglycemic patients (p=0.04).

Conclusion: In agreement with previously reported increased rates of T2D in BD, our preliminary results showed an increased proportion of T2D in BD. In addition, only half of bipolar patients had euglycemia; the rest of the sample showed some abnormality in glucose metabolism. Our completed study will look at the correlates of abnormalities in glucose metabolism, various clinical characteristics, prognosis and outcome.

Policy of full disclosure: Capital District Research Fund.

P-03-004 Bipolar disorders in emergency departments in Latin-America: Prevalence and associated comorbidity

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Objective: To investigate prevalence rates of BD and associated comorbidity in ED in Latin American countries.

Methods: To identify patients with BD, we used a combination of DSM IV-criteria interview and the Mood Disorder Questionnaire (MDQ). We analyzed data from patients from hospitals in Argentina, Brazil, Chile, Colombia, and Mexico and described the demographic and comorbidity between BD and non-BPD patients.

Results: The estimate was based on a total of 1,535 patients, mean age 37 years, with response rates of 83.0%. Prevalence of BD ranges from 3.8-6.0%. Compared to non-BPD patients, BD patients were more likely to be obese (39.7% vs. 26.9%) and to report a diagnosis of asthma (16.7% vs. 9.9%), thyroid problems (12.8% vs. 5.8%) and seizures (23.1% vs. 3.0%). All p <0.05. BD patients versus those without BD were also differentiated in their psychiatric comorbidity as follows: higher rate of alcohol abuse (30.8% vs. 10.0%), ADHD (50.0% vs. 12.0%), depression (81.6% vs. 45.7%), OCD (20.1% vs. 3.0%), panic disorders (23.1% vs. 12.3%) and other anxiety disorders (62.1% vs. 41.8%). Compared to non-BPD, suicidal plans and attempts were also significant higher in the bipolar group (11.5% vs. 2.8% and 10.3% vs. 1.8% respectively). Multivariate analysis identified ADHD, anxiety, depression, alcohol abuse, and last month suicide plan and attempts to be independently associated with BD.

Conclusion: Our data suggest that the prevalence of BPD is elevated among ED patients in Latin American countries. BPD patients in ED are likely to have complex psychiatric, and medical histories, which will be necessary to be taken into account when evaluate and design ED-initiated interventions.

Policy of full disclosure: Dr. Castilla-Puentes is currently working as Global Medical Safety Physician with Johnson & Johnson, Pharmaceutical Research and Development.

P-03-005 The HCL-32 is a useful tool in differentiating bipolar disorder from borderline personality disorder

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Objective: The selection of an adequate treatment strategy depends on an accurate diagnosis. A complex challenge in clinical practice is the differential diagnosis between bipolar disorder (BD) and borderline personality disorder (BPD). Previous studies suggest that phenomenologically, hypomania in BD is dissimilar to affective instability in BPD. Hence, a tool that discriminates hypomania form affective instability could aid in this difficult differential diagnosis. The HCL-32 is a ten minutes self administered scale for the screening of hypomania. The aim of this study is to determine the usefulness of the HCL-32 in differentiating BD from BPD patients.

Methods: Patients with a diagnosis of BPD (n=20) and BD (n=33) were assessed using the HCL-32. The diagnosis of BD or BPD was established by two clinicians with a vast experience in these disorders and blinded to the results of the HCL-32. Both groups were compared using one way ANCOVA, controlling for anxiety trait and depression. All statistical analyses were performed using the SPSS 17.0 software package.

Results: Non significant statistical differences were found in demographic variables between the two groups. The group of patients with BD scored higher on the HCL-32, even when controlling for anxiety and depression (p<0.001).

Conclusion: These results suggests that HCL-32 could be a very useful instrument helping to differentiate BD patients from BPD patients.

P-03-006 Utility of the INECO frontal screening (IFS) for the detection of executive dysfunction in patients with bipolar disorder

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Objective: Bipolar Disorder (BD) patients present not only changes on mood, but also cognitive deficits, even during euthymic periods. These cognitive deficits include important executive functioning failures. The detection of executive dysfunction usually requires the administration of an extensive neuropsychological battery, because there are few screening tests specifically designed to assess executive functions. The INECO Frontal Screening (IFS) is as solid and brief tool, which has proved useful for the assessment of the executive functions in patients with dementia. The aim of this study was to assess the utility of the IFS to detect executive dysfunction in BD patients.

Methods: A total of 46 subjects, 20 of which were diagnosed with BD, and 26 of which were healthy controls, were assessed with classical executive tests and the IFS. The cutoff score was established by the analysis of the ROC curve (Receiver Operating Characteristics).

Results: The IFS total score was significantly lower in patients (M =24.40) compared with controls (M =26.30). A cutoff of 26/30 points on the IFS was associated with a sensitivity of 73% and specificity of 68.4%. Also, the IFS total score correlated with performance on classical executive tests (Phonomological fluency task: r=0.03 < TMT-B: r=0.69, p=0.00; digitis backwards span r=0.63, p=0.00;
Altered feedback-related negativity in bipolar patients performing probabilistic reward learning

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Objective: Bipolar patients have the manic symptoms of grandiosity, increased goal-directed activity and excessive involvement in pleasurable activity indicating reward learning and behaviors. Feedback-related negativity (FRN) is elicited by positive feedback and appears as relatively more positive ERP deflection. We investigated if bipolar patients show impairments in adjusting behavior during and to examine the feedback-related negativity during reward learning process using probabilistic reward task.

Methods: We recruited 20 manic and 15 euthymic patients, and 26 healthy controls. We recorded the FRN to reward feedback while performing a probabilistic reward task. This task was designed to facilitate the response bias with signal-detection theory, which was consisted with three blocks.

Results: In response bias analysis, repeated measures ANOVA revealed the main effect of block (p = 0.04) and interaction of response bias and group (p = 0.05). In FRN amplitude analysis, repeated measures ANOVA revealed the main effect of block (p = 0.05). While FRN amplitudes were not different between block 1 and 3 in healthy controls (p = 0.90), FRN amplitudes in block 3 were more negative than that in block 1 in bipolar patients (p = 0.01).

Conclusion: Bipolar patients appeared to have the impaired acquisition of response bias and reduced FRN amplitude toward the more frequently rewarded stimuli. These results suggest that bipolar patients might have the dysfunctional reward learning over time and are related to the reduced electrophysiological activity during reward learning process.

Policy of full disclosure: This study was supported by grant A101915 from the Korea Healthcare Technology R & D Project, Ministry of Health & Welfare, Republic of Korea.

Impaired cognition in bipolar I disorder: Searching for a biological substrate

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Objective: It has been proposed that cognitive deficit could be found in bipolar I disorder (BDI) patients across different mood state. The goal of this study was designed to replicate previous findings in cognitive deficit in euthymic BDI patients and further explore the possible underlying substrates.

Methods: Thirty-three age, education matched healthy controls (HC) and twenty-three euthymic BDI patients who met the criteria of DSM-IV-TR were recruited. The definition of euthymia was that Montgomery-Asberg Depression Rating Scale (MADRS) scores less than 10 and Young Mania Rating Scale (YMRS) scores less than 7 within a 6-week consecutive period. Single photon emission tomography (SPECT) with radiotracer 123I-ADAM was used for the image of brain serotonin transporter (SERT). Specific uptake ratio (SUR) was determined for the measured outcome. Ten ml venous blood was drawn when subject underwent SPECT for the measurement of brain derived neurotrophic factor (BDNF).

Results: We found that SERT binding in both the midbrain and striatal regions was decreased in patients than that in HC. However, BDNF was not different in both groups. There was no correlation of SERT binding and BDNF. Although there were statistic significantly different in several sub-items of facial memory and Wisconsin Card Sorting Test (WCST) between patients and HC, the overall deficit in cognition was not significantly correlated with SERT binding and/or BDNF.

Conclusion: We replicated previous findings which showed the deficit of cognition in BDI patients. However, the underlying substrates of cognitive deficit may be beyond SERT and BDNF.

The change of cholesterol level and impulsiveness after pharmacotherapy in patients with bipolar disorder

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Objective: Many Studies supported significant relationships between low cholesterol levels and impulsiveness, aggression and mood. In this study, we investigated the association between total cholesterol levels and impulsiveness, and evaluated correlation between differences of total cholesterol level after pharmacologic treatments and changes of impulsiveness in patients with bipolar disorder.

Methods: Forty patients with bipolar disorder and 40 healthy normal controls were selected. They were evaluated twice with Korean version of Young Mania Rating Scale (K-YMRS), Clinical Global Impression Scale-severity (CGI-S) and Barratt Impulsiveness Scale (BIS) at admission (pretreatment) and after 6 weeks of treatment (post-treatment). The pretreatment and post-treatment serum total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) levels in the BD were measured, and were compared to those of healthy normal controls.

Results: Posttreatment YMRS scores were significantly lower than pretreatment YMRS scores in the patient groups. The TC levels were significantly higher in posttreatment patients groups than pretreatment group. Posttreatment BIS scores were significantly lower than pretreatment group. But it is found to be no correlation between TC levels and BIS scores after pharmacotherapy.

Conclusion: Our results supported earlier reports of significant increase in the cholesterol levels when BD patients were treated with pharmacotherapy for 6 weeks. Although the results in our study are statistically significant, their clinical significance requires further examination in longer-term studies and with larger subjects. Key words: Total Cholesterol, Barratt Impulsiveness Scale, Bipolar disorder.

Bipolar disorder and clarithromycin: More than a single manic episode

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Objective: To describe the onset of a Bipolar Disorder after being on treatment with clarithromycin, were found.

Methods: Systematic search of the literature of MEDLINE, EMBASE, and the Cochrane Library. No references about bipolar disorders which break out after starting treatment with clarithromycin, found.

Results: A 47-year-old woman with no previous psychiatry or substance abuse history, was brought to emergency department because of behavioral disturbances and manic symptoms. One week before the onset of the illness, the patient had an upper digestive haemorrhage due to a perforated ulcer. Infection by H pylori was confirmed, so she started taking clarithromycin, amoxicillin, and omeprazole 4 days after starting this treatment, she suddenly developed insomnia, hyperactivity, grandiosus delusions, irritability, pressure speech, tangenciale thinking and increased energy level. She was admitted in inpatient psychiatry service Clarithromycin was discontinued and Olanzapine 20 mg/day was administered from the beginning. One week after the admission the manic symptoms still persisted, so Divalproex sodium 2000 mg/day was added. Throughout the next days an improvement was noted, and manic and psychotic symptoms gradually dissipated, though expansive mood still persisted. She was discharged after three weeks of hospital stay. One month later, in the follow-up consultation, the patient still had hypomanic symptoms. She was diagnosed as Bipolar 1 Disorder, Single Manic Episode, Severe With Psychotic Features.

Conclusion: This patient developed an acute manic psychosis within a 4-day period. There was no evidence of infection, substance abuse, or hypoglycemia to account for her symptoms. The psychosis began approximately 3 days after the initiation of triple therapy with clarithromycin, amoxicillin, and omeprazole for H pylori peptic ulcer disease. In the reported Clarithromycin-induced manic episodes, a complete resolution of symptoms in 24 to 36 hours after finishing treatment is described [3]. Because of the severity and duration of the
affective symptoms and the family psychiatry history, the patient was finally diagnosed as bipolar disorder.

**P-03-011**  
Attitudes of investigators and staff toward placebo response in a global bipolar depression trial  
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**Objective**: Attitudes of clinical trials investigators and site staff were explored with respect to their ability to influence placebo response. Associations among responses were evaluated using the chi-square test statistic.

**Results**: 69.3% (n = 109) had previously received training to reduce placebo response. 66.2% (n = 100) indicated they could influence the magnitude of placebo response in a clinical trial “markedly or moderately”, whereas 33.8% (n = 51) responded “slightly” or “not at all”. 75.5% (n = 117) disagreed with the notion that “My role in a clinical trial includes ensuring that subjects improve clinically”, whereas 24.5% (n = 38) agreed. 62.9% (n = 95) disagreed that “It is unethical to continue subjects in a clinical trial who are not improving”, whereas 37.1% (n = 56) agreed. Increased exposure to placebo response training was associated with: 1) increased confidence that the individual respondent’s (p < 0.01) or the site staff’s (p < 0.01) behavior can influence the magnitude of placebo response in a clinical trial; and 2) disagreement with the notions that the respondent’s role in a clinical trial includes ensuring that patients improve clinically (p < 0.001) or that it is unethical to continue subjects in a clinical trial who are not improving (p < 0.05).

**Conclusion**: A high level of agreement was reported on the importance of placebo response and the ability to influence it in clinical trials. While the majority disagreed with the notion that clinical trials patients should improve clinically, a significant minority agreed. Increased exposure to placebo response training was associated with increased confidence in the ability to modulate placebo response and diminished belief that patients should improve during clinical trial participation. Further research should investigate which approaches to placebo response minimization are most effective.

**Policy of full disclosure**: David Daniel and Jean Dries are employees of United BioSource Corporation (UBC). UBC provided rater training to the investigators and provided funding for the statistical analyses. Antony Loeble and Josephine Cucchiara are employees of Sunovion. Sunovion conducted the clinical trials noted in the abstract.

**P-03-012**  
Phenotype definition and clinical correlates of antidepressant-induced mania  
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**Objective**: Although a random effects meta-analysis showed weak evidence of association of the S allele with antidepressant induced mania (+) status, a test of heterogeneity indicated significant differences in estimated genetic effects. It is likely that phenotypic variability is a source of heterogeneity. The purpose of this study was to rigorously define the AIM + phenotype and subsequently attempt replication of previous association of AIM + with variation in the serotonin transporter gene (SLC6A4).

**Methods**: Subjects with bipolar I or II disorder, confirmed by structured diagnostic interview, enrolled in the Mayo Clinic Bipolar Disorder Biobank. The medical record was reviewed by a psychiatrist with at least 10 years of clinical experience. AIM + was defined as within 60 days of starting or changing dose of antidepressant treatment. Each AIM + case was matched to two separate AIM- controls matching, in hierarchical order, on gender, SSRI antidepressant, I vs. II subtype, and age.

**Results**: 518 (95.7% Caucasian) subjects completed enrollment with 12.1% (n = 63) meeting criteria for a history of AIM+. The majority were female (60.7%), Bipolar I (88.5%) with onset of AIM + at start (85.3%) of SSRI (68%) treatment with rapid cycling present only 28% of the time. In comparison AIM+ (n = 122), AIM+ patients had a higher rate of past history of attention deficit disorder, both as children (20 vs. 10%, p = 0.056) and adults (25.4 vs. 11.6%, p = 0.018). Preliminary data on genetic variation of candidate genes will be presented.

**Conclusion**: This early analysis emphasizes the importance of phenotype assessment prior to genomic analysis. Identifying a genetic variation associated with SSRI induced mania or may have high clinical translational value in individualizing treatment for bipolar depression.

**Policy of full disclosure**: Disclosure Declaration Mark A. Frye, M.D. 2012 Grant Support Pfizer, National Alliance for Schizophrenia and Depression (NARSAD), National Institute of Mental Health (NIMH), National Institute of Alcohol Abuse and Alcoholism (NIAAA), Mayo Foundation Speakers’ Bureau NONE Financial Interest/Stock ownership/Royalties NONE.

**P-03-013**  
Neurological side effects due to GSK-3 inhibition by chronic lithium treatment can be prevented by blocking NFAT/FAS pathway  
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**Objective**: Despite lithium’s efficacy for treatment of bipolar disorder, its clinical use is often curtailed by its side effects. Lithium inhibits, among other enzymes, glycogen synthase kinase-3 (GSK-3) and this has been postulated to contribute to its therapeutic efficacy but also to its neurological toxicity. GSK-3 inhibition has been shown to result in increased apoptosis through intrinsic pathway. We reasoned that this may relate to the well-documented side effects of lithium therapy and that understanding the underlying molecular mechanisms might help to apply treatments based on GSK-3 inhibitors. Here we aim to genetically dissect whether GSK-3 inhibition induces toxicity in an NFAT/Fas-dependent manner.

**Methods**: We have combined pharmacological and genetic sustained GSK-3 inhibition with two different approaches to block NFAT/Fas signalling: 1) Cyclosporine A (CsA) or 2) lpr mice, Fas-deficient.

**Results**: GSK-3 activity was inhibited by chronic lithium (Gomez-Sintes and Lucas, 2010) or by a conditional transgenic mouse expressing a dominant negative form of GSK-3 (Tet/DN-GSK-3 mice; Gomez-Sintes et al., 2007). In good agreement with the common neurological side effects of lithium therapy, lithium treated mice and Tet/DN-GSK-3 transgenic mice showed sublethal motor deficits and neuronal apoptosis. We now demonstrate that NFAT/Fas signalling mediates both neuronal apoptosis and motor deficits induced by decreased GSK-3 activity (induced by two different approaches) as these are absent when NFAT nuclear translocation is prevented by CsA administration or when the experiments were conducted on Fas-deficient lpr mice.

**Conclusion**: Motor side effects and neuronal apoptosis induced by decreased GSK-3 activity are attenuated by blocking NFAT/Fas signalling. These findings may enable development of combined therapies not only to counteract the drawbacks of lithium treatment for mood disorders but also to extend the potential of GSK-3 inhibitors.

**P-03-014**  
Compatibility of pharmacotherapy for Korean bipolar disorder patients to treatment guidelines  
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**Objective**: The aim of the current study was to investigate the overall pattern of pharmacotherapy for patients with bipolar disorders in Korea and to compare the pattern to treatment guidelines proposed.

**Methods**: We retrospectively reviewed the medical records of 1,327 patients with bipolar disorders from ten hospitals. The daily...
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Objective: No research has yet focused on hypomanic states in early adulthood. The aim of the present study was therefore to assess hypomania in a large non-clinical sample of young adults, to differentiate between favorable (bright side) and unfavorable (dark side) hypomanic stages, and to relate hypomanic stages with sleep and physical activity.

Methods: A total of 862 participants (university students; 74.1% females; mean age: M = 24.67; SD = 5.91) took part in the study. They completed a series of validated self-report questionnaires assessing hypomania (HCL-32), psychological functioning, sleep and physical activity.

Results: Based on the HCL-32, 81% of the participants were categorized as currently not being in a hypomanic state; 19% of the participants were categorized as currently being in a hypomanic state. Of those, 57.6% were classified as “active/elated” (‘bright side’), whereas 42.4% were classified as “irritable/risk-taking” (‘dark side’). Compared to non-hypomanic participants the ‘bright side’ group, ‘dark side’ hypomanic participants reported more depressive symptoms, sleep disturbances, somatic complaints, perceived stress, negative coping strategies, and lower self-efficacy. By contrast, ‘bright side’ hypomanic participants had lower stress scores, more positive self-instructions, and higher levels of exploration, self-efficacy, and physical activity. Compared to the dark side hypomania, the bright side hypomania was associated with more goal-oriented and structured physical activity.

Conclusion: Among a non-clinical sample of young adults hypomania was frequently reported (19%). The present results underscore the notion of a continuity between a moderate mood state and both favorable (“bright side”) and unfavorable (“dark side”) hypomanic states. Moreover, ‘bright’ and ‘dark side’ hypomania differ with respect to psychological functioning and sleep. Our results suggest that ‘restlessness/overactivity’, a core symptom of hypomania, might be observed only in the dark side hypomania, whereas in bright side hypomania, amount of activity was related to more goal-oriented physical activity.
Conclusion: Long-term safety, consistent with OLZ’s known profile including weight/glucose/lipid increases, and sustained efficacy were shown in OLZ-treated Japanese patients with bipolar depression.

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P-03-018 Cognitive impairments profile in euthymic bipolar I disorder and their relation to functional recovery

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Objective: To demonstrate the range of neuropsychological deficits in the various cognitive domains in euthymic patients with bipolar I depending on the previous clinical state, to compare that to control and to correlate these cognitive deficits with illness characteristics and profile.

Methods: A case control study included 60 subjects they were organized into two major groups, one stratified random sample of 30 patients in the euthymic phase of bipolar I disorder and one control group. The patients group diagnosed using Structured Clinical Interview for DSM-IV (SCID-I) and the euthymic state determined using Young Mania Rating Scale (YMRS) and Hamilton Rating Scale for Depression (HRSD) and we used WIMS & WMS for cognitive assessment.

Results: Euthymic patients with bipolar I performed poorer than controls on tests of intelligence, attention, memory and executive functions. Performance on most domains of WAIS was associated with age of onset of illness and the number of depressive episodes. These differences were with statistical significance with residual symptoms not reaching clinical significance.

Conclusion: We conclude that cognitive deficits associated with euthymia in bipolar disorder are considered both a consequence of the disorder, determinant of outcome in recovery and could be trait markers for bipolar I disorder.

P-03-019 Effect of lithium and valproate on brain activation patterns in FMRI within a working memory paradigm of bipolar patients

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Objective: We seek to identify differences and identify the role of treatment in neurofunctional response in patients with Bipolar Disorder type I, compared to controls, specifically while challenged with working memory tasks.

Methods: Thirty-three euthymic patients with Bipolar Disorder type I and 10 controls were evaluated in a cross-sectional study; 13 of them were on treatment with Lithium, 9 on Valproic Acid and 10 without treatment for at least 2 months prior to the study. Correlation between functional Magnetic Resonance (fMRI) BOLD signal and working memory processes.

Results: There were no significant differences between the groups in demographic or clinical variables except for YMRS score. Patients and controls demonstrated significantly different patterns of brain activation in anterior cingulated (p: 0.05) during working memory tasks.

Conclusion: There were statistically significant differences in the anterior cingulate BOLD (Blood O2 level dependent) signal between patients with Type I Bipolar Disorder compared to controls. There were no other differences in the studied regions. Treatment with Valproic Acid and Lithium didn’t play a role in these differences.

REFERENCES

No potential conflict of interest.
task. There were no differences in the angular gyrus, fronto-orbital cortex and frontal lobe. There were no difference in activation patterns in fMRI between patients treated with Valproic Acid or Lithium and patients without pharmacologic treatment.

**Conclusion:** There are statistically significant differences in the anterior cingulate BOLD (Blood oxygen level dependent) signal between patients with Type I Bipolar Disorder compared to controls. There were no other differences in the studied regions. Treatment with Valproic Acid and Lithium didn’t play a role in those differences.

**Methods:** We present the case of a 65-year-old woman with manifestations of bipolar disorder since 15 years with history of neurocysticercosis.

**Results:** She was initially diagnosed as suffering from depression-like symptoms 13 years ago and she was treated successfully for cysticercosis. Afterward, she was retired due to her emotional and cognitive problems. During hospitalization she presented episodes characterized by elevated mood, hyperactivity and progressive development of psychomotor retardation, withdrawal, very poor speech and hypersomnia and dysphoric mood (HSRD 21). She was well oriented without memory dysfunction in clinical assessment (MMSE 26, 3-MS 89). The comprehensive neuropsychological evaluation by the use of Cambridge Neuropsychological Test Automated Battery has shown executive deficits. The MRI revealed brain atrophy and subcortical white matter lesions characteristic of cysticercosis infection, whereas, Tc99m -HMPAO (CERETEC) SPECT i.v. adu. 20 mCu revealed normal diffusion in the cerebral cortex. The patient’s symptoms were substantially ameliorated by olanzapine (20 mg/day) and valproic (500 mg/day) administration.

**Conclusion:** In our patient’s case neurocysticercosis was linked with manifestations of bipolar disorder which was substantially ameliorated by valproic and olanzapine combination.

**Objective:** BALANCE study was conducted to explore factors associated with better compliance from diverse practice settings in patients receiving treatment for Bipolar Disorder up to 24 months.

**Methods:** Adult outpatients, receiving olanzapine (mono- or combination therapy) for at least 4 weeks and stable, Clinical Global Impressions (CGI) severity ≤3, were enrolled. Observations were recorded at baseline and 3, 6, 9, 12, 18, 24 months. Compliance to each medication regimen prescribed by treating psychiatrist was assessed by investigators using a single-item measure as noncompliant (<20%), low (20–59%), medium (60–79%), high (80–100%). Baseline and post-baseline factors including socio-demographics, disease severity, attitude toward medication, olanzapine mono vs. combination therapy, insight into illness, strength of the patient-physician relationship were used to predict the likelihood of high compliance utilizing generalized estimating equations repeated measures logistic regression model. Other data analyzed included quality of life, tolerability, functional status, and relapse.

**Results:** A total of 891 eligible patients were recruited into the study from Austria (239), Hungary (167), Korea (145), Mexico (61), Romania (180), Taiwan (99), of whom 73% completed the 24 months observation period and demonstrated high compliance (>80% in 67%–80% of patients visit-wise). Results identified high baseline compliance as a strong predictor of later compliance (OR=6.9, 95% CI: 5.0-9.5, p<0.001), high compliance associated with higher life satisfaction (p=0.002), better insights into illness (p<0.001), lesser work impairment (p=0.007) and shorter hospital stay (p=0.002). Compliance also varied by country (p<0.001) and length of post-baseline treatment regimen (p=0.014).

**Conclusion:** Compliance to therapy in bipolar disorder was generally high and associated with baseline severity, insights into illness, work impairment and satisfaction with life.

**Policy of full disclosure:** Dr. David McDonnell is a full-time employee of Eli Lilly and Company.

**P-03-222 Reduced inferior frontal gyrus activation during emotion inhibition in young people at increased genetic risk for bipolar disorder**

**Objective:** There is growing interest in structural and functional brain imaging of young people at increased genetic risk for bipolar disorder as a means of identifying potential endophenotypes for this condition. Dysfunctional neural mechanisms for the cognitive control of emotion are postulated in the genetic predisposition to bipolar disorder, with aberrant activity in fronto-cortical, striatal, and limbic networks previously reported in subjects with established bipolar disorder during inhibitory and emotion processing tasks. We investigated functional brain activity during inhibition of emotional material in young people at increased genetic risk for bipolar disorder, using a facial-emotion go/no-go task during functional magnetic resonance imaging.

**Methods:** Data from 47 genetically high-risk individuals aged 18–30 years with at least one first-degree relative with bipolar disorder were compared with 49 controls (within the same age range but without a family history of bipolar disorder or other severe mental illness).

**Results:** Behavioural performance of all participants on the affective go/no-go task exceeded 75% accuracy. Whole brain corrected analyses revealed a highly specific significant lack of recruitment of the inferior frontal gyrus when inhibiting fearful faces in the at-risk participants compared to controls (p=0.011, FWE corrected).

**Conclusion:** This impaired inhibitory function of the inferior frontal cortex may represent a trait marker of vulnerability to bipolar disorder. These findings further implicate dysregulated cortical and sub-cortical brain networks as a neurocognitive endophenotype for bipolar disorder and add to the growing evidence for pre-existing functional and structural disturbances in those at high genetic risk for bipolar disorder.

**Objective:** Neurocysticercosis and bipolar disorder. A case report

**Methods:** An 85-year-old subacute meningitic patient with bilateral retinal vasculitis and serous detachment of the right retina was admitted to our hospital due to progressive mental deterioration. Anamnesis and neurological examination were suggestive of encephalitis. Computerized tomography (CT) and magnetic resonance imaging (MRI) disclosed a cystic lesion in the right parieto-occipital lobe. The patient was initially treated with high doses of corticosteroids for presumed vasculitis. However, after a few days the patient presented deteriorated mentation and severe motor inco-ordination. Laboratory tests were normal. Cerebrospinal fluid analysis was consistent with meningitis: increased protein content and glucose content was found. The fluid also revealed a high number of lymphocytes. Cysticercosis immunoglobulin M (IgM) and cysticercosis enzyme-linked immunosorbent assay (ELISA) were positive. The patient developed pneumonia and died one week later.

**Conclusion:** Diagnosis of neurocysticercosis was made by magnetic resonance imaging and serological tests. The patient’s condition worsened after treatment with corticosteroids and meningitis and meningo-encephalitis were diagnosed. A case of neurocysticercosis presenting with a subacute meningitic syndrome is reported. The patient died with progressive neurologic deterioration and died one week later.

**Policy of full disclosure:** Dr. Antonio A. Capistrano, Jr. is a full-time employee of Eli Lilly and Company.
Objective: MADRS score of 20. On 8th week (LTG 75 mg/day), her MADRS score became agitatedly depressed without any response to some anti-hypomanic symptoms disappeared with VPA treatment. However, 67-year-old female. She had had first depressive episode at the age of 60. She had been remitted with fluvoxamine treatment. Because she became hypomanic at age of 67, the drug was withdrawn. Her hypomanic symptoms disappeared with VPA treatment. However, she became agitationally depressed without any response to some anti-psychotics. LTG was coadministered to VPA (800 mg/day) at her MADRS score of 20. On 8th week (LTG 75 mg/day), her MADRS score became 2. Her serum BDNF levels before and after 8-week LTG were 21.1 and 43.0 ng/mL. Case B The patient was a 56-year-old female. She had first depressive episode at the age of 54. Her depressive symptoms showed no response to several antidepressants and to demonstrate the effectiveness of olanzapine in bipolar II disorder. The objective of this case report is to focus attention on the significance of avoiding unnecessary and potentially harmful psychopharmacology, and to demonstrate the effectiveness of olanzapine in bipolar II disorder. Methods: A case report. This case study was conducted with the written informed consent of the patient. This study was approved by the ethical committee of Kwansei Gakuin University.

Results: The patient was a 30’s woman with bipolar II disorder. Before her visit to our hospital, she had been treated with anti-anxiety agents (alprazolam, diazepam), 10 hypnotic drugs (triazolam, estazolam, lormetazepam, flurazepam, zolpidem, brotizolam, nitrazepam, flunitrazepam, rilmazafone), one antidepressant (paroxetine) and 2 antipsychotics (risperidone, chlorpromazine) for about 6 months. Her condition had gotten worse as a result of the polypharmacy. She had quit her company job and attempted suicides. At the first visit to our hospital, she showed mixed episodes and mood instability, and that olanzapine was effective as a maintenance therapy for bipolar II disorder.

Policy of full disclosure: This study was partly supported by Grants-in-Aid for Scientific Research of Japan (22507076).

Objective: Quetiapine (QTP) has been shown to be effective as an acute treatment in patients with bipolar depression. Nonetheless, the time of onset of QTP antidepressive action as well as its minimum effective dose have not been clarified. We aimed to evaluate the short-term efficacy of QTP XR in bipolar depression. We also compared the different efficacy and side effect profile of 300 mg and 600 mg/day dosages.

Methods: 31 acutely depressed patients were recruited; 14 were treated with QTP XR 300 mg/day and 17 with 600 mg/day. Assessment was performed with Hamilton Depression Scale (HAMD), Hamilton Anxiety Scale (HAMA), Dosage Record and Treatment Emergent Symptom Scale (DOTES), HAMD clusters “Core”, “Psychic anxiety”, “Somatic anxiety”, “Activity”, “Delusion”.

Results: QTP XR was effective since the first three days of treatment in reducing all the efficacy measures except for somatic anxiety. The comparison of 300 and 600 mg dosages did not show any significant difference in terms of efficacy, despite a clear trend was observed favoring the 600 mg group. The incidence of hypotension was significantly higher in patients taking QTP 600 mg (p = 0.004).

Conclusion: Our results suggest that QTP XR is effective against depressive symptomatology within the first days of treatment. Further, there is not a significant advantage for the 600 mg dose in comparison with the 300 mg one. The clinical effect seems to be not associated with sedation, suggesting that it may be due to the molecular drug effect. Nevertheless, further studies focusing on the first days of treatment are needed in order to confirm our findings.
Objective: The pharmacogenomics of bipolar disorder – acute and longitudinal treatment aspects: A systematic review

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Objective: Pharmacotherapy constitutes a mainstay in the treatment of both acute episodes and in maintenance therapy of bipolar disorder (BD). For more than two decades, there have been attempts to clarify the genetic basis of mechanisms of drug action, aiming at the possibility to offer a more personalized medicine. Here we compile the current state of pharmacogenomics of BD.

Methods: First, we decided to focus on the pharmacogenetics of first line treatments for BD on the basis of international guidelines. We focused on drugs recommended as monotherapies. PubMed was searched for articles published until using the search terms “bipolar disorder” or “manic-depressive illness” cross-referenced with drugs in question. We also manually reviewed reference lists of the identified publications. From these, we selected case-control-association studies, with the case-control-status being the drug response or the occurrence of adverse events.

Results: As regards response, we 28, with the following breakdown: lithium (25), lamotrigine (1), divalproex (1), olanzapine (1). As regards adverse events, our search algorithm yielded one study on divalproex. Most of the pharmacogenetic research in BD is about lithium, while there are only few case-control-association-studies concerning the other first line treatments. The candidate genes studied for lithium included 5-HT2A, 5-HT2C, 5-HTTLPR, AP-2β, BCR, BDNF, COMT, DAT1, D2K4, DRD1, DRD2, DRD3, DRD4, FYN, G13, GABRA1, G2, GRIA2, GRIN2B, GRIK3, GSK3B, HTR2A, IMPA1, IMPA2, INPP1, MAO-A, MARCKS, NR1D1, NTRK2, ODI4, SDC2, SERTPE, SV2B, and XBP1.

Conclusion: There is a striking lack of replicated findings. For only two genes, the 5-HTTLPR and the BDNF gene, positive findings could be replicated in a second study. Also, most studies included very small samples, with the majority totaling less than 200 subjects. Future pharmaco genetic research should be based on larger samples, unified, exact criteria for response and adverse events, integrate knowledge from biochemical pathways, and also include pharmacokinetic aspects.

P-03-030 Neurotrophin levels and the efficacy of single ketamine infusion in bipolar depression resistant to antidepressants

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Objective: In our previous study performed on 10 patients, we observed an antidepressant effect of single intravenous dose of ketamine, as an addition to mood stabilizing drugs in patients with bipolar depression resistant to treatment with antidepressants. We also found an increase of serum brain derived neurotrophic factor (BDNF) in ketamine responders. The aim of this study was to investigate serum levels of three neurotrophins: BDNF, neurotrophin 4 (NTF4) and glial-derived neurotrophic factor (GDNF) in relation to ketamine efficacy, in larger group of patients.

Methods: The study comprised 25 patients (4 male, 21 female), aged 27–67 years, with bipolar depression, receiving mood-stabilizing medications. They were resistant to treatment with antidepressants which were discontinued for at least 7 days before single intravenous ketamine infusion (0.5 mg/kg body weight) between 8:00–8:45 h. Psychometric assessment was done using 17-item Hamilton Depression Rating Scale (HDRS). Response to ketamine was defined as 50% reduction of HDRS after one week, compared to baseline. Serum BDNF, NTF4 and GDNF levels were estimated by the ELISA method.

Results: The mean intensity of depression before ketamine infusion was 21 ± 4 points on HDRS, reduced to 12 ± 7 points after one week. There were 16 ketamine responders and 9 ketamine non-responders. In ketamine responders, the increase of BDNF after one week was not significant, however, in such patients a reduction of GDNF serum level (statistical trend p = 0.07) was found. In ketamine non-responders, a significant reduction of BDNF level was observed. No relationship between serum levels of NTF4 and response to ketamine was found.

Conclusion: The results of present study confirm an antidepressant effect of ketamine infusion as an add-on to mood-stabilizing drugs in bipolar depression resistant to antidepressant treatment. They may also indicate a possible involvement of such neurotrophins as BDNF and GDNF in this effect.
P-03-031 Elevated levels of circulating inflammatory cytokines in euthymic individuals with bipolar disorder

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Objective: To test the hypothesis that euthymic individuals with bipolar disorder (BD) exhibit abnormalities in pro- and anti-inflammatory cytokines.

Methods: Prospectively verified euthymic individuals (N = 45, mean age = 41.02 ± 9.89) with DSM-IV-TR-defined BD-I/II as well as healthy volunteers (N = 29, mean age = 45.36 ± 12.15) were enrolled. Inflammatory cytokines [granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL) 1β, IL-2, IL-4, IL-5, IL-6, IL-10, tumor necrosis factor β (TNF-β) and interferon γ (IFN-γ)] were measured in plasma with an ultrasensitive 10-plex bead-based immunoassay for Luminex. The Mann-Whitney U Tests and multiple logistic regression were used to compare levels of inflammatory cytokines between euthymic individuals with BD and healthy volunteers.

Results: Both pro-inflammatory (GM-CSF, IL-1β, IL-2, IL-5, IL-6, IL-8, TNF-β, INF-γ) and anti-inflammatory cytokines (IL-4 and IL-10) were elevated in euthymic individuals with BD as compared to healthy volunteers (all p < 0.01). A multiple logistic regression revealed that a model containing GM-CSF, IL-2, IL-6, TNF-β and IL-10 significantly predicted BD (Model Nagelkerke R² = 0.001). Moreover, TNF-β was the strongest independent predictor of BD in this model (odds ratio = 1.883 95% CI: 1.28–2.76; p = 0.001).

Conclusion: Bipolar disorder is marked by elevated levels of inflammatory cytokines that persist into euthymia. These results suggest that the inflammatory cytokine network is salient to the pathophysiology of BD and may constitute a viable target for novel treatment development.

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P-03-032 Hypermethylation of serotonin transporter gene in bipolar disorder detected by epigenetic analysis of discordant monozygotic twins

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Objective: Bipolar disorder (BD) is a severe mental disorder characterized by recurrent episodes of mania and depression. Although high concordance rate of BD in monozygotic (MZ) twins supports the contribution of genetic factor in BD, importantly, it is not 100%. Because MZ twins have been regarded as having identical genomes, these facts suggest the importance of environmental or epigenetic factor for the onset of mental disorders.

Methods: We performed promoter-wide DNA methylation analysis of lymphoblastoid cell lines (LCLs) derived from two pairs of monozygotic twins discordant for BD. Promoter-wide DNA methylation profiles of the twins were examined by Affymetrix GeneChip Human Promoter 1.0R tiling arrays after methylated DNA was enriched using MBD2b and MBD3L1 conjugated beads. Fully unmethylated DNA obtained by whole genome amplification was used as an internal control.

Results: We found the copy number profiles were nearly identical between the twin pairs except for immunoglobulin-related regions. Three genes showing distinct difference of DNA methylation between the twin pairs were obtained as candidate regions. Among them, hypermethylation of SLC6A4, encoding serotonin transporter (HTT), in the bipolar twin was confirmed by bisulfitel sequencing. Promoter hypermethylation of SLC6A4 in LCLs of BD patients was confirmed in a case-control analysis. DNA methylation of SLC6A4 was significantly correlated with its mRNA expression level in individuals with the S/S genotype of serotonin transporter-linked promoter region (HTTLPR), and mRNA expression level was lower in BD patients carrying the S/S genotype. DNA methylation of the same site was also higher in the postmortem brains of BD patients.

Conclusion: This is the first study to report the role of epigenetic modification of SLC6A4 in BD using an unbiased approach, which provides a new insight to elucidate the pathophysiology of mood disorder.

P-03-033 “Paper-and-pencil” cognitive tests results in euthymic bipolar patients treated with lithium

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Objective: Cognitive deficits in bipolar patients may persist during remission. In our previous study using Cambridge Neuropsychological Testing Automated Battery (CANTAB) euthymic bipolar patients treated with lithium showed poorer performance on several neuropsychological tests than healthy controls and the quality of the response to prophylactic lithium treatment influenced the cognitive performance (Rybakowski and Suwalska, 2010). The aim of the study was to assess frontal lobe cognitive functions in euthymic bipolar Patients treated with lithium.

Methods: Fifty-six patients with bipolar disorder in remission lasting for at least 4 months (21 male, 35 female; mean age 52.6 ± 10.0) and 77 healthy controls (22 male, 65 female; mean age 51.6 ± 13.6) entered the study. Duration of illness was at least 5 years and prophylactic treatment lasted for at least 2 years. Sixteen patients were excellent lithium ELRs, defined as having had no affective episodes on lithium monotherapy. For the neuropsychological assessment, the following tests were used: the Trail Making Test (TMT), the Stroop test, the verbal fluency test, including semantic (categories: animals, fruit and vegetables) and phonemic fluency tasks (letters F, A, S).

Results: Bipolar patients performed significantly worse than healthy controls on semantic and phonemic verbal fluency, TMTA&B and Stroop test part B, whereas the results of excellent lithium responders did not differ from those of healthy people. Bipolar men performed significantly worse than bipolar women on semantic fluency test and Stroop test part B. Whilst bipolar women had worse results than healthy control women only in TMT A and TMTB, bipolar men performed poorer than healthy men on all tests.

Conclusion: Our results point to the presence of cognitive deficits in euthymic bipolar patients, protective effect of lithium in excellent lithium responders and gender-associated differences in the severity of neuropsychological dysfunctions. Rybakowski JK, Suwalska A (2010) Excellent lithium responders have normal cognitive functions and plasma BDNF levels. International Journal of Neuropsychopharmacology 13, 617-622.

P-03-034 Increased trans-membrane tumour necrosis factor in the anterior cingulate cortex of subjects with bipolar disorder

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Objective: Altered inflammatory signalling has been implicated in the pathophysiology of mood disorders and schizophrenia. We recently reported a 2.4-fold increase in the expression of a trans-membrane form of the pro-inflammatory cytokine, tumour necrosis factor (tmTNF) in Brodmann’s area (BA) 46 but not BA24 of the frontal cortex from subjects with major depressive disorder (MDD). The expression of soluble TNF (sTNF) was not altered in these subjects. We have examined TNF expression in the frontal cortex of subjects with bipolar disorder (BDP) and schizophrenia.

Methods: Western blotting was used to measure tmTNF and sTNF levels in post-mortem tissue from BA24 and BA46 from 10 subjects with BPD and 10 matched controls and from 20 subjects with schizophrenea and 20 matched controls.

Results: tmTNF was increased in BA24 (CON) (mean ratio of internal control ± SEM) = 2.77 ± 1.03 vs. BPD = 7.15 ± 1.75; p < 0.05), but not BA46 (CON = 0.89 ± 0.10 vs. BPD = 1.84 ± 0.47; p > 0.05) from subjects with bipolar disorder. There was no change in the level of
mTNF in BA24 (CON = 2.52 ± 0.55 vs. SCZ = 2.00 ± 0.38; p > 0.05) or BA46 (CON = 0.80 ± 0.07 vs. SCZ = 1.02 ± 0.171; p > 0.05) from subjects with schizophrenia compared to controls. Levels of sTNF were not changed in either BA24 or BA46 from subjects with BPD or schizophrenia compared to controls.

**Conclusion:** Our data further supports a role for mTNF in the pathophysiology of mood disorders but not schizophrenia. Furthermore, abnormal mTNF expression is localised to different cortical regions in BPD compared to MDD. Contrasting studies in the periphery, our data from the CNS does not support the involvement of sTNF-mediated, pro-inflammatory pathways in the pathophysiology of mood disorders.

**P-03-035 Molecular conformational changes in microglia and differentiated monocytic cells induced by therapeutic concentrations of lithium**

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**Objective:** Lithium (Li), a direct inhibitor of glycogen synthase kinase 3 (GSK-3), is a commonly prescribed mood stabilizer in the treatment of bipolar disorder. Li affects various types of immune cells, which play pivotal roles in the innate immune systems in both brain and peripheral tissues. Evidence suggests that GSK-3 regulates microglial migration and inflammation, and also mediates differentiation and activation of proinflammatory monocyte-derived dendritic cells (MoDCs).

**Methods:** Microarray gene expression profiles of resident differentiated monocytic cells (mouse microglia, mouse microglia and macrophage-like cell line, human MoDCs and monocyte-derived macrophages) along with undifferentiated mouse and human monocytes were evaluated using Illumina microarrays, and post prominently induced and suppressed molecules were validated using Q-RT-PCR and western blotting. Effects of GSK-3 inhibitors on the molecules were also evaluated.

**Results:** We found several molecules prominently induced by the therapeutic concentration of Li and GSK-3 inhibitors in the resident differentiated monocytic cells (mouse microglia, mouse microglia and macrophage-like cell line, human MoDCs and monocyte-derived macrophages), but not in undifferentiated mouse and human monocytes.

**Conclusion:** The findings indicate the mechanisms of lithium-induced functional changes in microglia and differentiated monocytic cells, and their possible involvements in the neuroprotective and mood stabilizing effects of Li treatment.

**P-03-036 Bipolar disorder in patients with suicidal behavior**

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**Objective:** to study prevalence of bipolar disorder (BD) in patients with suicidal behavior assisted at National Institute of Mental Health in a three-year period (2008–2010).

**Methods:** A prospective study using clinical assessment in ambulatory suicidal patients searching diagnostic criteria DSM IV-TR for BD.

**Results:** Over a sample of 1300 patients with suicidal behavior, 92 of them (7.1 %) were diagnosed as Bipolar: 25 males (27.2 %) and 67 females (72.8 %), being 70 % of them aged less than 33 years old. For Bipolar I: 71 patients (77.2 %), Bipolar II: 21 patients (22.8 %). There were 38 patients with bipolar depressive state (41.3 %), 36 for mixed episodes (39.1 %), 12 of them for pure manic episode (13 %) and other 6 considered rapid cycling patients (6.5 %). Psychotic features were found in 43 patients (47 %). Most important co-morbidities were: excessive smoking in 25 %, abuse of alcohol and other substances in 31 % and BPD in 24 %. Regarding suicidal behavior: it was found suicidal ideation in 35.8 %, suicide attempt in 59.8 %, and complete suicide in 44.4 %. About suicide attempts, near half of them diagnosed as bipolar depressive episode, 47 % as mixed episode and 56 % as manic episode. Almost 75 % of patients were in an inadequate treatment. Among 4 patients who completed suicide: 3 females/1 male, 2 of them diagnosed as mixed bipolar with psychotic features.

**Conclusion:** According the trial, prevalence of BD amongst suicidal patients is not too infrequent, being predominant in young female, mostly bipolar depression and mixed states, worsening in case of comorbidity with substances abuse and BPD, and also under inadequate approach; being authors advise an early and better identification of BD for it adequate treatment and effective suicide prevention.
Young Mania Rating Scale YMRS score $\geq$ Depression Rating Scale HAMD score $\leq$

Objective: The objective of this study is identifying specific domains of cognitive dysfunction for different phases of bipolar disorder.

Methods: We examined 60 bipolar (depressive; Hamilton Depression Rating Scale HAMD score $>17$, manic/hipomanic: Young Mania Rating Scale YMRS score $>12$, euthymic: 6 month of remission, HAMD score $<8$, YMRS score $<6$) patients (according to DSMIVTR). All the patients were free of psychotic symptoms at the moment of neuropsychological evaluation. The comparison group consisted of 20 healthy subjects without history of neurological/psychiatric disorder. The cognitive battery included standardized test of IQ, attention, working memory, visual memory, verbal memory and executive functioning. Demographic data (gender, age, years of education, socioeconomic status and current employment) were systematically obtained. Data about psychiatric history, past and current treatment, history of psychosis, duration of illness, age of onset and family history were collected. We analyzed statistically these data and identified specific domains of cognitive dysfunction for different phases of bipolar disorder.

Results: Cognitive deficits involving executive functioning (working memory, verbal fluency, mental manipulation and cognitive flexibility), verbal learning and memory and attention are evident across all phases of illness and persist during euthymic phase too. Sustained attention (vigilance) is impaired in bipolar patients regardless of whether they are studied during periods of mania or depression (not remitted completely during euthymia). In addition, selective attention deficits during acute episodes don’t normalize during euthymia. Depressed patients have the lowest verbal fluency and were particularly impaired in domains as affective processing. Performances on task that taps domains of verbal learning and memory, and sustained attention were particularly impaired in manic patients.

Conclusion: Bipolar patients exhibit widespread neurocognitive dysfunctions during their lives. There are persistent cognitive deficits over the course of bipolar disorder and specific cognitive impairment of each phase of the illness.

Objective: The objective of this study is identifying and assessing the risk factors for cognitive impairment in bipolar affective disorder.

Methods: We examined 60 bipolar (depressive, manic/hipomanic, euthymic) patients (according to DSMIVTR). The cognitive battery included standardized test of IQ, executive functioning, working memory, attention, visual and verbal memory. Demographic data (gender, age, years of education, socioeconomic status and current employment) were systematically obtained. Data about psychiatric history, past and current treatment, psychosis history, illness duration, age of onset and family history were collected. We analyzed statistically these data and assessed the relationships between cognitive deficits and clinical and demographic variables in bipolar patients.

Results: Cognitive deficits are more frequent in bipolar patients with more severe course of illness, as indicated by: longer durations of mood disturbance (negatively correlated with executive function, psychomotor speed and attention), concentration and verbal memory-associated with a higher number of past manic episodes too), younger age at onset, history of multiple and frequent episodes (with manic episodes impacting neuropsychological impairment most extensively; attention and executive function deteriorated by the recurrence of episodes) and higher number of hospitalization (negatively correlated with visual and verbal memory, verbal fluency, spatial memory, psychomotor speed and executive function). Other risk factors were: pharmacological treatments, individual response, familial risk factors (positive family history for mood disorders negatively influences cognition), rapid cycling and seasonality, too. There’s as well a specific relationship between executive functioning and admission for mania and between cognitive performance on several tasks and admission for depressive episodes. Females performed better on tests for verbal memory. Besides depressive and manic symptoms, anxiety and psychosis history negatively influence cognition too.

Conclusion: We evidentiated several risk factors that may influence cognitive function in bipolar disorder but there’s a growing need for further clarification regarding the magnitude, clinical relevance and confounding variables of cognitive deficits in bipolar individuals.

Objective: Asenapine demonstrated superiority over placebo in bipolar I disorder patients experiencing acute manic or mixed episodes in two 3-week, randomised, placebo-and olanzapine-controlled trials(1,2), and comparable efficacy to olanzapine in a 9-week non-inferiority double-blind extension trial(3). We assessed the effects of asenapine on manic and depressive symptoms in patients experiencing manic episodes with depressive symptoms.

Methods: 977 patients were randomised in the original trials to flexible-dose asenapine (10 or 5 mg twice daily), placebo, or olanzapine (5–20 mg once daily) for 3 weeks. In the intent-to-treat population, 295 patients had a mixed episode (placebo: 66, olanzapine: 122; asenapine: 107). Of these, 102 patients (olanzapine: 56; asenapine: 46) entered the 9-week extension study. Pooled data were analysed through analysis of covariance with treatment and centre as factors and baseline value as covariate on observed cases.

Results: Decreases in YMRS and MADRS total scores were significantly greater with asenapine (YMRS: −15.0; MADRS: −8.2) versus placebo (YMRS: −11.5; MADRS: −4.5) at week 3, differences between olanzapine (YMRS: −13.3; MADRS: −6.5) and placebo were not statistically different. The effect of asenapine on manic and depressive symptoms was maintained over the extension trial (week 12, YMRS: −22.4; MADRS: −11.9) non-statistically different from olanzapine (YMRS: −20.2; MADRS: −7.9). At week 3, asenapine was significantly superior to placebo in improving ‘inability to feel’, ‘elevated mood’, ‘sexual interest’, ‘language/thought disorders’, ‘reduced appetite’ and ‘inner tension’; asenapine was significantly superior to olanzapine in improving ‘inner tension’. At week 12, asenapine was significantly superior to olanzapine in improving ‘disruptive/aggressive behaviour’, ‘appearance’ and ‘inability to feel’.

Conclusion: In these post-hoc analyses, asenapine had significantly better treatment effects on both manic and depressive symptoms than placebo, and more pronounced effects than olanzapine in some symptom domains.

Reference

Policy of full disclosure: Emmanuelle Weiller is employed by H. Lundbeck A/S.
Objective: We previously reported a significant upregulation of selenium binding protein 1 (SELENBP1) in three different cohorts of subjects with schizophrenia. We also found a significant increase in SELENBP1 in the blood of a separate cohort. In this study we aimed to (i) measure the expression of SELENBP1 in mood disorders (ii) measure the expression of SELENBP1 in subjects with schizophrenia and (iii) measure the effect of exogenous selenium on the expression of SELENBP1 in SH-SY5Y cells.

Methods: Using qPCR we measured SELENBP1 mRNA in Brodmann’s area (BA) 9 from 10 subjects with major depressive disorder, 10 subjects with bipolar disorder and 10 matched non-psychiatric controls. We also measured SELENBP1 mRNA in BA 8, 9 and 44 from 30 subjects with schizophrenia and 30 non-psychiatric controls. SH-SY5Y cells were treated with vehicle or 175 μg/L selenium for one hour before RNA was extracted and SELENBP1 expression measured using qPCR.

Results: There was no significant difference in SELENBP1 expression in subjects with mood disorders compared to controls (p = 0.655). There were significant differences in SELENBP1 expression between subjects with schizophrenia and control subjects in BA8 (p < 0.001), BA9 (p = 0.036) and BA44 (p < 0.001). There was no significant effect of selenium treatment on the expression of SELENBP1 in SH-SY5Y cells (p = 0.200).

Conclusion: The increase in SELENBP1 expression in schizophrenia extends our previous findings, demonstrating that the change is widespread throughout the cortex. These results suggest that the increase in SELENBP1 is involved in the pathophysiology of schizophrenia, but not in mood disorders. Treatment with selenium had no significant effect on expression of SELENBP1, indicating that the increased expression of SELENBP1 in the brain may not be an acute response to increased selenium.

Policy of full disclosure: The authors declare no conflict of interest.

P-04. Anxiety Disorders

P-04-001 Prenatal exposure to modafinil alters anxiety-like responses in adult mice

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Objective: Modafinil (MDF), a psychostimulant drug currently indicated for treatment of narcolepsy, is often consumed by young generation in fertile age and thus there is an increasing importance to assess possible developmental behavioural toxicity. This study investigated influence of chronic prenatal exposure to MDF on anxiety-like measures in adult mouse males.

Methods: Pregnant female mice were given nine doses of saline (10 ml/kg/day) or MDF (50 mg/kg/day). The same drug dosage regimen was used in their adult male offspring. Thus, there were four experimental groups: SAL and MDF offspring from SAL mothers and SAL and MDF offspring from MDF mothers. Anxiety was assessed as % of entries to open and closed arms in the elevated plus maze on: Day 1 – naive mice, Day 8 – acute dose of SAL or MDF, Day 15 – one week repeated administration.

Results: Prenatal treatment with MDF increased % of entries to closed arms compared to SAL prenatal administration (but did not significantly alter % of entries to open arms). In prenatally naive mice neither acute nor chronic MDF treatment induced changes in anxiety-like behaviour compared to SAL treatment. However, in offspring of MDF treated mothers acute MDF dose significantly decreased % of entries to open arms and chronic MDF treatment significantly increased % of entries to closed arms compared to the prenatally naive controls.

Conclusion: We can conclude that MDF did not alter anxiety in prenatally naive mice but there was observed partial increase in anxiety-like behaviour induced by combination of prenatal and postnatal MDF treatment.

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P-04-002 Ensemble classifiers operating on multimodal random subsampling of fMRI data when ensembled so as to capture a maximum of interest-based (ROI) approach adherent to the Automatic Anatomical Labelling (AAL) atlasing framework. Functional data from 72 subjects (47 controls, 25 patients) performing a facial emotion discrimination task in two different scanning environments regarding scanner-hardware, stimulus-design and acquisition parameters was available for validating our approach.

Methods: Prior to data-aggregation principal component analysis (PCA) was applied to check for components related to scanning-environment within each isolated modality. Components displaying clear separation of both datasets were selectively excluded from back-projection into original feature-space. Subsequent to data-aggregation, random forest feature ranking was performed on the resulting 7389 features. Ensemble classifiers were built from nine leave one out cross-validated (LOOCV) linear discriminant analysis (LDA) base-learners operating on random feature-partitions of size = 12, thus effectively including only the 108 most informative features.

Results: Averaged performances of 100 ensembles gave an overall accuracy of 86.03 ± 2.08 %, a sensitivity of 79.48 ± 4.61 % and a specificity of 89.51 ± 1.90 % (mean ± SD). Pooled votes from all ensembles gave 8 misclassifications with an overall accuracy of 88.89 %, a sensitivity of 84.00 % and a specificity of 91.49 %. Conclusion: Our results indicate that even simple base-learners offer high potential for robust subject-level classification of multimodal fMRI data when ensembled so as to capture a maximum of informative features from the data at hand.

P-04-003 An investigation of attention process in chronic fatigue syndrome: Health-threat related attentional bias and the role of attentional control

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Objective: Attentional bias is an important psychological mechanism that has been extensively explored within literature for anxiety and more recently for chronic pain. Cognitive behavioural models of chronic fatigue syndrome (CFS) and chronic pain suggest an overlap in the mechanisms of these two conditions. The current study investigated attentional bias towards health-threat stimuli in individuals with CFS and in healthy controls, and also examined whether individuals with CFS have impaired executive attention, and whether this was related to attentional bias.

Methods: 27 participant with CFS and 35 healthy controls completed a Visual Probe Task measuring attentional bias towards health-threat stimuli, and an Attention Network Test measuring alerting, orienting and executive attention. Participants also completed a series of standard self-report measures.

Conclusion: We can conclude that MDF did not alter anxiety in prenatally naive mice but there was observed partial increase in anxiety-like behaviour induced by combination of prenatal and postnatal MDF treatment.
Results: When compared to the control group, the CFS group showed a significantly slower reaction time, and a trend of greater attentional bias towards threat-words than pictures. The CFS group was significantly impaired on executive attention compared to controls and CFS individuals with good executive attention.

Conclusion: This was the first study to investigate attention processes using a combined experimental paradigm and report an interesting relationship between attentional bias and executive attention in CFS. The study demonstrated that attentional biases in individuals with CFS are dependent on their capacity to voluntarily control their attention, which suggests that adding attentional control strategies to current intervention models may be beneficial for CFS.

P-04-004: Human translocator protein (18 kDa) and its genetic variation in relation to stress sensitivity in patients with atopic dermatitis

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Objective: Expression of the translocator protein (18 kDa) (TSPO), formerly known as the peripheral-type benzodiazepine receptor, is correlated with trait anxiety in normal human subjects (Nakamura et al., 2002). Many dermatological diseases become more serious under stress conditions, but their relations to individual's sensitivity to stress are not well understood.

Methods: To address this issue, we examined patients with atopic dermatitis (AD) for their expression and genomic variation of TSPO as well as their levels of anxiety using the STAI scores.

Results: The AD patients (30 males, 22 females) showed higher STAI scores, especially trait anxiety in males (p < 0.001), compared to healthy subjects. The expression of platelet TSPO was significantly higher in males (p < 0.001) and females (p < 0.05) compared to their normal controls (86 males, 70 females). A single-nucleotide polymorphism (SNP) of the human TSPO gene at exon 4 (485C>G) leading to an amino acid substitution of TSPO (Arg162His), which is associated with anxiety disorders (Nakamura et al., 2006), showed a significantly (p < 0.05) different frequency distribution in the AD patients compared to normal subjects: a lower frequency of G/G (44.2 %) and a higher frequency of G/A (50 %). The severity of AD (SCORAD) was significantly (p < 0.05) correlated with TSPO expression in male G/A patients.

Conclusion: The results suggest that the 485C>G SNP of the TSPO gene and the amino acid substitution of TSPO may be related to the sensitivity to stress and the pathogenesis of AD.

P-04-005: The long-term efficacy of escitalopram for the treatment of Korean panic disorder patients: A prospective, open-labeled, multi-center trial


Objective: Objective The purpose of this study was to examine the long-term efficacy of escitalopram for the treatment of Korean panic disorder (PD) patients.

Methods: The study subjects were 119 adult PD patients (18-70 years old) from 6 university hospitals in South Korea (Samsung Medical Center, Seoul Paik Hospital, Ilsan Paik Hospital, Wonkwang University Hospital, Ewha Womans University Mokdong Hospital, and Cheonbuk National University Hospital). The structured clinical interview for the DSM-IV (SCID-IV) was administered to all subjects by experienced psychiatrists. The primary outcome measures were improvement on the Panic Disorder Severity Scale (PDSS) and the remission rate of panic disorder. Secondary outcome measures included improvement on the Hamilton Depression Scale (HAMD), BDI and SDS at baseline and 4, and 12 weeks after beginning treatment. We used the LORCF method. Repeated measure ANOVA was used to test for the improvement on the PDSS and SDS.

Results: Among 119 PD patients, 87 patients (73.1 %) had attained a remission state during the 24 weeks of escitalopram treatment. The mean dose of escitalopram was 11.65 ± 3.83 mg/day. At the LOCF week 24 evaluation, a significant difference in PDSS total score was observed. (ITT: 11.16 ± 6.51, p-value < 0.0001) (t = 18.71). In the post-hoc analysis, we found a continuous significant improvement on the PDSS total score at baseline, week 4, week 12 and week 24. We found a continuous significant improvement on the 3 domains of SDS (work, social relationship, and responsibilities at home and with family) at baseline, week 4, week 12, and week 24. (p-value < 0.0001).

Conclusion: This study suggests that long term efficacy of escitalopram measured by the PDSS and SDS is high in the Korean PD patients.

P-04-006: Clinical characteristics of obsessive compulsive disorder with schizophrenia

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Objective: We investigated the prevalence of obsessive compulsive disorder (OCD) among patients with schizophrenia. We also investigated the differences in the psychotic symptoms and suicidality between patients with schizophrenia who did or did not have OCD symptoms.

Methods: Seventy-one subjects with the DSM-IV diagnosis of schizophrenia were evaluated by the Structured Clinical Interview for DSM-IV Axis I disorders, the Yale-Brown Obsessive-compulsive Scale and the Positive and Negative Syndrome Scale.

Results: The OCD patients with schizophrenia were 20 (28.2 %) among 71 subjects. The 20 subjects with OCD had significantly more severe negative and total psychotic symptoms evaluated with PANSS than subjects without OCD. The schizophrenia with OCD had significant higher recent suicidal attempt rate than the subjects without OCD.

Conclusion: The results of this study suggest the possibility that OCD symptoms in schizophrenia may be related to negative symptoms and the OC symptoms may be related to the impulsivity expressed as suicidal attempts.

P-04-007: Non-verbal memory dysfunction in checking type obsessive-compulsive disorder

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Objective: The purpose of this study is to examine the role of memory dysfunction in obsessive-compulsive disorder (OCD). Especially we tested the memory function of checking type obsessive compulsive disorder compare to that of cleaning type and that of normal controls.

Methods: Subjects were 16 patients aged 18-45 years who met the diagnostic criteria of obsessive compulsive disorder and 8 normal controls. Informed consent was done. 16 OCD patients was divided into two groups, 8 ‘checking’ type and 8 ‘cleaning’ type patients by evaluation of Yale-Brown Obsessive compulsive scale and Maudsley Obsessive compulsive inventory. All patients were tested memory functions by Rey-Osterrich comlex figure test (RCFT) for non-verbal memory function, Hopkins verbal learning test (HVLT) for verbal memory function, Wisconsin card sorting test (WCST) and evaluated depression and anxiety by Beck Depression Inventory (BDI) and Taylor Anxiety scale.

Results: The Reimmediate and Reydelayed memory test scores were significantly lower (P<0.05) in checking types than in cleaning types and normal controls (student t-test). There were no significant differences of Reyecopy test scores, and verbal memory test (HVLT) scores, BDI and Taylor Anxiety scale scores in checking, cleaning type groups and normal controls.

Conclusion: The non-verbal memory function of checking type OCD patients was significantly decreased than other OCD patients and normal controls. This non-verbal memory dysfunction is not related to depression and anxiety. This results suggest that checking symptoms development of OCD is related to non-verbal memory dysfunctions.
Objective: Obsessive-compulsive disorder (OCD) is a common neuropsychiatric disorder, characterized by persistent intrusive thoughts (obsessions), repetitive actions (compulsions) and excessive anxiety. Numerous functional neuroimaging studies have suggested that OCD patients had a neurobiological abnormality in the orbitofrontal-cingulated-striatal-thalamic circuits. Voxel-based morphometry (VBM) is a fully automated and unbiased whole-brain method, which assesses regional differences between subjects in gray matter (GM). Several VBM studies have been conducted for OCD, showing volume alterations in these regions, although the findings were not entirely consistent. The application of high magnetic field MRI with increased scanner (Signa, GE). MR images were spatially normalized and segmented using the VBM8 package. Statistical analysis was performed using statistical parametric mapping software. We compared the GM volume between two groups.

Methods: Thirty-one patients diagnosed with OCD according to DSM-IV criteria and 31 age- and gender-matched healthy controls were participated in this study. T1-weighted three dimensional spoiled gradient echo (SPGR) images were acquired via 3-T MRI scanner (Signa, GE). MR images were spatially normalized and segmented using the VBM8 package. Statistical analysis was performed using statistical parametric mapping software. We compared the GM volume between two groups.

Results: Compared with healthy controls, OCD patients had a significantly lower GM volume in the left caudate, right thalamus, right medial prefrontal and anterior cingulated cortex (P<0.05, FWE corrected), on the contrary, significantly higher right caudate GM volume (P<0.05, FWE corrected).

Conclusion: This is the first study that revealed the asymmetry of caudate volume in OCD patients. Other findings are consistent with previous studies reporting abnormality in the orbitofrontal-cingulated-striatal-thalamic circuits.

Objective: We describe the successful tapering out of panic disorder (PD) patients treated for 3 years with clonazepam or paroxetine or their combination.

Methods: 94 asymptomatic PD patients after three years of drug treatment and wishful to leave the medication participated in this trial. The protocol envisaged a dose discontinuation phase protracted over 8 weeks and 12 months of follow-up. The dose of clonazepam was decreased in 2-week intervals by increments of 0.5 mg clonaza- pem until reaching 1 mg/day followed by weekly dose reduction of 0.25 mg; or 10 mg paroxetine until reaching 20 mg/day followed by weekly dose reduction of 5 mg.

Results: The mean dose at staring the tapering out was 1.9±0.5 mg/day of clonazepam and 38.8±3.9 of paroxetine. 57.8% of clonazepam and 18.2% of paroxetine patients were free of the medication after the 2 months of tapering as the protocol. 19 (26.0%) needed another 3 months to leave the medication. 9 (12.3%) of this last group used also mirtazapine or carbamazepine as adjunct therapy during this period. 3 (4.1%) patients gave up the tapering due to return of anxiety symptoms. The withdrawal symptoms were mild and observed in 55 (75.3%) patients. Insomnia, tremor, nausea, sweating, headache, and subjective anxiety were the main complains. Patients of the clonazepam group had during the withdrawal period fewer side effects/withdrawal symptoms than those of the paroxetine or combination group and significantly more patients of the clonazepam group were drug free, asymptomatic and without AE at the end of the first follow up year.

Conclusion: It is possible to take the clonazepam and paroxetine slowly out even after a long treatment without any major withdrawal symptom. The dose should be tapered slowly and some adjunct drug may be useful for some cases.

Objective: We have conducted investigation of vegetative status of women with polycystic ovary syndrome having anxiety-depressive symptoms. This study presents results of evaluation of vegetative status of women with polycystic ovary syndrome (E 28.2 according ICD-10).

Methods: We have examined 50 women of reproductive age (18–45 years) with polycystic ovary syndrome (E 28.2 according ICD-10). Control group has been entered by 25 practically healthy women matched in age. Presence of vegetative dystonia syndrome was identified with “Questionnaire for Revealing the Signs of Vegetative Changes” (Veyn A.M., 2003). We rated spectral and time characteristics of variability of heart rhythm with apparatus-program complex “VNS-Micro” (Neurosoft). Results of the investigation were processed with program Statistica (version 8.0).

Results: According to results of testing with questionnaire of Veyn A.M. (2003) syndrome of vegetative dystonia has been diagnosed in 84% of the examined. Investigation of variability of heart rhythm has demonstrated reduction of current functional state (TP = 1132.6 ± 112.8 mc²/Hz; in norm 2093.0 ± 107.6 mc²/Hz, p<0.01), excessive activation of the sympathetic-adrenal system (ratio LF/HF = 1.93±0.18; in norm 0.72±0.08; p<0.01) and reduction of activity (tonus) of parasympathetic system of regulation (HF-component = 426.2±21.8 mc²/Hz; in norm 984±7.81 mc²/Hz, p<0.01). These changes are pathogenetic basis of development of reactions of dis-adaptation that manifest themselves clinically as vegetative dysfunction syndrome.

Conclusion: Vegetative dysfunction accompanies mental symptoms. Disorder of vegetative provision of the activity worsens quality of life of women with anxiety-depressive disorders co-morbid with polycystic ovary syndrome, conditions insufficient adaptation and is a predisposition to development of anxiety-depressive disorders. Complex investigation of status of vegetative neuroses system allows rating current functional state of the organism and its adaptive reserves, giving prognosis of the disease, developing recommendation in choice of optimal therapy taking into account background of neurohumoral regulation as well as accomplishing the subsequent control of conducted treatment.
P-04. Anxiety Disorders

homozygous made fewer commission errors than the L-allele carriers. Given that the S/S homozygous of the 5-HTTLPR gene could relatively increase neuroticism or anxiety, this result is consistent with our earlier study showing the positive correlation between a high tendency toward neuroticism and a more inhibited response style in a Go/No-Go task when it entailed the probability of receiving punishment (Masui, Kashiho, Nomura, 2009).

Conclusion: These results suggest the impulsivity are modulated by sensitivity to punishment as a function of the 5-HT genotypes; this was clarified in Japanese population that present results lead to the question that whether this effect could be also intermediated by various environmental factors including culture.

P-04-012 Disagreement between adolescent and parent reports of anxiety symptoms: Who is right?

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Objective: It is known that adolescent and parent ratings of adolescent mental health are poorly correlated. In a previous study of adolescent and parent estimations of anxiety using the Spence Children’s Anxiety Scale (SCAS), a correlation of 0.41–0.66 was reported. This result, however, says little about whose ratings are most accurate. The aim of our study was to: 1) investigate the correlation between adolescent and parent ratings in a Swedish child- and adolescent psychiatric outpatient population, and 2) to compare these ratings with a semi-structured diagnostic interview (K-SADS), in this study regarded as gold standard.

Methods: 275 consecutive patients in a child and adolescent psychiatric outpatient clinic in the county of Vastmanland (adolescents 13–18 years and their parents) completed the SCAS. Cut-offs in each diagnosis was set to ±1 Std. dev. above the mean. Thirty of these patients and their parents also completed a diagnostic interview (K-SADS) by a specially trained member of the staff, where the interviewers were blinded for the results from the self-assessments.

Results: Overall, parent ratings indicated lower levels of anxiety in their adolescents compared to the adolescents’ own ratings. Kappa correspondences between parent and adolescent ratings ranged from 0.07–0.19. Preliminary results suggest, that adolescent derived compared with interview derived diagnoses, have a high concordance with the diagnoses Generalized Anxiety Disorder and Social Phobia, (kappa value 1.0).

Conclusion: This study extends the literature in terms of evaluating adolescent self-reported anxiety symptoms. Unlike previous studies, our study demonstrates low concordance between adolescent and parent ratings with the SCAS, and a very high agreement between adolescent self-reported anxiety and diagnostic interview.


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Objective: Background: While the research in adult population suggests an association between anxiety disorders and risk for alcohol use disorders, available studies in youth population have inconsistent and at times, conflicting results. Adolescents may show a relatively heightened sensitivity to some of positive alcohol effects e.g. social facilitation. The relationship of early onset anxiety disorders to alcohol use disorders appears to be complex and perhaps bidirectional.

Objective: The present review was planned in order to examine and describe the nature of association between early-onset (<18 years) anxiety disorders and alcohol use disorders.

Methods: Relevant studies from English language literature were included from PUBMED/MEDLINE, PsychINFO and EMBASE search between 1990–2012 using key words such as [Anxiety or Panic or Phobia or Agoraphobia, Sarness]. [Alcohol or Substance or Drugs] and [Youth or Early or Child or Adolescent OR Students]. Inclusion criteria were as follows (a) studies focusing on children and adolescents or, samples with mean age <18 years (b) reporting the original data (c) assessing the concurrent/prospective prevalence of (any or all) anxiety disorders and (any or all) alcohol use disorders as per DSM/ICD, or standard research instruments. Duplicate study data from same group of researchers were excluded, with the larger sample retained.

Results: The evidence and strength of relationship differs across the spectrum of anxiety disorders and whether the alcohol use is problematic, non-dependent or dependent. Some studies have shown a high concordance between parent and adolescent ratings ranged +1 Std. dev. above the mean. Thirty of these patients and their parents also completed a diagnostic interview (K-SADS) by a specially trained member of the staff, where the interviewers were blinded for the results from the self-assessments.

Conclusion: This result, however, says little about whose ratings are most accurate. The reason for this paradoxical effect is unknown, but revealing it would probably enhance our insight into the physiological role of serotonin for the regulation of fear and related emotions.

Animal experiments performed in an attempt to investigate the effect of short-term SSRI administration on anxiety have shown diverse results: some have revealed increased anxiety-like behavior, whereas others have shown the opposite, with an immediate decrease in anxiety-like behavior after acute SSRI administration. In this study the effect of acute SSR intake (escitalopram, 10 mg/kg, 60 min prior to the test) on the acoustic startle reflex in a putative animal model of anxiety, i.e. contextual conditioned fear, was investigated.

Methods: Startle reactivity was measured following fear conditioning. Furthermore, baseline startle, as well as startle in control animals that had not undergone fear conditioning, was investigated.

Results: Fear-conditioned animals treated with escitalopram 60 min prior to test exhibited significantly greater startle than controls. No significant effect of the drug was seen in non-conditioned animals.

Conclusion: These findings imply that conditions similar to those in humans are at hand also in rat, i.e. that short-term SSRI administration may exacerbate anxiety. This further supports startle reactivity as measurement of contextual conditioned fear as a useful animal model for investigating the mechanisms underlying the influence of serotonin on anxiety.

P-04-014 Association of elevation endocannabinoid plasma levels with mild cognitive impairment and anxiety in people with obesity

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Objective: The endocannabinoid (EC) system has been proposed as a regulator of anxiety, and modulator of cognitive, behavioral responses to stressful stimuli. (1, 2). Also obesity has an association with anxiety and depression (3). This study focuses on the effects of EC system modulation in people with obesity of cognition and emotion (anxiety).

Methods: Aim of this study was to evaluate a possible association between EC plasma levels, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and mental processes such as, cognitive functions and anxiety in obesity. Methods and results. Study participants (n = 67) were divided into three groups due to their body mass index (BMI): control group BMI ≤24, 9, (n = 21); overweight group, BMI ≥25–30 (n = 27), obese group, BMI ≥30 (n = 19). All subjects were passed through tests: MMSE, HADS, and HARS.

Results: Elevation 2-AG plasma level, was significantly associated with BMI in all groups (0.62, p < 0.5; 0.62, p < 0.5; 0.33, p < 0.5). Low MMSE data were significantly associated with elevation AEA plasma level in control group (–0.44, p < 0.5) and elevation 2-AG in obese group (–0.52, p < 0.5). In normal and obese group only elevation of AEA plasma level was associated with high anxiety (0.61, p < 0.5).
In overweight subjects high anxiety was associated with high 2-AG plasma level (0.47, p < 0.5).

**Conclusion:** Conclusions. Increased EC plasma levels of AEA or 2-AG are associated with increasing of anxiety and poor cognition up to the mild cognitive impairment.

**P-04-016** Psychological problems in relatives of patients with severe mental disorder: Assessment and intervention

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**Objective:** This work has two objectives: 1) to identify the psychological problems in relatives of patients with severe mental disorder (SMD), and 2) to show the main components of psychological intervention with relatives.

**Methods:** Relatives of patients were examined in the Day Hospital of Mental Health of Granada (Spain). The Spanish versions of "Beck’s Anxiety Inventory", Beck’s Depression Inventory-II” and “Coping Strategies Inventory” were used. The psychological intervention consisted of 20 weekly sessions of two hours each one. It included: 1) psycho education; 2) elaboration of mourning; 3) acceptance of life experiences and commitment to values-based living; and, 4) skills training. The sessions followed all of them a similar structure consisting of exercise review, functional analysis, use of metaphors, experiential exercises, and training techniques for emotional regulation and assertive communication.

**Results:** Regarding the first objective, 48 relatives were evaluated. 64.7% of them had depression and 52.2% anxiety. A high relationship between these two variables was found \( r = 0.734, p = 0.000 \). With regard to the second objective, nine relatives participated in a psychological intervention program. Wilcoxon test showed that for people participating in the program the level of depression decreased and the use of strategies focused on problem solving increased \( p < 0.05 \). Although anxiety also decreased as a result of treatment it not reached a significant level. 88% of relatives said that the intervention was useful, and that they applied what they have learned to their daily lives. 62.5% of relatives have recovered many valued activities of their lives.

**Conclusion:** The presence of psychological problems seems high prevalent among relatives of patients with SMD. The intervention program was successful, reducing some psychological problems and improving some coping strategies in relatives. They reported to have decreased their distress and have recovered valued activities previously abandoned because of their implication with the care of the patient.

**P-04-017** Relationship between attachment styles and personality traits to wellbeing and stress related disorders

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**Objective:** The five most common worldwide diseases planned for 2020 will have stress as an underlying factor. People with this type of patient.

**Results:** Regarding the first objective, 48 relatives were evaluated. 64.7% of them had depression and 52.2% anxiety. A high relationship between these two variables was found \( r = 0.734, p = 0.000 \). With regard to the second objective, nine relatives participated in a psychological intervention program. Wilcoxon test showed that for people participating in the program the level of depression decreased and the use of strategies focused on problem solving increased \( p < 0.05 \). Although anxiety also decreased as a result of treatment it not reached a significant level. 88% of relatives said that the intervention was useful, and that they applied what they have learned to their daily lives. 62.5% of relatives have recovered many valued activities of their lives.

**Conclusion:** The presence of psychological problems seems high prevalent among relatives of patients with SMD. The intervention program was successful, reducing some psychological problems and improving some coping strategies in relatives. They reported to have decreased their distress and have recovered valued activities previously abandoned because of their implication with the care of the patient.

**P-04-018** Assessment of allostatic load and stress related disorders through translational evaluation of alprazolam on MHPG, cortisol and cognitive domains

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**Objective:** To assess impact of Alprazolam on salivary MHPG and cortisol, cognitive functions and parameters of allostatic load in anxiety disorders and stress related disorders.

**Methods:** Fifty volunteer participants, 15 male (26.6%) and 37 female (74.4%) over 21 years, meeting following criteria: NEFOFFI scoring over 18 points, HARS over 7 points, over 3 parameters of Seeman – McEwen Allostatic Load Parameters and comorbid anxiety disorder plus at least a stress related disorder. Evaluations were conducted on days –7, 0, 7, 14, 28, 60 and 90, receiving Alprazolam on day 0 between 0.75 to 3 mg/day according to clinical status. Salivary concentrations of Alprazolam were monitored from day 7. Clinical progression was followed up with HARS, STAI, NEO-FFI, neuro-psychological test battery (Continuous Performance Test, Digit Symbol, Digit Span, Verbal Fluency Test, Five Points Test, Revised Taylor Complex Figure Test, Stroop Test), and parameters of allostatic load measured through clinical and neurobiochemical trials (salivary MHPG and cortisol).

**Results:** Saliva MHPG significantly reduced 57.3% from visit 1 to visit 7 with Alprazolam correlating with descending levels of HARS and STAI (43.1 % and 9.4 %, respectively), along with steady decrease in cortisol (15.4 %). Females score significantly higher than males in Neuroticism and symptoms of anxiety (n = 37; p < 0.001) MHPG appeared influenced by life events. Improvement in executive functions through modulation of anxiety, stabilization in sustained attention, interference control and decrease in impulsivity rates.

**Conclusion:** MHPG appears as useful marker to assess stress response. Alprazolam impacts rapidly and steadily on endorphinergic activation to stress response, lowering anxiety scores and promoting clinical progression through modulation of response to allostatic load.

**P-04-019** Efficacy and tolerability of agomelatine in generalized anxiety disorder (GAD): A randomised double-blind, placebo-controlled trial with escitalopram as validator

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**Objective:** Agomelatine, a MT1/MT2 receptor agonist and 5-HT2C receptor antagonist, has demonstrated efficacy in GAD. This 12 weeks multi-centre, randomised, double-blind, parallel group study in GAD aimed to confirm the superiority of agomelatine (25-50 mg/day) vs. placebo, using escitalopram (10-20 mg/day) as a validator, on the Hamilton Anxiety Rating Scale (HAMA) total score.

**Methods:** 412 patients with a DSM-IV diagnosis of GAD were randomised to receive agomelatine (139), placebo (131) or escitalopram (142). The HAMA total scores at baseline in the Full Analysis Set (FAS) (n = 409) were respectively: 28.6; 28.2 and 28.6.

**Results:** At last value, the HAMA total score decreased significantly more with agomelatine –15.6 (p < 0.0001) and with escitalopram –15.6 (p < 0.0001) compared to placebo –10.6. In patients with more severe GAD symptoms (HAMA total score >= 25 and CGI-S >= 5 at baseline), the between group difference vs. placebo was 5.61
Objective: This study investigated the consensus about treatment strategies for initial treatment, long-term treatment and comorbid conditions in generalized anxiety disorder (GAD) in Korea.

Methods: The executive committee for Korean medication algorithm project for GAD developed questionnaires about treatment strategies for patients with GAD based on guidelines or algorithms and clinical trial studies previously published. Fifty-five (64%) of 86 experts on a committee reviewing GAD in Korea responded to the questionnaires.

Results: For initial treatment of GAD, antidepressants monotherapy and combination of antidepressants and benzodiazepines were recommended as the 1st line strategies. Escitalopram, paroxetine CR and venlafaxine XR were selected as 1st line treatments. Xanomeline and 1.55 for escitalopram (SE=0.0001) showed significant freezing behavior on re-exposure to the box. The most commonly reported AESs were headache, nasopharyngitis, diarrhoea, and nausea.

Conclusions: This study confirmed that agomelatine is efficacious and well tolerated in the treatment of GAD.

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P-04-022 Anxiolytic effects of Yokukansan, a traditional Japanese medicine, via serotonin 5-HT1A receptors on anxiety-related behaviors in rats experienced with aversive stress


Objective: Yokukansan, a traditional Japanese medicine (Kampo), is used for the treatment of Alzheimer’s disease (AD), post-stroke dementia, and various neurological diseases. In the present study, we investigated the anxiolytic effects of yokukansan on anxiety-related behaviors in rats that have experienced aversive stress.

Methods: We used male Wistar/ST rats which received an electrical footshock as aversive stress. Yokukansan at a dose of 1.0 g/kg was administered orally once a day for 14 or 16 days before behavioral tests. To evaluate the anxiolytic effects, we used the contextual fear conditioning (CFC) test and elevated plus maze (EPM) test.

Results: In the CFC test, rats that had experienced footshock showed significant freezing behavior on re-exposure to the box 14 days after footshock stress. Yokukansan significantly suppressed freezing behavior in the CFC test. In the EPM test on the 16th day after the CFC test, yokukansan significantly increased the time spent in open arms after footshock stress compared to control rats.
P-04-023 Study of benzodiazepine reception in C57Bl/6 and Balb/c mice
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Objective: The decrease of benzodiazepine binding in anxiety states is proved in a number of clinical and experimental investigations. In our previous experiments, stress in the “open-field” test (OF) caused reduction of benzodiazepine reception in Balb/c mice. In C57Bl/6 mice such effect was not observed. In the present research benzodiazepine reception in inbred mice C57Bl/6 & BALB/c with different OF behavior was studied: (1) anxiety factors affecting benzodiazepine reception, (2) duration of the anxiety-induced benzodiazepine reception reduction.

Methods: Open field, Elevated Plus Maze, Short Immobilization, Exposure to a predator, Radioligand binding assay.

Results: The level of specific [N-methyl-3H]-flunitrazepam binding with P1 + P2 membrane fraction of C57Bl/6 and Balb/c mice brain tissue was studied after tests OF, “Elevated Plus Maze” (EPM), 3 h immobilization, “Exposure to a predator”. Stress-induced decrease of benzodiazepine reception was registered after test OF, EPM only in Balb/c mice. After test “Exposure to a predator” and 3 h immobilization significant decrease is obtained for both Balb/c and C57Bl/6 mice. We found that stress in OF significantly changed the level of specific [N-methyl-3H]-flunitrazepam binding in Balb/c mice brain for 1.5 h. The restoration of reception to the control level occurred in Balb/c mice brain after 8 h and after 24 h in C57Bl/6 mice brain after the test “Exposure to a predator”.

Conclusion: Thus, the duration of recovery of change in benzodiazepine binding depends on the phenotype of stress response, the strength of stress factors and can serve as an important marker of anxiety.

P-04-024 A novel open-field stress-induced activation of GAD67-containing 5-HT neurons in the dorsal raphe nucleus of rats
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Objective: The presence of GABA and its synthetic enzyme glutamic acid decarboxylase (GAD) has been reported in 5-HT neurons in the dorsal raphe nucleus (DRN). However, neurochemical and functional properties of the GAD-positive 5-HT neurons remain unclear.

Methods: In the present study, we characterized GAD67-expressing 5-HT neurons in the rat DRN and also examined regional differences in neuronal responsiveness to emotional stress.

Results: Mild emotional stress induced by open-field exposure caused c-Fos expression in all three subdivisions of the DRN, particularly in the DRL. This response was selectively suppressed in the DRL by potentiation of GABA receptors with diazepam. In the DRL, the open-field stress-induced c-Fos expression was more prominent in 5-HT/GAD67 neurons than in 5-HT neurons.

Conclusion: These findings indicate that 5-HT/GAD67 neurons constitute a unique neuronal population in the DRN and high responsivity to mild emotional stress.
centers, while meeting the highest data protection standards. By combining resources, the aim is to have a cohort of 100,000 patients by 2020. This cohort will not be restricted to genetic or other biological psychiatric research but constitute a valuable resource for research on epidemiological aspects, quality of care, and socio-demographic aspects of psychiatric morbidity.

P-05-002 Expression of Wnt/β-catenin signaling pathway genes in peripheral blood correlate with negative symptoms among Individuals with psychosis

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Objective: To correlate blood-based gene expression of the Wnt/β-catenin signaling pathway with negative and positive symptom severity indices of patients with a history of psychosis (i.e. schizophrenia or bipolar disorder).

Methods: A total of 19 subjects meeting DSM-IV criteria for at least one episode of psychosis were recruited and assessed using the Scales for the Assessment of Positive and Negative Symptoms (SAPS/ SANS). Twenty-five of the most well-characterized genes involved in the Wnt signaling pathway were selected, based on the Kyoto Encyclopedia of Genes and Genomes database. Spearman’s correlations were conducted between expression intensities for each of the 25 selected Wnt pathway genes and SAPS/SANS global severity scores, adjusting for gender, ethnicity, age, education, current smoking (yes/no), and past six-month substance use (yes/no). A Bonferroni-adjusted alpha threshold of 0.05/50 = 0.001 was used to reduce the risk of Type I errors.

Results: Two (DVL2 and GSK3β) of the 25 Wnt signaling pathway genes examined were correlated with scores on the SANS; however, only DVL2 remained significant after Bonferroni correction. DVL2 (r = -0.70, p = 0.0008) showed a negative correlation whereas, GSK3β (r = 0.48, p = 0.039) was positively correlated with the SANS ratings. Post-hoc exploration of the four subscales of the SANS revealed significant negative correlations between DVL2 expression and affective flattening (r = -0.55, p = 0.015) and aloxia (r = -0.65, p = 0.003) severity. GSK3β expression was positively correlated with aloxia (r = 0.60, p = 0.007) only. None of the 25 gene transcripts examined were significantly correlated with severity scores on the SAPS.

Conclusion: Our findings suggest that the Wnt signaling pathway may harbor biomarkers for severity of negative but not positive symptoms.

Policy of full disclosure: There is no financial conflict of interest.

P-05-003 Meta-analysis of COMT Val158/108Met association findings in major depression

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Objective: Many studies described the association of Val158/108Met polymorphism of the Catechol-O-Methyltransferase (COMT) Gene and psychiatric disorders including major depressive disorder (MDD). The COMT Val158/108Met polymorphism has been investigated regarding its role in aetiology, course of illness and therapy-response, although with conflicting results. In the present study we therefore perform a meta-analysis of the current literature.

Methods: To identify studies eligible for meta-analysis, we search the PubMed and Medline with the Keywords: “unipolar depression”, “major depression”, “depressive disorder” and “affective disorder” combined with “COMT”, “polymorphism”, “gene” and “allele”. Based on this literature research we aim to identify case-control-studies published in peer-reviewed journals which provide enough data to calculate an effect size. Studies are excluded from further examination if cases were selected by questionnaires assessing symptoms of depression, if the study didn’t include a control group of subjects or included bipolar patients. The distribution of genotypes has to be in Hardy-Weinberg Equilibrium to be considered in this meta-analysis. In addition, references cited in these studies are reviewed to identify further publications not obtained by MEDLINE.

Results: The included case-control studies selected in this manner will be analysed by random effects meta-analysis.

P-05-004 Search of rare genetic variants of psychotic disorders in Algerian consanguineous families

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Objective: Several recent studies have reported associations of schizophrenia (SZP) with rare copy number variations (CNVs), such as 1q21.1 and 15q13.3 deletions. These CNV results suggest a broader neuropsychiatric spectrum of phenotypes, and support a “Common Diseases – Many Rare Alleles” hypothesis. The majority of these CNVs are de novo, and we lack information about the phenotypes associated with such variants when they are transmitted. These results also suggest that other types of rare mutations could be associated with psychotic disorders. We are studying four families from North-West Algeria identified through patients with psychiatric disorders, in order to identify new rare variants responsible for these disorders.

Methods: We are studying four consanguineous families from Tlemcen in North-West Algeria with 30 patients with psychotic disorders, in order to identify new rare variants. Information was collected about direct interview (DGI) and medical records. The Agilent Human Genome CGH Microarray Kit 44K is used for the genome-wide DNA copy number variation profiling, and the Illumina’s Genome Analyzer IIe for exome high-throughput sequencing.

Results: In three families all the affected members analyzed up to now are schizophrenics and in one bipolar I (BDI) with psychotic symptoms. Three new CNVs have been identified, one 1.6 Mb duplication on chromosome 4q26 and on small 28.8 deletion on chromosome 16q21.3 and deletion 21q21.1. Segregation of these new CNVs is currently analyzed. Sequencing data are not yet available.

Conclusion: This ongoing study of three Algerian families with SZP and one with BDI allow us to identify two new CNVs. Complete CNV analysis and exonic sequencing will be presented.

P-05-005 Quantitative smoking effects differences in male mu opioid A118G alleles

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Objective: The objective of the present study was to provide additional support for a role of mu opioid receptors in tobacco smokers. There are basic and clinical studies indicating that the endogenous mu opioid system is involved with several substances of abuse.

Methods: After overnight tobacco abstinence, 14 genotyped males smoked denicotinized (denic) and average nicotine (avnic) containing tobacco cigarettes in a PET brain imaging study using 11C-raclopride. Carriers of the G allele demonstrated minus avnic tobacco smoking. Carriers of the G allele demonstrated larger magnitudes of DA release in response to avnic smoking than those homozygous for the more prevalent AA allele in the right caudate and right ventral pallidum (t = 3.03; p = 0.008 and t = 3.91; p = 0.001). A voxel by voxel whole brain SPM analysis using an independent samples t test did not reveal any other differences between genotype groups. In addition, the venous plasma cortisol levels of the volunteers from 8:30 a.m. to 12:00 p.m. were lower in the AG/GG alleles. Avnic smoking increased plasma cortisol in both groups, but they were higher in the AA group.

Conclusion: The present results indicate that the mu opioid receptor function has important tobacco smoking effects.
**P-05-006** Investigating telomere length and psychological stress in South African rape victims

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**Objective:** Women are at an increased risk of depression and other mental health problems following rape. Various aetiological factors for depression, including predisposing genetic factors, have been identified. Telomeres are repetitive nucleoprotein structures located at chromosomal ends that protect them from premature degradation. Telomeres reduce in length with each cell division, resulting in cellular senescence and apoptosis. Additional factors, such as oxidative and psychological stress, can further induce telomere shortening.

**Methods:** This study performed relative quantification of telomeric repeats with the use of real-time PCR methods to investigate whether shorter relative leukocyte telomere length (LTL) in a cohort of rape victims was associated with resilience, the development of trauma-related major depressive disorder (MDD), as well as the development of PTSD after three months.

**Results:** No significant associations were observed between relative LTL and resilience or the development of MDD at either baseline or after three months in this cohort. However, a significant association was evident between relative LTL and PTSD status.

**Conclusion:** The significant association between relative LTL and PTSD suggests that shorter relative LTL might have acted as a predisposing factor to the development of PTSD after a severe traumatic event. Telomere shortening may be an important marker of PTSD risk, which has implications for early intervention and timely treatment.

**P-05-007** Epigenome analysis in neurons of bipolar disorder and schizophrenia

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**Objective:** Epigenetic factors such as cytosine and histone modifications are involved in long-lasting gene expression change and are believed to play important roles for the pathophysiology of major psychiatric diseases. Here we performed comprehensive DNA methylation analysis using brains of patients with schizophrenia (N = 35), bipolar disorder (N = 35) as well as controls (N = 35).

**Methods:** Postmortem brains (prefrontal cortex, BA10) were obtained from the Stanley Medical Research Institute. We have previously established a method for the separation of neuronal and non-neuronal nuclei from the fresh-frozen postmortem brain using NeuN-based cell sorting. By using this separation method, neuronal (NeuN+) and non-neuronal (NeuN−) fractions were obtained from each brain sample. After the enrichment of methylated DNA with MB2B protein, DNA methylation profiles were obtained with Affymetrix promoter tiling arrays. Methylated region was identified with MAT software.

**Results:** In both psychiatric diseases, we identified specific DNA methylation differences compared to control subjects. Representative methylation differences were extensively confirmed by qPCR analysis.

**Conclusion:** Some of DNA methylation differences were only found in neuronal or non-neuronal nuclei, suggesting the cell-type specific DNA methylation changes in patients’ brain. Such DNA methylation change may contribute to the pathophysiology of psychiatric diseases.

**P-05-008** Association between the CLOCK gene and autism symptoms in a Swedish twin sample


**Objective:** Autism spectrum disorders (ASDs) are pervasive developmental disorders that include Autistic disorder, Asperger syndrome, and pervasive developmental disorder—not otherwise specified (PDD-NOS). Many patients with ASD have sleep impairments and timing problems, suggesting disturbances in the regulation of circadian rhythm as causative factors for these disorders. Indeed, low levels of melatonin are recurrent biological findings and we have previously found association between genes in the melatonin pathway and ASDs. Melatonin is closely related to the circadian rhythms, which is mainly regulated in the suprachiasmatic nucleus (SCN) by a set of clock genes. Genetic variation in the clock genes have previously been investigated in autism patients showing an association with the clock genes PER1 and NPAS. In this study, we have investigated the possible association of five circadian clock genes on autism symptoms in a Swedish twin sample.

**Methods:** Single nucleotide polymorphisms in five circadian clock genes were genotyped in The Child and Adolescent Twin Study in Sweden (N = 1771, 9-12 years old). The measured autism symptoms were flexibility, language and social interaction. In addition, the CLOCK gene was screened for mutations in patients with autism (N = 90).

**Results:** Our results show a significant association in girls between rs1801260, in the 3-UTR, of the CLOCK gene, and the symptom flexibility (p = 0.0003), but not with the symptoms language and social interaction. The mutation screening revealed five rare, previously not reported, variants in six different patients.

**Conclusion:** In conclusion, our results support the hypothesis that clock genes may be involved in autism related disorders. Moreover, since all symptoms of autism did not show similar association with the investigated clock genes in this study, our findings also emphasizes that genetic research may benefit from taking a symptom-specific approach to finding genes associated with autism.

**P-05-009** Involvement of the 5-HT2A receptor gene polymorphism in trait anxiety, in activity of VLPFC and in impulsivity: A NIRS study

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**Objective:** A polymorphism of the 5-HT2A receptor gene has been suggested to underline the impulsivity behavior. However, relations among this gene polymorphism, impulsivity and activity of brain (especially ventro-lateral prefrontal cortex, VLPFC) remain unclear. We examined whether and how this 5-HT2A receptor gene polymorphism modulates impulsivity in a reward-punishment Go/No-go task and related brain activity measured by near infrared spectroscopy (NIRS).

![Image](https://academic.oup.com/ijnp/article-abstract/15/Supplement_1/1/650920/7)

1. P-05-007
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Methods: Participants: Twenty-seven women (age 21.26 ± 2.91; AA carriers (AA, n = 7) and G carriers (AG and GG, n = 20)) gave written informed consent and participated in the experiment. Stimuli and Procedure: Participants were required to respond to target stimuli and to inhibit their response to non-target stimuli with either monetary reward or monetary punishment. The Go/No-go task was performed by each participant under two conditions (reward condition and punishment condition). Hemodynamic responses of the brain were acquired using fNIRS. After the task, participants answered the STAI questionnaire.

Results: G carriers compared to AA carriers responded slower to Go stimuli (p < 0.05, Fig. 1 (a)) and made more omission errors (p < 0.10) in Go/No-go task. Correspondingly, STAI scores showed high trait anxiety of the G carriers compared with the AA carriers (p < 0.05, Fig. 1 (b)). Moreover, the AA carriers showed more activation in the right VLPFC under the risk of punishment (Fig. 1 (c)).

Conclusion: These results suggest that 1) G carriers are more cautious than AA carriers; which is consistent with previous study (e.g., Nomura et al., 2006), and 2) AA carriers have the possibility, under certain risky conditions, to show decreased function of the right VLPFC, which might trigger the impulsive behavior. Further behavioral studies with measurement of 5-HT2A receptor gene polymorphisms should be carried out to clarify the complex relationships between personality traits and vulnerability to impulsive behaviors.
P-05-013  Neurropsychological correlates of transcription factor AP-2β in healthy females

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Objective: Studies have shown that transcription factors indirectly influence the catecholamine metabolism. In particular, AP-2β is associated with the transcription of genes important for the function of the dopaminergic system. Studies postulated an association of the AP-2β-polymorphism to behavioural traits and CSF-HVA levels. As the dopaminergic system is associated with cognitive performance, this hypothesis-driven investigation focusses on the relationship between AP-2β, COMT, and cognitive performance.

Methods: 194 healthy, non-smoking females (mean-age 24.01y; SD = 3.35) are neurropsychologically tested. The Trail-Making-Test part-B (MTM-B), Stroop, and dsCPT (degraded stimulus Continuous Performance Task) were performed. Furthermore, blood samples (5-15 ml) for the genetic characterization (AP-2β & COMT) were withdrawn.

Results: Homocytogous carriers of the short (4/4) alleles (M = 40.33s; SD = 9.01) are significantly faster in the TMT-B compared with the long (5/5) allele carriers (M = 50.12s; SD = 11.54; p < 0.0001; Bonferroni corrected). Furthermore, the results show on trend-level that the 4/4 allele carrier made less mistakes during the dsCPT compared to 5/5 carrier. Additionally, participants with at least one short AP-2β allele show significant effects of COMT on TMT-B performance. In this group, allele carriers of val/val or val/met perform significantly better than met/met carriers (T = 2.172; p = 0.034).

Conclusion: The study followed a hypothesis-driven approach. The results show that AP-2β has a highly significant and clinically relevant impact on cognitive performance. TMT-B and dsCPT results point to the same direction (4/4 better than 5/5 carrier). Moreover, AP-2β seems to interact with COMT on cognitive performance. Further investigations have to replicate these results and need to prove whether these results are based on differences in the dopaminergic transmission/turnd-over.

P-05-014  Transcription factor activating protein 2 beta (tfap2-beta) genotype and co-occurring symptoms of attention deficit hyperactivity disorder and depression in two samples

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Objective: Familial studies of Attention Deficit Hyperactivity Disorder (ADHD) suggest that there may be a genetically determined subtype of ADHD, most common among girls, which is characterized by comorbid depression. Furthermore, variation in the first intron of the Transcription Factor Activating Protein 2 Beta (TFAP2-β) gene has been shown to influence monoaminergic neurotransmission in rodents and several genes of importance for monoaminergic function have binding sites for the TFAP2-β. The present study examines the possible role of a functional Variable Number of Tandem Repeats (VNTR) polymorphism located in intron 1 of the TFAP2-β gene in the context of co-occurring symptoms of ADHD and depression.

Methods: Symptoms of ADHD and depression were measured by self-reports in two population-based samples of adolescents (group A, n = 175 and group B N = 1506) from Sweden.

Results: There were 6.1 to 7.8 % of adolescents who screened positively for ADHD and depression symptoms. In both samples symptoms of depression were more common among girls who screened positively for ADHD and who were not carriers of the 9 repeat version of the TFAP2-β intron 1 VNTR genotype.

Conclusion: The presence of the 9 repeat variant of the TFAP2-β intron 1 VNTR appears to protect girls with ADHD symptoms from developing symptoms of depression.

P-05-015  Influence of family and education factors on the inclination to commit crimes in Soviet times and today

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Objective: 35 reports of the Commission of forensic psychiatric experts over the period March 2010–1, 35 archive acts of outpatient forensic psychiatric examination that covered the period March 1991–2 were analyzed.

Methods: The statistic, comparative analysis and the method of random sampling.

Results: The study found out that 20-of 1 were held criminally responsible under article 131 of the RF Criminal Code-CC, 13–under article 132, and 2–135. Out of them 14-received incomplete secondary education, 7 did not receive any education at all, 6-received full secondary education, 4-incomplete secondary vocational education, 4-higher vocational education and 1-received education in the form of 8 years of special school. 10 patients were brought up in the family in which either 1 or both parents abused alcohol, 9-were raised and developed in a one-parent family, 8-did not have parents at all and only 8 were brought up in secure families. The 35-of 2 included 9-that were held criminally responsible under article 131 of the RSFSR CC, 13–under article 148, 188, 212, 224. In 2 there were 15-with incomplete secondary education, 13-incomplete secondary vocational education, 8–under article 108; 4–103, 145; 2–under each of articles 117, 206, 246; 1-under each of articles 89, 102, 120; 148, 188, 95, 224. In 2 there were 15-with incomplete secondary education, 13-incomplete secondary vocational education, 8–full secondary education and 2–full secondary vocational education. The anamnestic data showed that 18 patients from 2 were brought up in the family where either one or both parents abused alcohol, 28 were raised in a two-parent secure family, 4-raised in a one-parent family and 3 did not have parents.

Conclusion: The study demonstrated clear relationship between the education level and some family factors affecting the inclination to commit criminal offences. In Soviet times there were mainly property crimes and they were committed by individuals whose education by the time of criminal responsibility was 9 years of secondary school and who were raised in two-parent families.

P-05-016  A novel mutation in exon 2 of the MAPT gene causing frontotemporal dementia

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Objective: Mutations in the microtubule-associated tau gene (MAPT) are associated clinically with frontotemporal dementia (FTD) with or without supranuclear palsy, corticobasal syndrome or Parkinsonism. The pathogenic mutations are located mostly in exons 9–13, and in intron 10. Only two mutations are located in exon 1, coding for N-terminal part of the tau protein. The aim of the study was to identify the genetic basis of clinically diagnosed frontotemporal dementia in a female patient.

Methods: Clinical evaluation of the patient and genetic analysis of the MAPT.

Results: A novel mutation G55R located in exon 2 of MAPT was identified in a female patient with age of onset 51 y. and with a positive family history for dementia. The mutation is absent in a group of
45 FTD cases (familial, and some sporadic), as well as in a group of 100 neurologically healthy subjects (>65 y). Three years after the first symptoms developed the patient presented aphasic disturbances and spatio-visual disturbances with no psychotic symptoms, and no aggresive behaviors. In neurological examination deliberative symptoms were observed. Her MMSE score was assessed by means of functional magnetic resonance imaging at 3 Tesla.

**Conclusion:** A novel FTD-causing mutation located in exon 2 of the MAPT gene was identified. In silico analysis predicted that the mutation is damaging on protein structure and function, and could influence the ability of tau protein to regulate the dynamic behavior of microtubules.

**P-05-017** Association between polymorphisms in sex steroid related genes and autism symptoms in a Swedish population

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**Objective:** Sex differences in psychiatric disorders are common, which is particularly striking in autism that is five times more prevalent in boys. It has been hypothesized that high levels of testosterone during early development may be a risk factor for autism. This theory has been supported by several studies showing fetal testosterone levels, as well as indirect measures of prenatal androgenization, to be associated with autism and autism-related personality traits. Further, the importance of sex steroid related genes in autism is supported by studies reporting associations between polymorphisms in genes involved in sex steroid synthesis/metabolism and autism and/or autistic traits. The aim of the present study was to investigate possible associations between 29 polymorphisms in 8 genes related to sex steroids and autism symptoms in a general population.

**Methods:** Subjects used in the study are a subset from The Child and Adolescent Twin Study in Sweden (CATSS, N = 1771). The parents of the subjects were asked to fill out the telephone interview Autism–Tics, ADHD, and Other Co morbidities inventory (A-TAC). Factor analyses in CATSS, using A-TAC, have revealed that the three dimensions of autism symptoms were social interaction, communication and flexibility. DNA was extracted from saliva samples using OraGene® DNA self-collection kit. The polymorphisms were genotyped with KASP® PCR SNP genotyping system (Kbioscience, Herts, UK). The genotyping success rate was >95% and all SNPs were in Hardy-Weinberg equilibrium.

**Results:** About 14 associations between any of the investigated polymorphisms and autism dimensions were found at p < 0.05. For two SNPs in (ESR1 and SRD5A2) the associations survived Bonferroni correction for multiple testing.

**Conclusion:** In conclusion, polymorphisms in sex steroid related genes known to affect gene expression (the polymorphism in ESR1) and enzymatic activity (the polymorphism in SRD5A2) seem to increase the risk of autism symptoms in boys and girls respectively.

**P-06. Pharmacogenetics/Pharmacokinetics**

**P-06-001** Influence of dopamine D3 receptor gene variation on electroconvulsive therapy response in depression

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**Objective:** The pathogenesis of major depression has been linked to dysfunction of the dopaminergic system, particularly in the mesocorticolimbic system. In turn, antidepressant medication and electroconvulsive therapy (ECT) have been shown to enhance dopamine D3 receptor binding in the striatum. Thus, in the present study the influence of dopamine D3 receptor gene (DRD3) variation on ECT outcome in treatment-resistant major depression was investigated applying a combined molecular and imaging genetic approach.

**Methods:** In a sample of 104 (t = 71, m = 33) Caucasian patients with treatment-resistant major depression, ten representative DRD3 gene variants were analyzed for association with response to electroconvulsive therapy. Additionally, in two independent samples of depressed patients (N = 34) ventral striatum responsiveness to happy faces was assessed by means of functional magnetic resonance imaging at 3 Tesla.

**Results:** We observed significant association of DRD3 rs3732790, rs3732679 and rs9817063 SNPs with response (p = 0.02 – 0.03) and remission (p = 0.01) after electroconvulsive therapy. The rs3732790 ‘T’ allele conferring a better treatment response was additionally found to be associated with stronger striatal responsiveness to happy facial expressions (sample 1: p = 0.002; sample 2: p = 0.023).

**Conclusion:** In conclusion, the present data suggests DRD3 gene variation to impact electroconvulsive therapy response in major depression. Alleles associated with a more favorable response to ECT were also associated with stronger striatal responsiveness to positive, emotionally rewarding social cues, suggesting a potential neurobiological underpinning for the beneficial effects of these alleles.

**P-06-002** Clinical and pharmacogenetic study on psychotropic drug induced weight gain and other metabolic complications in a Swiss psychiatric population

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**Objective:** The weight gain-related side-effects of psychotropic drugs and their consequences on metabolic complications (hypercholesterolemia, obesity) in a large Swiss cohort of psychiatric patients (n = 561) were studied. Pharmacogenetic factors influencing these side-effects were also analyzed.

**Methods:** A cross-sectional observational study (n = 188) was performed in an out-patient psychiatric division with patients having received for more than one year the following drugs: clozapine, olanzapine, quetiapine, risperidone, lithium, amisulpride, arpiprazole and/or valproate. Another longitudinal study consisted of a follow up of patients being prescribed the same drugs for up to one year (n = 373).

**Results:** For the cross-sectional study, the mean age was 41 years (range: 18–69). Weight gain (> 10% of initial weight) following drug treatment was reported in 43% of these patients. A high prevalence of overweight (BMI: 25–30) or obesity (BMI > 30) was found in this cohort (63%). For the longitudinal study, the mean age was 48 years (range: 12–96). An increase in the overweight or obesity prevalence was found during treatment in adults (33%, 35%, 46% and 57%, before, after one, 3 and 12 months of treatment, respectively) and in children (21%, 29%, 31% and 50%, respectively).

**Conclusion:** In conclusion, high prevalence of overweight or obesity was found in an out-patient psychiatric population and confirms drug-induced weight gain complications during long-term treatment. Results on other clinical factors of the metabolic syndrome as well as on analyses of genetic factors linked to obesity and metabolic syndrome will also be shown. This study supports the recently published recommendations of monitoring of metabolic side effects during treatment with atypical antipsychotics and/or mood stabilizers. Moreover, the clinical and genetic weight gain predictors found in the present study could help to highlight patients with special health care management requirements.
antidepressant response to SSRIs and/or augmentation with Seroquel XR which has been suggested as an augmentation therapy for nonresponders.

Methods: 93 patients with major depression were treated with SSRIs or SSRIs augmented with Seroquel XR (300 mg) for 6 weeks. The severity of depressive symptoms was weekly assessed by means of the Hamilton Rating Scale for Depression. Allelic variation of 5-HTTLPR in each subject was determined using a polymerase chain reaction-based technique.

Results: Both homozygotes for the long variant (l/l) of the 5-HTTLPR and heterozygotes (l/s) showed a better response to SSRI’s than homozygotes for the short variant (s/s). In the group treated with SSRI’s and Seroquel XR all the genotypes acted like l/l treated with SSRI alone.

Conclusion: Seroquel XR augmentation may ameliorate the rate of response in 5-HTTLPR short variant subjects, thus reducing the difference in the response rate among the genotype variants. If confirmed, these results may improve patient care by helping the clinician to individualize treatment according to the patient’s genetic 5-HTTLPR pattern.

**P-06-004** Effect of triallelic polymorphism in 5-HT transporter linked polymorphism on remission after selective serotonin reuptake inhibitor treatment

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Objective: Functional rs25531 polymorphism in 5-HTTLPR (5-HTT linked polymorphism region) effects on the transcriptional activity of 5-HTT (serotonin transporter) gene by changing the binding affinity of transcription factor, AP2 and produces triallelic polymorphism in 5-HTT, known as the primary target of selective serotonin reuptake inhibitors (SSRIs). We hypothesized whether the triallelic polymorphism in 5-HTT gene effects on the outcome after SSRI treatment during 6 weeks in late-life depressed patients.

Methods: Two hundred seventy seven patients with late-life depression enrolled and entered a 6 week clinical trial with an SSRI, with documentation of plasma drug concentrations. Patients were classified from genomic DNA for 5-HTTLPR polymorphism in the 5-HTT gene using primer flanking the promoter region. Then PCR products were determined by visualizing on agarose gel. 5-HTTLPR polymorphism, and also processed the sequencing analysis for rs25531. Remission was defined as the decrease of HAM-D score >50% and HAM-D <7 score at 6 week after antidepressant treatment. Genotypic comparison between two groups was analyzed using Fisher’s exact test in SPSS ver.10.1.

Results: No differences were any characteristics of subjects such as age, gender, age of onset, duration of illness between remission and non-remission group. An association to treatment outcome was found in the triallelic polymorphisms between 106 remission group and 171 non-remission (p = 0.048, by Fisher’s exact test).

Conclusion: Functional triallelic polymorphism of 5HTT gene affect on the outcome to SSRI treatment in late-onset depressed patients. This is first reports of the association between rs25531 and remission after SSRI treatment in Asian population. These results underscore the importance of study in evaluation of candidate genetic marker as predictor of outcome to treatment of late-onset depression.

**P-06-005** Estimation of unbound drug cerebral exposure using a merging approach of in vitro and in vivo assays

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Objective: It is openly accepted that the unbound cerebral drug concentration is the main pharmacokinetic determinant of CNS activity of neurotherapeutics. A clinically relevant picture of the extent of brain drug delivery can be achieved by evaluation of neuropharmacokinetic parameters: unbound volume of distribution in the brain (Vu, brain), unbound brain-to-plasma concentration ratio (Kp, uu, brain) and unbound extracellular-to-intracellular concentration ratio (Kp, uu, cell).

Methods: Thirty compounds developed at Janssen R&D covering a wide range of physicochemical properties and various pharmacological CNS targets were selected. Vu, brain was measured using the rat brain slice method. Unbound brain (fu, brain) and plasma (fu, plasma) fractions were determined using equilibrium dialysis. Brain partition coefficient was measured in rats and/or mice.

Results: The compounds were distributed in the brain tissue with Vu,brain 2.9–624 ml.g brain-1, i.e. all compounds showed binding to brain parenchyma (Vu, brain >0.8 ml.g brain-1). Estimated Kp, uu, cell was 0.15–24 with 8 of the compounds indicating the ability to accumulate in the cell (Kp, uu, cell >1). Assessment of Kp, uu, brain showed that BBB equilibration was 0.02–2.65 showing active efflux of 20/30 compounds (Kp, uu, brain <1), dominating passive transport for 4/30 compounds (Kp, uu, brain >1), and active uptake into the brain of 6/30 compounds (Kp, uu, brain >1). Among the 8 effluxed compounds with Kp, uu, brain <0.1 only two were identified as P-glycoprotein substrates in vitro.

Conclusion: The brain slice method combined with in vivo brain partition coefficient measurement is a reliable tool for the assessment of unbound CNS exposure in early drug discovery stages, increasing the probabilities of success in early drug discovery stages.

**P-06-006** Association between serotonin transporter gene promoter-region polymorphism and 4- and 12-week treatment response to sertraline in posttraumatic stress disorder

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Objective: We examined the association between serotonin transporter (5HTTLPR) genotype (SS vs. SL vs. LL) and sertraline treatment outcome in posttraumatic stress disorder (PTSD).

Methods: Outpatients (n = 330) with PTSD underwent 5HTTLPR genotyping. All patients received sertraline (100 mg/day) for 12 weeks. Patients were assessed using the Clinician-Administered PTSD Scale (CAPS) and other instruments. Patients and rater were blind to the genotyping results. The primary outcome was complete sample CAPS improvement at 12 weeks. Response was defined as >30% improvement in CAPS total score with a CGI-I score of 1 or 2.

Results: The discontinuation rate was 31.5%. Adverse events led to drop out in 18.1%, 15.3%, and 5.9% of SS, SL, and LL patients, respectively (P = 0.038). Among completers, there were 95, 43, and 88 patients with the SS, SL, and LL genotypes, respectively. At endpoint, CAPS total scores improved by 26% vs. 46%, respectively, in SS and SL vs. LL patients (P < 0.001); much of this improvement (15% vs. 31% in SS and SL vs. LL patients, respectively; P < 0.001) was apparent by week 4. The findings were largely similar for the other outcome measures. The response rate was 0%, 0%, and 47.7% in the SS, SL, and LL groups, respectively (P < 0.001). Limitations: We administered a fixed dose of sertraline. For geopolitical reasons, we planned a complete analysis only.

Conclusion: Relative to the SS and SL 5HTTLPR genotypes, the LL genotype is associated with greater responsiveness of PTSD to sertraline (100 mg/day) and with lower drop out due to adverse events.

**P-06-007** Pharmacogenetic analysis in psychiatry: A descriptive study of a clinical experience with 21 patients

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Objective: To perform a pharmacogenetic analysis to 21 psychiatric patients, with 39 different psychiatric drugs.
Methods: We have conducted a descriptive study of 21 patients of whom 16 were admitted to the inpatient unit of the Psychiatry Service at the Hospital Ramon y Cajal in Madrid, and 5 in the psychiatric day hospital in the same center, who underwent the test Neurofarmagen (AB-Biotics), that search for genetic biomarkers in the DNA. Molecules were analyzed individually, and in its therapeutic group, (antidepressants, antipsychotics, anticonvulsants, mood stabilizers, and miscellaneous).

Results: Grouping antidepressants, 9.5% did not associate any favorable marker to any antidepressant, 28% for one antidepressant, for two 23.8%, for three 14.3%, for four 19.9%, and one patient for seven. The clustering of antidepressants with potentially favorable response markers: 33% for one antidepressant, 28.6% for two antidepressants, 14.3% for three antidepressants, 1 patient for four antidepressants, 14.3% for six antidepressants, and one patient for 7 antidepressants. The Mood Stabilizers group included lithium, and Valproic Acid, the presence of favorable response markers, for lithium occurs in 85.7%. The Anticonvulsant drugs: 76.2% had a marker associated with potentially adverse effects for 8 of the drugs analyzed. The Miscellaneous group includes: Clobazam, Clonazepam, Atomoxetine, Methadone, Naloxone, Naltrexone, Pramipexole, and Pregabalin. There were none positive indicators for any of the group molecules in 26.6%. For one drug in 57.1%, for two drugs in 9.5%, and a patient for four drugs.

Conclusion: We decided to change the treatment in 57.1%. We identified that 81% were receiving suboptimal treatment. We evaluated, how many of our patients had received previous treatment with unfavorable, or insufficient, response 61.9%. Without the test results of Neurofarmagen, this change presumably would not have occurred, and in many of these cases, would have been unlikely to obtain an adequate therapeutic response.

P-06. Pharmacogenetics/Pharmacokinetics

P-06-008 Cytochrome P450 2D6 genetic polymorphisms of Ugandans

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Objective: Marked interindividual variation in the cytochrome P450 (CYP) 2D6 activity has been reported. This variation can be explained, at least in part, by genetic polymorphisms causing defective, decreased, or increased enzyme activity. Therefore, genotyping of CYP2D6 might be useful in predicting individual drug response to the substrate drugs (e.g. haloperidol, risperidone, paroxetine, mirtazapine). Therefore, this study investigates the CYP2D6 genetic polymorphisms of Ugandans, which have not been studied so far.

Methods: Healthy black Ugandans (n = 99) were recruited from among students at Butabika School of Psychiatric Nursing, Uganda. CYP2D6*1, *3, *4, *5, *10, *17, *2N and *4Xn were determined by LA-PCR or PCR-RFLP methods. The CYP2D6*1 allele was assumed when none of the above-mentioned alleles were found. The protocol of this study was approved by the ethics committees of Hiroaki University Graduate School of Medicine and Makerere University Faculty of Medicine.

Results: The allele frequency of CYP2D6*1, *2, *4, *5, *10, *17, *2N and *4Xn was 20.5%, 40%, 2.5%, 9%, 1.5%, 22%, 4% and 0.5%, respectively. None of CYP2D6*3, *6, *7, *8, *10, *11, *12, *17, *3 alleles and gene duplication were determined by LA-PCR or PCR-RFLP methods. The CYP2D6*1 allele was assumed when none of the above-mentioned alleles were found. The protocol of this study was approved by the ethics committees of Hiroaki University Graduate School of Medicine and Makerere University Faculty of Medicine.

Conclusions: We decided to change the treatment in 57.1%. We identified that 81% were receiving suboptimal treatment. We evaluated, how many of our patients had received previous treatment with unfavorable, or insufficient, response 61.9%. Without the test results of Neurofarmagen, this change presumably would not have occurred, and in many of these cases, would have been unlikely to obtain an adequate therapeutic response.

P-06-009 Integrating clinical and biomarker data to predict antidepressant treatment outcomes

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Objective: To report the results of the integration of both clinical and genomic factors designed to predict antidepressant treatment outcomes.

Methods: A pharmacogenomic probe study of 398 treatment-adherent subjects with major depressive episodes compared to either set of biological variants associated with treatment outcomes provides a novel strategy for the future development of more individualized methods of antidepressant treatment.

P-06-010 Case-control association study for 10 genes in patients with schizophrenia: Influence of 5HTR1A variation rs10042486 on schizophrenia and response to antipsychotics

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Objective: The aim of this study is to investigate possible associations between a set of single-nucleotide polymorphisms (SNPs) within 10 genes with Schizophrenia (SCZ) and response to antipsychotics in Korean in-patients treated with antipsychotics.

Methods: Two hundred and twenty-one SCZ in-patients and 170 psychiatrically healthy controls were genotyped for 42 SNPs within ABCB1, ABCB4, TAP2, CLOCK, CEPLX1, CEPLX2, SYN2, NRG1, 5HTR1A and CPRIN2. Baseline and final clinical measures, including the Positive and Negative Symptoms Scale (PANSS), were recorded.

Results: Rs10042486 within 5HTR1A was associated with both SCZ and clinical improvement on PANSS total scores as well as on PANSS positive and PANSS negative scores. The haplotype analyses focusing on the four, three and two blocks’ haplotypes within 5HTR1A confirmed such findings as well. We did not observe any significant association between the remaining genetic variants under investigation in this study and clinical outcome.

Conclusion: Our preliminary findings suggest that rs10042486 within 5HTR1A promoter region could be associated with SCZ and with clinical improvement on PANSS total, positive and negative scores in Korean patients with SCZ. However, taking into account the several limitations of our study, further research is needed to draw more definitive conclusions.
**P-06-011** Cytochrome P450 2D6 polymorphism and its impact on decision-making in psychopharmacotherapy: Finding the right way in an ultrarapid metabolizing patient

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**Objective:** The cytochrome P450 (CYP) superfamily represents the most important phase I drug metabolizing enzyme system. Genetic mutations play an important role in the activity especially of CYP2D6. Genetic polymorphisms within CYPs affect the metabolism of drugs as substrates for the particular enzymes, resulting in variations in plasma levels of the drugs, differences in drug response, or altered risk for adverse effects.

**Methods:** We report the case of a 55-year-old woman from Turkey. She neither reached therapeutic drug concentrations of different drugs (metabolized via CYP1A2, CYP2D6, and CYP3A4) “natively” nor reached therapeutic plasma levels by pharmacologic blocking of CYP1A2 or CYP2D6.

**Results:** Genotyping of the patient revealed an ultrarapid metabolizer status for CYP2D6 with identification of the CYP2D6*22 allele with at least more than 1 copy of *2 variant in chromosome 22. For CYP2C19, the allele CYP2C19*1 was identified, reflecting normal enzyme activity.

**Conclusion:** Neither daily doses above the approval limit nor the well-directed use of pharmacokinetic blockade of the cytochrome system was able to improve clinical response. Only with a therapeutic regimen that bypasses liver function was partial remission finally achieved. Considering the normal activity of CYP2C19 in our patient, and that very high activity of CYP2D6 can result in increased metabolism of the substances via usually negligible metabolic byways, it is possible that drugs exclusively metabolized by CYP2C19 or other CYP isoenzymes (like agonolatine) or drugs that have no CYP-related metabolism such as mexitacipran may exert sufficient antidepressant effects.

**P-06-012** Plasma levels and cerebrospinal fluid penetration by venlafaxine in a patient with a non-fatal overdose during a suicide attempt

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**Objective:** Newer antidepressants seem to be less toxic than tricyclics even in suicidal attempts. Very few is known about the penetration of venlafaxine into the cerebrospinal fluid especially in the case of acute intoxications.

**Methods:** We report a case of an acute intoxication with 15 grammes of venlafaxine. Due to unclear unconsciousness a lumbar puncture was done. Therapeutic Drug Monitoring for Venlafaxine in plasma and csf was done two hours after ingestion. Later on genotyping as well for the cytochrome P450 2D6 subsystem was done as well as for the ABCB1 gene. The expecting influence on CSF levels of venlafaxine due individual characteristics in p-gp activity.

**Results:** TDM revealed plasma levels for venlafaxine (VEN) and O-desmethylvenlafaxine (DES) of more than 24.000 ng/mL (active moiety). CSF-Levels for VEN and DES were more than 6.400 ng/mL. Genetic testing revealed an extensive metabolizer for 2D6 and showed the constellation of ABCB1 G2677T; GC and C3435T; CT.

**Conclusion:** This case shows the very high rate of CSF penetration of venlafaxine with the massive amount of 6.400 ng/mL in the CSF. This high rate of CSF penetration requires more understanding of active transporter mechanisms like p-gp clearing venlafaxine into CSF.

**P-06-013** Biotransformation of alcohol is increased by systemic administration of methamphetamine

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**Objective:** Methamphetamine (METH) is a central nervous system stimulant that causes feeling of increased self-confidence, sociability and energy. Drugs of abuse are often used together with alcohol as it is the most frequent combination that leads to visit of Emergency Department in U.S. in 2008. However, the opposite point of view – the influence of METH on alcohol metabolism is still poorly understood. The recent study was focused on the influence of chronic systemic administration of METH on the biotransformation of alcohol in the preclinical study.

**Methods:** The experiment was carried out on male Wistar albino rats. Animals were randomly divided into two groups per 10 individuals. Animals from the control group were injected intraperitoneally with a single dose of saline. The other group was administered with METH at the dose of 10.0 mg/kg/day. After 10 days the in vivo animal pharmacokinetic experiment was performed. Both groups of animals were treated with alcohol (ethanol) at the dose of 2.0 g/kg in 5% glucose solution administered by intragastric probe. Blood was sampled in the 40th, 120th, 240th and 300th minute after the p.o. administration of alcohol. The alcohol levels were measured using GC method. Measured concentrations were statistically analyzed by ANOVA method with subsequent Fisher post-hoc test.

**Results:** Taken together our results suggest that repeated pre-treatment with MET led to the acceleration of alcohol biotransformation in time points between minutes 0–120 after single acute alcohol administration.

**Conclusion:** The present preclinical experiment suggests that chronic administration of METH increased biotransformation rate of alcohol in animal model. It is found in humans that with simultaneous administration of alcohol and METH, slowdown of METH p-hydroxylation and N-demethylation occurs. To our best knowledge the effect of METH on the biotransformation of alcohol has not been described in the literature available, either in humans or in animals.

**P-06-014** The clinical utility of ABCB1 genotyping in antidepressant treatment

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**Objective:** The gene product of the ABCB1 gene, the P-glycoprotein (P-gp), functions as a custodian molecule in the blood brain barrier and regulates the access of most antidepressants into the brain. Studies showed that ABCB1 polymorphisms predict the response to antidepressants that are substrates of the P-gp, whereas the response to non-substrates was not influenced by ABCB1 polymorphisms. The aim of the present study was to evaluate the clinical utility of ABCB1 genotyping in clinical depression therapy.

**Methods:** Data came from 57 depressed inpatients from the MARS (Munich-Antidepressant-Response-Signature, www.mars-depression.de) study whose ABCB1 gene test results were implemented into the clinical decision making process. Hamilton scores, remission rates and duration of hospital stay were documented with dosage and kind of antidepressant treatment.

**Results:** The group where ABCB1 genotyping was conducted had higher remission rates (Chi-square(1) = 3.436, p = 0.032, one-sided test) and lower Hamilton scores (t(22.72) = 1.780, p = 0.044, one-sided test) at the time of discharge from hospital as compared to a group without ABCB1 testing. Among patients with the less favourable genotype, an increase in dosage was associated with a shorter duration of hospital stay (rho(24) = −0.364, p = 0.034, one-sided test) whereas other treatment strategies (e.g., switching to a non-substrate) showed no significant associations with treatment outcome.

**Conclusion:** Results suggest that the treatment of depression can be optimized by an application of an ABCB1 gene test. Especially patients carrying the unfavourable ABCB1 genotype that impedes brain penetration seem to benefit from an increase in dosage. The efficacy of specific ABCB1 genotype-dependent treatment strategies is currently tested in a controlled prospective clinical study.

**Policy of full disclosure:** The presenting author is an employee of HolboerMachsmeyerNeuroChemie GmbH.
**P-06-015** Lymphoblastoid cell lines as models for pharmacogenomics

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**Objective:** Drug treatment of depression is characterized by a high rate of therapy failure, and so far it is not possible to predict the individual response to a particular antidepressant drug therapy in individual patients. There is therefore an urgent need for biomarkers for depression treatment that could be used to tailor the individual therapy. The aim of this project is to use individual genomic and transcriptomic information for assessing pharmacogenomic variability in cytoxic effects of antidepressant as a surrogate of treatment response in lymphoblastoid cell lines from patients. Epstein-Barr virus (EBV) immortalized human lymphoblastoid cell lines (LCL) are generated from blood cells of patients who have been treated with antidepressant drugs and characterized for the clinical course of drug response in the context of the Munich Antidepressant Response Signature (MARS) study by the Max Planck Institute of Psychiatry.

**Methods:** We examined the effects of 3 different antidepressants on cell growth and viability at different concentrations. The experiments were repeated three-times in each cell line.

**Results:** In 21 cell lines screened so far, between-subject variability was 2-fold higher than within-subject variability. The concentration ranges leading to 100% inhibition of cell growth were 110 μM, 30 μM, 600 μM for imipramine, paroxetine, mirtazapine, respectively. We determined the approximate drug concentration that inhibited the cell growth by 50% (IC50: imipramine 80 μM, paroxetine 15 μM, mirtazapine 300 μM) and tested the correlation between gene expression of CYP1A1, a gene that had been previously described to be associated with paroxetine growth inhibition in cell lines as well as with toxic effects of antidepressant drugs in patients from the Star*D study. Basal gene expression of CYP1A1 was associated with cell growth at IC50 of imipramine (r=0.54, p=0.017) and mirtazapine (r=0.71, p<0.002).

**Conclusion:** Polymorphisms in CYP1A1 and other gene regions will be tested as potential prognostic biomarkers in patient cohorts that are characterized for antidepressant therapy outcome.

**P-06-016** Relationship of DRD2 TAQ1A polymorphism with perospirone and aripiprazole efficacy in Japanese schizophrenia patients – a randomized controlled study

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**Objective:** To detect the therapeutic efficacy and tolerability effect by DRD2 Taq1A gene polymorphism on perospirone (PER) and aripiprazole (ARP) in patients with schizophrenia.

**Methods:** All patients were diagnosed as schizophrenia according to DSM-IV-TR. The patients who gave the informed consent to this 12-week and flexible-dose trial were randomly assigned to PER (n=51) or ARP (n=49). The clinical symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) before and every 4 weeks after treatment. The efficacy was assessed by changes from baseline for PANSS score. Genotyping for DRD2 TaqlA polymorphism was analyzed. The study was approved by the Ethical Review Board of Kansai Medical University.

**Results:** The clinical efficacy of PER and ARP were almost the same. In the total sample (PER+ARP sample), no significant difference was observed for catalyzing levomepromazine in human liver. However, in the ARP treatment group, the significant difference was found in the improvement of PANSS total, PANSS positive, negative and general psychopathology subscales between Taq1A genotype. In subsequent subsyptom analysis, the patients with A1/A1 allele (n=17) group showed significant better reduction overtine for PANSS-Excited Component (EC) scores (<0.05) compared to A2 carrier group (n=83). In stratified analysis by each drug, a similar significant difference was found in the ARP group only (A1/A1 allele: n=9, A1/A2 and A2/A2 allele: n=40, p<0.05). When separated by each genotype groups, no significant difference was observed for improvement of PANSS-EC between two drugs in both genotype.

**Conclusion:** Our findings show that PER and ARP exhibit similar efficacy in the treatment of Japanese schizophrenia patients in both genotype. Our data suggest that PANSS-EC significantly improves in A1 homozygote group as compared with A2 carrier group, especially in ARP treatment group.

**Policy of full disclosure:** This poster was supported by a grant from Promotion and Mutual Aid Corporation for Private Schools of Japan and National scientific research fund of Japan (No.23791357).

**P-06-017** Association study of the neuropeptide Y gene polymorphism and sertraline antidepressant response in major depressive disorder

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**Objective:** The goal of this study was to elucidate whether the NPY polymorphisms are associated with the Sertraline antidepressant response in subjects with MDD.

**Methods:** In a sample of fifty-six Chinese Han patients with MDD, 6 single nucleotide polymorphisms (SNPs) in NPY gene with minor allele frequencies >20% were successfully genotyped by ligase detection reaction. MDD patients were evaluated during 12 weeks of sertraline treatment. The severity of depression was assessed with the 17-item Hamilton Depression Rating scale (HAM-D-17). The response to 12 weeks' treatment with antidepressant was determined by changes in HAM-D-17 score. Genotypes of single SNP associations with treatment response were analysed by Flink software.

**Results:** At 12 weeks, 71 % of patients treatment with sertraline met response (decreased score rate of HAMD-17 >50 %). All SNPs NPY was not significantly associated with antidepressant response.

**Conclusion:** Response rate was 71 % in MDD patients treatment with Sertraline. We did not find that SNPs of NPY gene were associated with sertraline treatment response in this sample.

**P-06-018** The metabolism of levomepromazine by human cytochrome P450 isoforms

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**Objective:** Levomepromazine, a phenothiazine neuroleptic, is used in psychiatry as a sedative and in the management of schizophrenia. It is also used in terminal pain control and postoperative analgesia, and in the control of nausea. The contribution of cytochrome P450 isoforms (CYPs) to the metabolism of levomepromazine has not been studied in humans so far. Therefore, the aim of the present screening study was to identify CYPs involved in the 5-sulfoxidation and N-demethylation of levomepromazine in human liver.

**Methods:** Levomepromazine metabolism was examined in vitro using cDNA-expressed human CYPs (CYP1A2, CYP2A6, CYP2B6, CYP3A4, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4) at a therapeutic concentration of the neuroleptic (10 microM). The amount of levomepromazine and its metabolites formed by CYPs was assayed using HPLC with UV detection.

**Results:** The preference of CYPs for catalyzing levomepromazine metabolism was as follows (pmol of product/pmol of CYP isoform/min): 3A4 >A12 >A2B6 >2D6 >CYP1A1 >A2E1 >2C9 >A2M >E1 >2C9 for 5-sulfoxidation and 3A4 >A12 >A2B6 >CYP2C9 >2B6 >2D6 >CYP2E1 >2C9 >A2M =E1 for N-demethylation. Considering the obtained results and the relative expression of various CYPs in human liver, it has been estimated that CYP3A4 is the main isoenzyme responsible for levomepromazine 5-sulfoxidation and N-demethylation at a therapeutic concentration of the drug. Moreover, CYP1A2 contributes to a lesser degree to 5-sulfoxidation of the neuroleptic. The role of CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 in the catalysis of the reactions studied seems negligible.

**Conclusion:** The obtained results may have significant implications for the prediction of potential drug-drug interactions involving levomepromazine and CYP3A4. Supported by grant no. 2011/01/B/ NZA/04859 from the National Science Centre, Krakow, Poland and by statutory funds from the Institute of Pharmacology, PAS, Krakow, Poland.
P-07-003 Cytokine environment in PTSD patients of armenian nationality

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Objective: Post-traumatic stress disorder (PTSD) is a serious and debilitating condition triggered by terrifying events. It is proposed that the inflammatory mediators may have a significant input in PTSD-associated neuronal and behavioral changes that resemble some key features of this disease. Our aim was to evaluate the relationship between the levels of the proinflammatory and chemotactic cytokines IL-1β, IL-6, IL-8, TNF-a, MCP-1 in PTSD patients.

Methods: Patients with chronic PTSD (DSM-IV; mean age M±E2±4.6) and nontraumatized healthy controls (mean age 39±3.1) were examined. Blood levels of cytokines were determined by ELISA.

Results: Compared to healthy controls, patients with chronic PTSD had significantly higher levels of IL-1β, IL-6, IL-8, TNF-a and MCP-1 (p<0.05). In addition, a significant correlation has been observed between the blood levels of: IL-6 and IL-1β; IL-8 and IL-1β; IL-8 and MCP-1.

Conclusion: PTSD is associated with altered cytokine environment. Inflammatory processes are among pathological processes, which play a decisive role in PTSD progression.

P-07-004 Measuring symptom exaggeration in PTSD using the MMPI-2 and the PAI symptom validity scales

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Objective: We investigated whether PTSD patients have a higher tendency of exaggerating the extent of their psychological symptoms compared to other psychiatric patients.

Methods: Medical records of patients, who had received psychiatric treatment at 4 University hospitals in Korea between January 2009 and December 2010, were retrospectively reviewed. We compared a group of 37 patients diagnosed with PTSD, and another group of 41 patients diagnosed with Neurotic, stress-related and somatoform disorders according to the ICD-10. To compare the extent of malingering in the two groups, we compared the validity scales of MMPI-2 and PAI. We detected the number of participants feigning their responses from both groups using various cutoff scores of the validity indicators.

Results: The PTSD group showed significantly higher scores on all the validity scores. Fp(p<0.001), Fd(p<0.0001), Fp(Fd(p=0.030), F-Kp=0.003) scale of the MMPI-2 compared to the Other psychiatric patients group. The PTSD group had a significantly higher NIM score (p=0.001) but a lower PIM score (p=0.020) of the PAI compared to the Other psychiatric patients group. Using the cutoff scores, the PTSD group showed significantly more participants with feigned responding compared to the Other psychiatric patients group: Fp=7.5 (p=0.010), F-Kp=1 (p=0.005), F-K>10 (p=0.011) from the MMPI-2, and NIM>80 (p=0.001) from the PAI.

Conclusion: These results suggest that PTSD patients have a tendency of exaggerating symptoms by overreporting their condition on standardized personality assessments such as the MMPI-2 or PAI, compared to patients diagnosed with other psychiatric disorders. Additional research is required to determine the factors influencing symptom exaggeration in PTSD.

P-07-005 Effects of stress and corticosterone on glutamate release: Modification of the readily releasable pool of vesicles in prefrontal and frontal cortex

L. Musazzi1, G. Trrecinni2, M. Milanes3, C. Perego1, A. Malil3, E. Racagni1, A. Malgaroli1, G. Bonanno3, M. Popoli1, 1University of Milano, Milano, Italy; 2University of Genova, Italy; 3Milano, Italy

Objective: Stress and its mediators cause structural changes and in turn lasting consequences in the brain, which may be associated with triggering of neuropsychiatric disorders. Several studies suggest a critical role of glutamatergic neurotransmission in the stress response. In previous studies, we demonstrated that footshock
(P)S-stress induces a marked increase of depolarization-evoked glutamate release from prefrontal and frontal cortex (P/FC) synaptosomes, via glucocorticoid receptor activation and SNARE complexes accumulation in synaptic membranes. The increase of glutamate release was prevented by chronic antidepressants.

Methods: In order to investigate the presynaptic mechanism whereby acute stress enhances glutamate release in P/FC we performed the following studies: 1. Measurement of release of endogenous glutamate evoked by depolarization or hypertonic sucrose (which mobilizes exclusively the pool of synaptic vesicles ready for release, RRP) from isolated superfused synaptosomes of P/FC from F3-stressed rats. Measurement of depolarization-evoked or hypertonic sucrose-evoked release of glutamate from control synaptosomes incubated in vitro with corticosterone. 2. Analysis of RRP in synaptosomes by Total Internal Reflection Fluorescence Microscopy, which allows visualization of the synaptic region within about 100 nm from the membrane. Synaptic vesicles were labeled with FM1–43, and synaptosomes were incubated in vitro with corticosterone, ± selective inhibitors of glucocorticoid or mineralocorticoid receptors. 3. Patch-clamp recordings in slices of prefrontal cortex from control PFC slices incubated with corticosterone (± selective inhibitors of glucocorticoid or mineralocorticoid receptors).

Results: The results obtained suggest that the increase of the RRP size induced by acute stress is promoted by a local action of corticosterone on (presumably membrane-located) synaptic glucocorticoid receptors. However, in vitro incubation with corticosterone blocks the depolarization-dependent glutamate release, suggesting that additional mediators released by postsynaptic neuron and/or glia are necessary to trigger release.

Conclusion: The combined results of this study give more insight into the basic mechanisms whereby behavioural stress affects excitatory transmission in the forebrain.

**P-07-006** Valproate use in posttraumatic stress disorder: report of 3 cases and literature review

Z. Pablo, G.F. Oviedo

**Objective:** Our aim is to review the possible implied mechanisms and appraise the evidence for the use of the anticonvulsant Valproate for the treatment of Posttraumatic Stress Disorder.

**Methods:** Case Reports and Literature Review.

**Results:** Three cases of non-combat related posttraumatic stress disorder refractory to conventional treatment are treated with Valproate as an adjunct medication. These patients showed adequate response by measuring outcomes with the Post Traumatic Diagnostic Scale (Spanish Version) and the Beck Inventory Depression Scale (Spanish Version).

**Conclusion:** Anticonvulsants have been used in clinical practice for the treatment of Posttraumatic Stress Disorder (PTSD). Several biologic models have been discussed as contributing significantly to PTSD symptoms with a focus on alterations in noradrenergic and serotonergic systems and in the endocrine hypothalamus-pituitary-adrenocortical axis. In addition, kindling has been proposed by several investigators to be involved in the pathophysiology of PTSD. This hypothesis suggests that anticonvulsants may be promising in the treatment of PTSD, since they are thought to exhibit their efficacy in part through an antikindling activity. Valproate is an anticonvulsant with antikindling activity and enhances the inhibitory effect of the neurotransmitter γ-aminobutyric. A systematic investigation of their effects in the context of the treatment of PTSD is currently lacking from the literature.

**P-07-007** DRD2 receptor polymorphism carries a higher risk for PTSD development

A. Hadji, A. Elsheshat, H. Abou El Wafa, O. Elkholy, M. Mokhtar

**Objective:** Dopaminergic neurotransmission is implicated in stress responses. The dopamine D2 receptor gene (DRD2) has been studied by the authors to assess its possible role as a predictor of those who are at a higher risk to develop PTSD after major psychological trauma.

**Methods:** Over one year period 75 children and adolescents 6-18 yrs of age who had been exposed to moderate to severe burns were recruited from the burn unit at the Alexandria University Hospital for the study. Patients and their family were interviewed within the first 10 days of exposure. After signing a written consent form a 2 ml blood sample was obtained for genetic studies of the TaqA1/A2 polymorphism site of the DRD2 gene. Patients were re-evaluated three and six months later for assessment of PTSD.

**Results:** Among the 75 children recruited in the study, 26 died due to their burn injury, 19 dropped out as parents refused follow up and 30 continued the study follow up visits. Fourteen carried the A1A2 genotype. Of these 11 (78.6 %) developed PTSD. Sixteen carried the A2A2 genotype. Of these only one child (6.3 %) developed PTSD. The results were significant at p < 0.001 with a relative risk 12.5.

**Conclusion:** Following exposure to severe stress, the presence of the Taq A1 allele of the DRD2 gene results in a significant increase in the risk of developing PTSD.

**P-07-008** Facing violence and burnout in health services: Intervention and prevention program

M.A. Ramos, R.M. Gloria, L. Garrido Mateo, J.M. Ramos Navas-Farre

**Objective:** The aim of this work is to present the experience of a group psychological intervention program conducted with professionals from emergency health services.

**Methods:** Three intervention groups were made (N = 39) with doctors, nurses, guards/drivers, administrative assistants, social workers and physiotherapists from emergency health services in the province of Granada. The program had eight weekly sessions of three hours each one, structured into three modules: 1) prevention and management of violent situations, 2) coping of burnout, 3) assertiveness training. An active-participatory methodology was followed using modeling, role-playing and homework. After the program, a questionnaire for evaluating the program was given.

**Results:** 87.5% of professionals evaluated the program as very useful for their professional activity, 65.6% reported a high level of learning and 90.6% showed high levels of satisfaction.

**Conclusion:** The professionals valued the experience as very useful and satisfactory, and considered very important to have well structured coping skill training programs available to professionals working in health services, in order to help them to face violence in working environment and burnout.

**P-07-010** Brain-derived neurotrophic factor, posttraumatic stress disorder and memory

S. Seeda, S. Sulinman, D. Stein

**Objective:** Brain-Derived Neurotrophic Factor (BDNF) is a neurotrophin that helps to support the survival and encourage the growth and differentiation of neurons in both the central and peripheral nervous systems. BDNF has been associated with mood disorders and trauma exposure, but there is less information regarding its association with Posttraumatic Stress Disorder (PTSD). The first aim of this paper was thus, to compare BDNF levels in trauma-exposed adults with and without (i) Acute Stress Disorder (ASD), (ii) PTSD, or (iii) depression. As BDNF levels have also been associated with memory, the second aim of this paper was to correlate BDNF levels with memory.

**Methods:** We collected blood samples from 37 participants who had been involved in a motor vehicle accident in the previous 2 weeks (59.5% male; mean age: 33.35 ± 11.54 years). We used clinical and self report measures to assess for ASD, PTSD and depression, both at the time of blood collection and 3 months later. Neuropsychological measures were used to assess for disturbances in auditory, visual and working memory.

**Results:** We did not find any significant differences in BDNF levels between those with and without ASD, PTSD or depression at the baseline visit, as well as in those with PTSD or depression at the 3 month follow-up. Additionally, BDNF levels and memory did not correlate. We did, however, find that those with PTSD 3 months post-trauma had higher levels of depression than those without PTSD.
Conclusion: Our findings suggest that in our sample, alterations in BDNF level could be due to trauma exposure, rather than to a psychiatric diagnosis. These findings are, however, limited by the small sample size.

Objective: To assess the effects of earthquake that occurred on April 6, 2009 on the use of antidepressant and antipsychotic drugs in the province of L’Aquila.

Methods: We conducted a cross-sectional, drug utilization study. Data sources of this study were the dispensings database of the Southern Italian Local Health Unit (LHU) of L’Aquila and Caserta. All the antidepressant and antipsychotic drugs (except for prescriptions in dementia patients) are reimbursed by Italian National Health System and therefore are retrieved in such a database. We measured the monthly prevalence of use of these drugs one year prior and after the date of earthquake in L’Aquila LHU. We used as control the LHU of Caserta, as this area was not affected by the earthquake. All the analyses were stratified by age groups, gender and drug classes (Selective Serotonin Reuptake Inhibitors, Tricyclics, and other ADs; atypical and typical antipsychotics).

Results: Overall, the monthly prevalence of use of ADs and APs was higher in L’Aquila than Caserta. With respect to trend over time, we observed an increase in the use of antidepressants (mostly SNRIAs) and antipsychotics in the first two months after the earthquake in L’Aquila but not in Caserta. This increase was almost two-fold higher in women older than 75 years. The use of ADs and APs in general tended to decrease in the summer period in Caserta, while such a trend was not observed in L’Aquila after the earthquake. After the first two months from the earthquake, the use of ADs and APs is stabilized at the pre-earthquake levels in L’Aquila.

Conclusion: The earthquake determined a very short term increase in the use of antidepressants and antipsychotics mostly in older women. Long term evaluations of the effects of the earthquake on mental health in L’Aquila are needed.

Objective: The objective of research is to study the types of somatoform disorders in individuals that were found mentally sane during the first two months after the earthquake in L’Aquila. The CBGT therapists were blind to patients’ whether taking the clinical and therapeutic outcomes.

Methods: Thirty mentally sane persons (25 males and 5 females aged between 16 and 55) against whom the criminal cases were opened underwent outpatient forensic psychiatric examination. Development of somatoform disorders in individuals found mentally sane during the outpatient forensic psychiatric examination

E. Valzdorf
Irkuts, Russia

Objective: The objective of research is to compare the effectiveness of combined therapy about which of these forms of treatment is more effective. The aim of this study is to compare the effectiveness of combined therapy (CBGT + pharmacotherapy) with psychotherapy alone (CBGT).

Methods: Thirty-six patients with an OCD diagnosis, according to DSM-IV criteria were recruited into the study. 20 of them randomly assigned to antidepressant pharmacotherapy plus Cognitive behavioral group therapy and 16 of them were received only CBGT. The CBGT therapists were blind to patients’ whether taking

Objective: The research reveals that according to the reports of the outpatient forensic psychiatric examination of teenagers aged between 15 and 18 such criminally punishable acts as homicide and infliction of grave harm to health, causing manslaughter by negligence) initially liable under article 111 part 4 of CC of the Russian Federation RF (homicide), of them 4 showed light mental retardation, 2 – organic personality disorder against the background of brain injuries and epilepsy, 1 – socialized conduct disorder, 7 individuals turned out to be mentally sane; 18 individuals were held criminally liable under article 111 part 4 of CC of RF (intentional infliction of grave harm to health, causing manslaughter by negligence) including 4 teenagers with light mental retardation, 3 – with organic personality disorder against the background of brain injuries and epilepsy, 2 – individuals exhibited light cognitive impairment, 1 – emotionally unstable personality disorder. 1 person showed opioid addiction, and 7 teenagers appeared to be mentally sane.

Conclusion: Thus, the research revealed that according to the reports of the outpatient forensic psychiatric examination of teenagers aged between 15 and 18 such criminally punishable acts as homicide and infliction of grave harm to health, causing manslaughter by negligence, were most often committed by teenagers without psychopathology and by those exhibiting light mental retardation.

Objective: The research aims to study the impact of the revealed mental disorders (or their absence) in teenagers on commission of homicide or infliction of grave harm to health, causing manslaughter by negligence. 32 reports of the Commission of the forensic psychiatric examination over the past half a year were analyzed. The forensic psychiatric examination was carried out on an outpatient basis. The analysis revealed that out of 32 examined teenagers, 30 were males and 2 – females at the age of 15–18.

Methods: The statistical method along with the analysis of data of forensic psychological- psychiatric and forensic psychiatric examinations was applied.

Results: The research revealed that 14 individuals were held criminally liable under article 105 of Criminal Code (CC) of the Russian Federation (RF) (homicide), of them 4 showed light mental retardation, 2 – organic personality disorder against the background of brain injuries and epilepsy, 1 – socialized conduct disorder, 7 individuals turned out to be mentally sane; 18 individuals were held criminally liable under article 111 part 4 of CC of RF (intentional infliction of grave harm to health, causing manslaughter by negligence) including 4 teenagers with light mental retardation, 3 – with organic personality disorder against the background of brain injuries and epilepsy, 2 – individuals exhibited light cognitive impairment, 1 – emotionally unstable personality disorder. 1 person showed opioid addiction, and 7 teenagers appeared to be mentally sane.

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pharmacotherapy or not. CBGT process consists of 14 sessions. Efficacy of treatments was rated according to the reduction in scores on the Yale-Brown Obsessive Compulsive Scale (YBOCS), Beck Anxiety Inventory (BAI), Beck-Depression Inventory (BDI) and the Clinical Global Impression Scale (CGI). The trial was performed in four successive periods from August 2011 to January 2012.

Results: According to end-point analysis both groups did well in therapy. Patients treated with only CBGT obtained a mean YBOCS reduction of symptoms of 45%, while those treated with antidepressant plus CBGT treatment have 53% reduction. The reduction rates were found statistically significant according to initial scores (Paired t-test; CBGT only group (z = -2.81, p < 0.002), combined therapy group (z = -3.07, p = 0.001)). There was no significant difference between these two groups at the end of CBGT (Mann-Whitney U = 50, p = 0.54). Also there was significantly reduction for BAI, CGI and GAF scores.

Conclusion: Cognitive-behavioral group therapy has shown to be effective in reducing OCD symptoms regardless of antidepressant treatment. We suppose that CBGT could be an effective treatment choice for OCD.

P-07-016 The use of aripiprazole in serotonin reuptake inhibitor resistant obsessive-compulsive disorder: A naturalistic, retrospective case series of 24 patients

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Objective: We conducted a naturalistic, retrospective chart review to evaluate the effectiveness and safety of aripiprazole augmentation-or mono-therapy for the treatment of resistant obsessive-compulsive disorder (OCD).

Methods: A total of 24 patients diagnosed with OCD according to DSM-IV-TR criteria and having a history of resistant to treatment with serotonin reuptake inhibitors (SRIs) were included in the study. Aripiprazole was started at 3 mg/day and increased to 24 mg/day at the clinician’s discretion. The patients were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), the Clinical Global Impressions-Improvement (CGI-I) Scale, and the Global Assessment of Functioning (GAF) Scale at baseline and at the final visit of aripiprazole treatment. Safety assessments included evaluation of vital signs, weight, and treatment-emergent side effects. Follow-up period for a case was one year and a case who discontinued the drug for less than one year was also counted. Data were collected from January 2007 to December 2010.

Results: The mean daily dosage of aripiprazole at endpoint was 12.0 ± 7.2 mg/day. The mean total Y-BOCS score decreased from 27.2 at baseline to 18.0 at endpoint (P < 0.001) and the mean GAF score increased from 47.1 at baseline to 60.6 at endpoint (P < 0.001). The mean CGI-I score was 2.4 points (much improved minimally improved). The observed side effects included weight gain (2 patients), akathisia (2 patients), mild sedation (2 patients) and insomnia (1 patient).

Conclusion: These results suggest that aripiprazole augmentation-or mono-therapy can modestly improve the outcome for the treatment of resistant OCD. Larger, randomized, double-blind studies are necessary to establish the efficacy and safety.

P-07-017 Clinical predictors of drug response in patients with obsessive-compulsive disorder

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Objective: The aim of this study was to evaluate which clinical variables might influence the antidepressive response to proserotonergic drugs in a sample of patients with obsessive-compulsive disorder (OCD).

Methods: Two hundred forty-nine patients with DSM-IV OCD underwent mean 13-month treatment with selective serotonin reuptake inhibitors. According to treatment response, defined as a reduction of the Yale-Brown Obsessive Compulsive Scale total score >35% and CGI 1 or 2, patients were divided into two groups.

Results: One hundred fourteen patients responded to treatment and one hundred thirty five patients did not. Responders had a significant long high duration of treatment, short duration of pre-treatment medication and higher frequency of drug naïve cases and lower baseline Y-BOCS scores.

Conclusion: The pre-treatment factors including pre-treatment period, drug naïve or not and baseline OCD symptoms and the factor of duration of treatment may influence drug treatment response in OCD patients.

P-07-018 Relationships between plasma fluvoxamine levels and OCD symptoms in adult patients

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Objective: Different randomized, double-blind, controlled studies confirm the efficacy of fluvoxamine in obsessive-compulsive disorder (OCD). An experimentally determined relationship between plasma levels and the pharmacological effect of fluvoxamine may represent an useful method in monitoring clinical response and in the identification of predictors of response in order to maximize the therapeutic effectiveness, but the information on this topic is limited. Therefore, in this study we explored the possible relationship between plasma fluvoxamine levels and clinical features in OCD patients treated with this drug for at least 6 months.

Methods: Twenty OCD outpatients of both sexes taking fluvoxamine were included in the study. The symptoms severity was assessed by means of the Y-BOCS. The fluvoxamine plasma levels were measured by HPLC analysis. All evaluations were performed after 4 weeks (t1) and six months (t2) of fluvoxamine intake.

Results: The plasma levels of fluvoxamine remained stable at the two assessment times, with no sex-related differences. Sixteen (80%) patients showed a significant improvement, but men's compulsions ameliorated more than those of women. Significant and positive correlations were detected between fluvoxamine plasma levels at t1 and t2 and the difference (delta) of the Y-BOCS total score at t1 and t2. Another significant, albeit negative, correlation was measured between the delta of drug concentrations and that of the compulsion subscale score.

Conclusion: These findings underline the potential importance of evaluating fluvoxamine plasma levels in OCD and their relationships with specific symptoms, as well as the influence of gender on drug response.

P-07-019 Neuroanatomical correlates of naturalistic long-term outcome of OCD treated with selective serotonin reuptake inhibitors

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Objective: The structural imaging studies have reported the involvement of areas in the fronto-subcortical regions as neurobiological substrates in OCD. We hypothesized that baseline volumes of orbitofrontal cortex, cingulate cortex, dorsolateral prefrontal cortex, caudate nucleus and globus pallidus would predict improvement in obsessional symptoms in long-term. With this hypothesis we aimed at elucidating the structural brain predictors of naturalistic outcome in drug naïve adult subjects with obsessive-compulsive disorder (OCD).

Methods: We examined the brain volumes using optimized Voxel-Based Morphometry (VBM) paradigm and examined their relationship with 2 to 5 year naturalistic outcome in 29 drug naïve OCD patients. Statistical parametric maps were constructed to examine correlations between regional gray matter volume in the a priori hypothesized regions and percentage reduction in YBOCS scores at the endpoint.

Results: VBM analysis revealed significant positive correlation between the percentage of reduction on Y-BOCS total score and left anterior cingulate gyrus volume (r = 0.52, p < 0.01). Another significant, albeit negative, correlation was measured between the delta of drug concentrations and that of the compulsion subscale score.
Antiserotonergic second generation antipsychotics are associated with obsessive-compulsive symptoms in schizophrenic patients

Objective: Epidemiological investigations show that up to 30% of schizophrenic patients suffer from obsessive compulsive symptoms (OCS). The comorbidity is associated with negative impact on the general prognosis. It has been proposed that antiserotonergic second generation antipsychotics (SGA) might induce OCS, but investigations of large samples integrating psychopathology, neuropsychology and psychopharmacology are missing.

Methods: We stratified 70 patients with schizophrenia according to their mode of antipsychotic treatment: clozapine and olanzapine (group I) compared with aripiprazole and amisulpride (group II). The groups were matched according to age, sex, educational levels and severity of the psychotic disorder (PANS: Positive and Negative Syndrome Scale). As primary endpoint, we evaluated the OCS-severity (VBOS: Yale-Brown-Obssesive-Compulsive Scale) in a cross-sectional evaluation.

Results: OCS was significantly more prevalent and severe in group I, in which OCS severity correlated with dosage of clozapine and duration of treatment. Pronounced cognitive deficits in group I were found in visuo-spatial perception and visual memory (WAIS-R block design, Rey-Osterrieth Complex Figure Test), impulse inhibition (Go/NoGo-Test), and perseveration scores (Wisconsin Card Sorting Test) and reduced set-shift abilities (Trail Making Test B, Set-shift Task). These cognitive domains also correlated with OCS severity.

Conclusion: OCS in schizophrenia is associated with antiserotonergic SGA treatment, but longitudinal studies have to provide further evidence for a causal interaction. Before starting treatment with antiserotonergic SGA, as well as clozapine, specific neuropsychological domains should be evaluated, that might indicate an increased risk for second-onset OCS and further allow the early detection of OCS secondary to antipsychotic treatment in schizophrenia.
Objective: To understand the safety and tolerability of aripiprazole intramuscular depot for maintenance treatment in schizophrenia.

Methods: In a 6-week, multicenter, placebo-controlled, parallel-group study (NCT01058096) evaluated the efficacy, safety, and tolerability of cariprazine in patients with acute mania associated with bipolar I disorder: A double-blind, flexible-dose study, patients (18–65 years) with acute mania (Young Mania Rating Scale, YMRS) >20 were randomized (2 : 1) to cariprazine (120 mg injectable depot) or placebo (52-week, stabilization (400 mg/injection) with co-administration of oral aripiprazole (oral aripiprazole stabilization phase; P1) followed by 4–12-week oral aripiprazole (oral conversion phase; P2). Subjects meeting stability criteria (4 weeks) entered an ARI-IMD or placebo (52-week, P4). Primary endpoint was time to impending relapse. Safety was assessed across phases by time of first-onset of AE(s), changes in movement disorder rating scales and changes in weight/metabolic parameters.

Results: The study stopped early because efficacy was demonstrated by pre-planned interim analysis (after 64 relapses). ARI-IMD was well tolerated with similar rates of AEs across phases. Discontinuations due to TEAEs: 3.8% (P1); 3.0% (P2); 4.9% (P3); 7.1% (P4). Most AEs were mild/moderate. Severe AEs were <5.0%, all phases. AEs ≥5% were: insomnia (all phases), headache (P1, P3 and P4), anxiety, akathisia, weight increase (P3, P4), injection site pain (P3) and tremor (P4). Headache, somnolence, nausea had a peak first-onset within 4 weeks of study initiation. EPS-related events were: P4: ARI-IMD 14.9% vs. placebo 9.7%. Mean baseline weight ranged 80.4–84.8 kg (all phases). Mean baseline weight changes: −0.2 kg (P1); 0.1 kg (P2); −0.2 kg (P3); −0.2 kg (ARI-IM-depot, P4). −0.4 kg (placebo, P4). No unusual shifts in laboratory values or fasting metabolic parameters (all phases). Normal-to-high shifts in metabolic values were low in P4.

Conclusion: No unexpected AEs emerged with ARI-IM-depot. Similar rates of AEs in P1 and P2 suggest that the switch strategy was well handled. ARI-IMD offers a new option with a different risk–benefit profile than currently available treatments.

Policy of full disclosure: John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Esai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischhacker has received research grants from Alkermes, Janssen Cilag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programs from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Cilag, Roche, Lundbeck, BMS/Otsuka and advisory board honoraria from BMS/Otsuka, Wyeth, Janssen Cilag NeuroneX, Amgen, Lundbeck, Endo, United Biosource, Targacept, MedAvante and AstraZeneca. Raymond Sanchez, Pamela Perry, Na Jin, Brian Johnson, Robert A Forbes, Robert D McQuade, William H Carson and Ross Baker are all employees of Otsuka Pharmaceutical Development and Commercialization, Inc.

Objective: Prepulse inhibition (PPI) is the reduction in the startle response caused by a low intensity non-startling stimulus (prepulse) which is presented shortly before the startle stimulus (pulse), and is an operational measure of sensorimotor gating. PPI may reflect the functioning of a pre attention filtering system protecting the brain from sensory overload. Deficits in PPI have been observed in several neuropsychiatric disorders, including schizophrenia and can be induced in rats by systemic administration of N-methyl-D-aspartate (NMDA) glutamatergic antagonist. The inferior colliculus (IC) is a critical part of the auditory pathway mediating acoustic PPI. The activation of the IC by the acoustic prepulse reduces startle magnitude. The aim of this study was to investigate the role of glutamatergic transmission of the IC on the development of acoustic PPI.

Methods: Male Wistar rats were unilaterally implanted with stainless steel guide cannula in the IC. Seven days after the surgery, the animals received unilateral intracollicular microinjections of the glutamate NMDA receptor antagonist MK-801 (30 mmol/0.5 µl); of the NMDA receptor agonist N-methyl-D-aspartate (NMDA, 30 mmol/0.5 µl) or of physiological saline (0.5 µl). Five minutes later, the animals were tested to PPI. They were exposed to 4 types of stimuli: a startle pulse [P-alone: a 120 dB 40 ms broad band burst] and 3 types of prepulses [68, 71 or 77 dB 20 ms broad band burst] presented 100 ms prior to the startle pulse. During test session, 50 trials (12 P-alone, 8 NOSTIM, and 10 of each prepulse trial types) were presented in pseudorandom order. A variable inter-trial interval averaged 15 s.

Results: The results showed that microinjections of MK-801 into the IC disrupted PPI while microinjections of NMDA into this structure did not alter PPI.

Conclusion: We concluded that glutamatergic neurotransmission of the IC can be involved in the mediation of PPI in rodents.

Objective: Several studies of normobaric hyperoxia in neurological conditions have found positive results. The impaired energy metabolism due to mitochondrial dysfunction and frontal lobe hypofunction in schizophrenia might be improved by increasing O2 supply to the brain. Normobaric hyperoxia may be a potential treatment for schizophrenia.

Methods: Participants in this study, outpatients suffering from chronic schizophrenia and inhabitants of community-based psychiatric institutions (hostels), underwent baseline psychiatry/cognitive assessment and were randomly assigned to either a treatment intervention of oxygen enriched air inhalation (normobaric hyperoxia of 40% FiO2), or to regular air inhalation (21% FiO2), through a nasal tube, for four weeks. Patients were given the air/oxygen inhalations during the night (mainly while sleeping), for at least 7 hours a night. After completing four weeks of treatment, patients were switched (cross-over) to the other treatment intervention.

Results: Fifteen patients completed the entire study. Five additional patients completed Phase A only. There was significant improvement in total PANSS score of patients that received oxygen compared with control group. There were positive effects of oxygen on memory and attention in neuropsychological performance tests. The effect size is small despite the statistical significance, but the patient group was extremely chronic and severely impaired.

Conclusion: These results are a proof of concept and normobaric hyperoxia should be studied in patients with milder forms of the illness and earlier in the course of illness.

Objective: Cariprazine in the treatment of acute mania in bipolar disorder: A double-blind, placebo-controlled, phase III trial

Methods: In a 6-week, multicenter, placebo-controlled, parallel-group, flexible-dose study, patients (18–65 years) with acute mania and a Young Mania Rating Scale (YMRS) score >20 were randomized.
Objective: Cognitive deficits negatively affect recovery in schizophrenia and poorly respond to pharmacotherapy. Cognitive remediation therapy (CRT) is effective in improving cognition in schizophrenia, but results are still variable and putative predictors of successful remediation need to be better analyzed in order to optimize individual outcomes. The COMT Val158Met polymorphism is known to have a functional effect on the rate of dopamine (DA) degradation and thus DA availability in the prefrontal cortex (PFC), which may affect CRT response. Two studies evaluated the effect of COMT genotype on cognitive improvement following CRT, with contradictory results [1,2]. Among factors affecting CRT outcomes, pharmacotherapy appears of major relevance. Antipsychotics could interact with COMT polymorphism on DA availability, influencing individual capacity to recover from deficit. The present study aims to analyze the possible effect of COMT Val158Met polymorphism and antipsychotic treatment (clozapine vs. drugs with greater dopaminergic D2 receptor blockade activity) on CRT outcomes. We hypothesized that antipsychotic induced changes in PFC DA availability may interacts with COMT genotype.

Methods: 91 clinically stabilized patients with diagnosis of schizophrenia, receiving antipsychotic monotherapy since at least 3 months, were recruited. Patients attended a CRT program for three months. Cognitive performances were evaluated, at baseline and after 3 months, with "Brief Assessment of Cognition in Schizophrenia" (BACS).

Results: Analysis conducted by Repeated Measures ANOVA showed a significant interaction (F = 4.0212, p = 0.0484) between COMT genotype and pharmacological treatment, on symbol coding performances change.

Conclusion: The findings support the hypothesis of an interaction between Val158Met COMT polymorphism and pharmacotherapy on dynamic modulation of cognitive functions through CRT. Val/Val subjects, only when treated with clozapine, show an improvement in symbol coding, a task related to speed of processing and executive functioning and currently regarded as a possible endophenotype of schizophrenia. Clozapine, known to increase prefrontal DA levels, could recover the genetic disadvantage.
Objective: There is little information about gender differences concerning treatment of schizophrenia. We have used data from the e-STAR (electronic Schizophrenia Treatment Adherence Registry), an international, prospective, observational study assessing use of risperidone long acting injection (RLAI) in patients with schizophrenia or schizoaffective disorder. The aim was a comparison between male and female patients participating in e-STAR in both Czech and Slovak Republics.

Methods: The e-STAR was designed to evaluate clinical outcome in patients who have initiated RLAI as part of their continuing therapy in routine clinical practice. The decision to initiate pts on RLAI and their clinical management was determined solely by the treating physician. The demographic, clinical and treatment related data were collected at baseline and than prospectively for 2 years. We have focused on gender differences in demographic and clinical data (hospitalization, concomitant medication and clinical improvement using CGI, GAF and PSP).

Results: Totally 868 patients, 488 male and 380 female were included. At baseline women were significantly older than men 42.1 (12.8) respective 34.8 (11.1) years. Women were also significantly more frequently diagnosed as schizoaffective disorder. Concerning the proportion of pts hospitalized in the retrospective and prospective period there was no difference between men and women (including length of stay). Comparing the concomitant medication at 24 month the male group used less antidepressants and benzodiazepines than the female group (controlled for baseline values). The improvement in CGI-S and PSP scores was similar. However, the improvement in GAF score was slightly lower in men than in women.

Conclusion: The comparable severity of illness is achieved in women later. In spite of comparable severity women reacted better in some measures of social functioning. The gender differences should be more intensively studied and should be taken into consideration in guidelines. Supported by research grant from Janssen CR and the project CEEITC (CZ.1.05/1.1.00/02.0068).

Positively biased recognition of emotional valence in schizophrenia

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Objective: Schizophrenia is characterized by impairments in recognizing affect. To evaluate affect recognition of patients with schizophrenia, facial expressions or words have been used in most previous studies. Few studies have tackled the issue via reading written sentences, which is another important component of perceiving social contexts. The present study aimed to evaluate affect recognition of various emotionally valenced sentences in patients with schizophrenia.

Methods: A 28-item questionnaire was devised based on preliminary survey consisted of one hundred written sentences with various emotional valence selected from newspapers and Korean novels. The questionnaire was administered to both healthy control (N=32) and patients with schizophrenia (N=9). Participants were asked to rate the emotional valence of each sentence in a 7-point Likert scale, ranging from 1 (very negative) to 7 (very positive). The independent samples t-test was conducted to compare the difference in the means of two groups.

Results: Of the 28 items, seven showed either statistically significant (three items p<0.05) or a trend of group differences (four items p<0.10). On all cases showing group differences, the patients showed positively biased emotional recognition. For example, the patients responded more positively to a sentence ‘Yuna Kim became Olympic gold medalist getting over difficult times’ (6.89±0.33 versus 6.25±0.62, p<0.01 in patients and control subjects respectively).

Conclusion: The tendency to recognize emotion more positively than normal people may influence on patients with schizophrenia to overlook negative emotions or exaggerate positive emotions of others, and consequently, may interfere with successful social interaction.

Negative symptoms of schizophrenia, antipsychotics and clinical outcome

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Objective: Negative symptoms such as social withdrawal, emotional blunting, apathy and anhedonia are more subtle in nature, more insidious and more difficult to treat with antipsychotic drugs compared with positive symptoms in schizophrenia. Nearly one third patients with schizophrenia have predominant and persistent negative symptoms. In schizophrenia the presence of negative symptoms has been associated with poorer clinical outcome. In this study we correlated changes in negative symptoms, as measured by scores on the 16-item Negative symptoms Assessment scale (NSA-16), with changes on the Global Assessment of Functioning (GAF), and on the Social and Occupational Functioning Assessment Scale (SFAS), and with anti-psychotic used in therapy.

Methods: In the study authors assessed in total 60 patients with schizophrenia or schizoaffective disorder. The patients were treated...
with antipsychotics: olanzapine, quetiapine and risperidone. They were assessed with 16-item Negative symptoms Assessment scale (NSA-16), with Global Assessment of Functioning (GAF), and Social and Occupational Functioning Assessment Scale (SOFAS), at the baseline, after one month of the treatment and after 3 months of the treatment. All of the patients were out-treated.

**Results:** Changes in negative symptoms rated with NSA - 16 showed statistically significant correlation with changes recorded on all of the outcomes measured by GAF and SOFAS scales (HI2 = 4.27, p < 0.05: HI2 = 5.69, p < 0.05). There were no statistically significant changes between the groups of patients treated with different anti-psychotic drugs (olanzapine, risperidone, quetiapine).

**Conclusion:** In this study, negative symptoms assessed by NSA-16 showed association with improvements on GAF and SOFAS. We can conclude from the results of this study that treatments that are effective in reducing negative symptoms, also reduce the functional disability associated with these symptoms in patients with schizophrenia.

**Objective:** The present analyses were conducted to compare treatment outcomes for patients initiating olanzapine long-acting injection (LAI) within 5 years of onset of illness (“Early Phase” group) versus those initiating olanzapine LAI greater than 5 years after illness onset (“Later Phase” group).

**Methods:** Data were obtained from the 8 studies in the clinical trial database involving olanzapine LAI (dose range: 45 mg/4 weeks to 300 mg/2 weeks). Outcome measures included rates of and time to study discontinuation, relapse, remission, and sustained remission, as well as mean changes from baseline to endpoint in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) total and subscale scores.

**Results:** Of the 1879 patients in the analysis, 24.2% were in the Early Phase group and 75.8% were in the Later Phase group. The Early Phase group showed a longer median time to discontinuation (P = 0.003), longer time to relapse (P = 0.018), and, among patients not in remission at study initiation (45.8%); a shorter median time to sustained remission (P = 0.032). Rates of remission and sustained remission were also higher for the Early Phase group relative to the Later Phase group (P < 0.001, both measures). The Early Phase group also showed greater symptom reduction in their mean PANS total, negative, positive, and general psychopathology scores, and in their BPRS total, positive and anxiety/depression scores (P < 0.001, all measures).

**Conclusion:** Consideration must be given to the post-hoc nature of this analysis and the fact that these clinical trials were not specifically designed to address the issue of treatment timing and clinical outcomes. Nevertheless, these findings support the assertion that clinical outcomes with use of a depot antipsychotic such as olanzapine LAI are significantly improved in patients who begin the depot earlier in the course of their illness compared with patients who begin the depot later.

**Policy of full disclosure:** Dr. Holland Detke is a full-time employee of Eli Lilly and Company. Research funded by Eli Lilly and Company.

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**Methods:** Subjects were 1192 patients with the opportunity for ≥2 years Olanzapine LAI treatment for schizophrenia. Frequencies of key benefits and risks were evaluated versus average duration of those events for all patients. Next, authors independently rated olanzapine LAI using the Transparent Uniform Risk/Benefit Overview method (TURBO), weighting the 2 most seriously related to the objective outcomes and adverse events (TURBO ratings) versus primary benefit (effectiveness) and an ancillary benefit. Averaged ratings were placed on a t-score grid from 1–7 (worst balance to excellent).

**Results:** The most frequent event was remaining relapse-free (91% at 1 year; 88% at 2 years). Mean cumulative days without relapse was 306 at 1 year and 546 at 2 years. Next most frequent was meeting symptomatic remission criteria at anytime (82% at 1 year; 84% at 2 years). Incidence of ≥7% weight gain was 33% at 1 year and 42% at 2 years; mean days duration = 54±49 at 1 year and 124±210 at 2 years. Per-patient post-injection delirium/sedation syndrome (PDSS) incidence = 0.8% at 1 year and 1.5% at 2 years; mean duration = 0 days at 1 and 2 years. For those with an event (9 patients at 1 year; 18 at 2 years), mean duration was 2 days at 1 and 2 years. For TURBO analysis, PDSS and weight gain were selected as key risks; choice of ancillary benefit varied. Mean benefit rating was 5; mean risk rating was 2.8 of 7, yielding a benefit/risk balance t-score of 5 (“acceptable”).

**Conclusion:** Olanzapine LAI’s benefit/risk balance was in the “acceptable” range based on TURBO ratings. Quantitative evaluation showed benefits (such as remission, relapse-free days) outweighed lower-probability events (PDSS), but higher-probability risks (weight gain) remained a significant clinical concern.

**Policy of full disclosure:** Dr. Holland C. Detke is a full-time employee of Eli Lilly and Company. Reported research was funded by Eli Lilly and Company.
**P-08-017** Biological and psychotherapeutic models of chronic acoustical hallucinations therapy at a paranoid schizophrenia

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**Objective:** To study the clinical and psychological factors causing synchronization and resistance of acoustical hallucinations at paranoid schizophrenia for the purpose of optimization of conducted therapy.

**Methods:** Clinical, the standardized scales according to alarm level of, depression of Zung, a questionnaire of vital styles an original scale of understanding of the patient's frustration.

**Results:** Results of research it has been revealed that patients suffering the paranoid schizophrenia over 5 years (57%), had persistent synchronization of acoustical hallucinations where according to clinical and psychopathological level acoustical hallucinations differed with their stereotype, defining a plot of insane designs. The prevalence of MPD depended on duration of frustration for less than 3 years replacement 0.086 (P < 0.01) and normalization 0.279 (P < 0.01).

**Conclusion:** Acoustical hallucinations with a duration over 5 years with the diagnosis of the paranoid schizophrenia make (57%). Duration of disease till 3 years and till one year 26% and 17% respectively, probably cause presence, first of all, prevalence of alarm component, as one of basic, defining synchronization and resistance of acoustical hallucinations. Prevalence of moderate depression of 50%, easy depression of 32%, it display of personal reaction it promote the process of activation specific MPD. At term of disease for less than 3 years there is replacement of 0.086 (P < 0.01) and normalization of 0.279 (P < 0.01). For more than 3 years, hyper indemnification of 0.183 (P < 0.01), and rationalization 0.279 (P < 0.01).

**Conclusion:** The increase of 5HT2A receptor binding in frontal cortex of schizophrenic subjects: Effect of aging and antipsychotic drug treatment

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**Objective:** Neuroimaging and postmortem studies have reported alterations of the 5HT2A receptor (SHT2AR) in brain of schizophrenic subjects. However, striking differences have been obtained in relation to the different methodologies and intrinsic confounding factors. The aim of the present study was to assess the SHT2AR mRNA (qRT-PCR) and protein expression (western blot and [3H]Ketanserin binding (10 nM)) in prefrontal brain cortex (BA9) of schizophrenics (n = 45) and matched controls (n = 45).

**Methods:** Displacement curves of [3H]Ketanserin binding (2 nM) by the agonist DOI were performed in order to delineate the high affinity state of SHT2AR. Subjects who gave negative results for anti-psychotic drugs in the postmortem toxicological screening were considered antipsychotic (APfree). To control the effect of suicidal behaviour, suicide victims (n = 13) with other psychiatric diagnosis were also included. Controls were individually matched by gender, age and postmortem delay.

**Results:** Decreased SHT2AR mRNA expression was observed in APtreated schizophrenics (−37 ± 9%; n = 9; p < 0.05) compared to matched controls, without changes in APfree subjects (n = 18). Immunodetection of SHT2AR protein was unchanged. [3H]Ketanserin binding was increased in APfree schizophrenics (+23 ± 11%; n = 29; p < 0.05), but not in APtreated subjects (n = 16) and suicide victims. Notably, an increase in the fraction of high-affinity sites for DOI displacing [3H]Ketanserin was found in APfree schizophrenics (12.4 ± 1.4% vs. 6.2 ± 0.8%; p < 0.001). [3H]Ketanserin binding correlated negatively with age in schizophrenic, suicide and control subjects. This effect of aging was more pronounced in APtreated (slope = −7.4 ± 3.1) than in APfree (slope = −3.6 ± 2.6) or control subjects (slope = −2.3 ± 0.8).

**Conclusion:** These results suggest that the active conformation of SHT2AR is upregulated in schizophrenia, a modulation that tends to be reversed by chronic treatment with antipsychotic drugs. Progressive aging may indicate the identification of the upregulation more difficult in schizophrenic subjects under treatment. The lower expression of SHT2AR in older subjects may also underlie an association between fewer positive symptoms and increased age.
scale for global functioning were assessed. The sample was divided into two groups according to the treatment received: oral vs. long-term atypical antipsychotics. For comparisons, Mann-Whitney U-test and Chi-square test were used.

**Results:** 18 delusional disorder (DD) patients and 18 patients on schizophrenia were included. Mean age (SD) at onset of illness was higher in delusional disorder compared to schizophrenia [45.9(6.5) years vs. 27.9(12.1); \( p = 0.03 \)] and patients with schizophrenia started follow-up earlier \( (p < 0.001) \). No statistically significant differences were found between delusional disorder and schizophrenia patients attending to educational level, marital status, number of children and cohabiters. Mean (SD) score in GEOPTE scale was similar in schizophrenia than in DD \( [34.7(7.6) \text{ vs. } 30.2(7.2); \ p = 0.082] \). Patients receiving oral antipsychotic treatment displayed more deficits in social cognition compared to those treated with long-acting atypical antipsychotics, according to GEOPTE scale score \( [34.43(8.08) \text{ vs. } 29.47(6.02)] \) but this result was not statistically significant. General functioning was similar between the two treatment groups.

**Conclusion:** Social cognition may be an important target in the pharmacological treatment of DD and schizophrenia. Long-term atypical antipsychotics could improve social cognition in patients with chronic psychotic disorder.

**P-08-021** Pharmacological characterization and exploration of novel transcripts of a developmentally regulated and phencyclidine-inducible gene, SAP97, in mammalian brains

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**Objective:** Recently accumulated evidence supports that the disturbed N-methyl-D-aspartate (NMDA) receptor-mediated glutamate neurotransmission is involved in the pathophysiology of schizophrenia. We have explored the transcripts induced by phencyclidine (PCP), an NMDA receptor antagonist, in the mammalian cerebral cortex.

**Methods:** Using differential screening, and quantitative RT-PCR methods, we isolated the neocortical transcript that was up-regulated in the adult but unchanged in infant rats, after a systemic administration of PCP. We further examined the expression and characterization of SAP97 in both rat and human specimens. All studies were approved by the ethics committees of the University.

**Results:** We have identified the synapse-associated protein-97 (SAP97)/discs large (DLG1) mRNA as a PCP-responsive transcript. The up-regulation of the SAP97 transcript in the adult neocortex after the acute PCP injection was mimicked by another NMDA antagonist, dizocilpine, but not by the indirect dopamine agonists, methylphenidate and cocaine, a selective D1 receptor antagonist SCH23390, a D2 receptor-preferred antagonist haloperidol and a GABAergic anesthetic pentobarbital. The pretreatment with a typical antipsychotic haloperidol failed to antagonize the increased neocortical SAP97 gene expression by PCP.

**Conclusion:** SAP97 gene encodes the synaptic scaffolding PDZ proteins that interact with ionotropic glutamate receptors. By using single nucleotide polymorphism (SNP) analyses, we have found a significant association between the human SAP97 gene and schizophrenia (Yamamoto et al., 2012 CINP abstract). These findings together suggest that SAP97 might be involved in the molecular basis of the development-dependent onset of the non-dopaminergic symptoms seen in schizophrenia and the schizophrenia-like psychosis induced by NMDA receptor blocking. Currently, we are further examining the expression of novel splicing variants of SAP97 in the human brain and their possible functional relationship with the symptoms.
Trace amines, endogenous compounds structurally related to classical biogenic amines, represent endogenous ligands of the trace amine-associated receptor 1 (TAAR1). Because trace amines modulate monoaminergic neurons ex vivo, and for its properties in vivo using pharmacokinetic properties, for its effects on the firing frequency of receptors stably expressed in HEK293 cells, for its physicochemical and affinity and functional activity at rodent and primate TAAR1 receptors, the trace amine-associated receptor 1 (TAAR1) shows high affinity for TAAR1, has potent functional activity with selectivity over other molecular targets and has good pharmacokinetic properties. In mouse brain slices, the TAAR1 partial agonist increased the firing frequency of dopaminergic and serotonergic neurons in Taar1 expressing regions, the ventral tegmental area and the dorsal raphe nucleus, respectively. In vivo, examining the consequences of activating TAAR1 selectively on various behavioral paradigms in rodents and monkeys, the TAAR1 partial agonist demonstrates antipsychotic-, anxiolytic- and anti-depressant-like activities. Furthermore, it attenuates drug-taking behavior and is highly effective in promoting attention, cognitive performance and wakefulness.

**Conclusion:** Using the first potent and selective TAAR1 partial agonist we show that TAAR1 is implicated in a broad range of relevant physiological, behavioral and cognitive neuropsychiatric dimensions. Collectively, these data uncover important neuromodulatory roles for TAAR1 and demonstrate its therapeutic potential in psychiatric disorders such as psychosis, depression and substance abuse.

**Policy of full disclosure:** F. Revel, J.-L. Moreau, R. Norcross, J. Wettstein and M. Hoener are employed by F. Hoffmann-La Roche. R. Gainetdinov is supported in part by research grants from F. Hoffmann-La Roche Ltd. and Compagnia di San Paolo Fondazione (Torino, Italy). J. Canales has no interests to declare. T. Wallace, M. Hoener and T. Kilduff are supported in part by research grants from F. Hoffmann-La Roche Ltd., Basel, Switzerland; F. Hoffmann-La Roche, Basel, Switzerland; Italian Institute of Technology, Genova, Italy; SRI International, Menlo Park, USA; University of Canterbury, Christchurch, New Zealand; Duke University Medical Center, Durham, USA; Italian Institute of Technology, Genova, Italy; Neuroservice, Aix-en-Provence, France.

**Methods:** The TAAR1 partial agonist was evaluated for its binding affinity and functional activity at rodent and primate TAAR1 receptors stably expressed in HEK-293 cells, for its physicochemical and pharmacokinetic properties, for its effects on the firing frequency of monoaminergic neurons ex vivo, and for its properties in vivo using genetic and pharmacological models of CNS disorders.

**Results:** The TAAR1 partial agonist shows high affinity for TAAR1, has potent functional activity with selectivity over other molecular targets and has good pharmacokinetic properties. In mouse brain slices, the TAAR1 partial agonist increased the firing frequency of dopaminergic and serotonergic neurons in Taar1 expressing regions, the ventral tegmental area and the dorsal raphe nucleus, respectively. In vivo, examining the consequences of activating TAAR1 selectively on various behavioral paradigms in rodents and monkeys, the TAAR1 partial agonist demonstrates antipsychotic-, anxiolytic- and anti-depressant-like activities. Furthermore, it attenuates drug-taking behavior and is highly effective in promoting attention, cognitive performance and wakefulness.

**Conclusion:** Using the first potent and selective TAAR1 partial agonist we show that TAAR1 is implicated in a broad range of relevant physiological, behavioral and cognitive neuropsychiatric dimensions. Collectively, these data uncover important neuromodulatory roles for TAAR1 and demonstrate its therapeutic potential in psychiatric disorders such as psychosis, depression and substance abuse.

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the response of sBDNF to the quantified stimuli applied with repetitive Transcranial Magnetic Stimulation (rTMS).

Methods: Right-handed twenty inpatients, with chronic schizophrenia, on stable medication whose minimum duration of illness was 10 years were recruited. The handedness was assessed using Edinburgh Handedness Inventory. Consecutive 10 weekday sessions with 20 Hz rTMS (a total of 20,000 stimuli) were applied over the left dorsolateral prefrontal cortex at 100% of motor threshold. There was no change in the medication for at least 2 week before enrollment and 4 weeks thereafter. Primary outcome measure was the change in the mean concentration of duplicated sBDNF pg/ml. Clinical severity or change was measured using the Clinical Global Impression scale (CGI) and the Positive and Negative Symptom Scale (PANSS).

Results: Eighteen participants (male, 10; female, 8) completed the study and were analyzed. The mean (SD) of chlorpromazine equivalent (CPZE) of antipsychotics were 1,325.69 (761.58)mg. The mean (SD) of baseline CGI-severity and total PANSS score were 4.61 (0.50) and 68.44 (6.05), respectively. The differences from baseline, in the level of sBDNF, just after the completion of rTMS sessions were statistically significant (paired t-test: t = 2.245, df = 17, p = 0.038). At 2 weeks after the completion of rTMS sessions, however, the significance in the level of sBDNF was not manifest (t = 1.381, df = 17, p = 0.185).

Conclusion: The findings of this study suggest that in patients with chronic schizophrenia, sBDNF may serve as a biomarker of neuroplasticity, but the change pattern of sBDNF might manifest both positive and negative implications on psychiatric rehabilitation.
**P-08-031** Effects of zonisamide on tardive dyskinesia: A preliminary open-label trial

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**Objective:** Once developed, tardive dyskinesia (TD) is a challenging condition to treat. The recent evidence has demonstrated that zonisamide, an antiepileptic drug indicated for partial-onset seizures, may also have beneficial effects for ameliorating dyskinesia in Parkinson’s disease. However, this finding has not systematically been tested in patients with TD associated with antipsychotic treatment. The objective of this study was to examine the efficacy, tolerability, and safety of zonisamide against TD in these patients.

**Methods:** In this 4-week open-label study, subjects who suffered TD were given 50–100 mg/day of zonisamide. Severity of TD was evaluated at the baseline and endpoint, using the Abnormal Involuntary Movement Scale (AIMS).

**Results:** Eleven subjects (6 females; mean ± SD age; 75.5 ± 4.7 years; schizophrenia [N = 6], bipolar affective disorder [N = 2], schizoaffective disorder [N = 1], mental retardation [N = 1], mental retardation with epilepsy [N = 1]) participated in this study. The AIMS total score (mean ± SD) was significantly decreased from 24.1 ± 5.5 to 19.5 ± 5.9, with 36.4% of the subjects (N = 4) demonstrating a >20% decrease in the AIMS total score.

**Conclusion:** Treatment with zonisamide was well-tolerated and no participants dropped out prematurely. Zonisamide may be safe and effective for the treatment of TD in a subgroup of patients. These preliminary findings need to be further explored by larger well-designed trials.

**P-08-032** Optimal D2 receptor occupancy rate of antipsychotics for the treatment of dopamine supersensitivity psychosis and late-onset psychosis

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**Objective:** Our aim is to estimate optimal D2 receptor occupancy rate of antipsychotics for the treatment of treatment-resistant schizophrenia, especially for patients with dopamine supersensitivity psychosis.

**Methods:** Under assumptions that there is an optimal range of the number of D2 receptors available for dopamine binding, which is constant under different D2 receptor density, we estimated optimal D2 receptor occupancy with different D2 density.

**Results:** The results showed that the optimal occupancy rate and optimal plasma level of antipsychotics increase with an increase in the D2 density, but decrease with a decrease in the D2 density.

**Conclusion:** Optimal D2 receptor occupancy of antipsychotics may change with D2 receptor density of each patient with schizophrenia. Patients with up-regulated D2 density may need higher doses of antipsychotics for the treatment.

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**P-08-033** Efficacy of aripiprazole-IM depot for long-term maintenance treatment of schizophrenia

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**Objective:** To evaluate the efficacy and tolerability of once-monthly aripiprazole intramuscular depot (ARI-IMD) for maintenance treatment in adult schizophrenia.

**Methods:** Subjects were cross-titrated to oral aripiprazole (10–30 mg/day) during a 4–6-week oral conversion phase (Phase 1). Phase 2 was a 4–12-week oral aripiprazole stabilisation phase. Subjects meeting stability criteria (4 weeks) entered an ARI-IMD stabilisation (400 mg/injection) phase with co-administration of oral aripiprazole for 2 weeks (Phase 3). Subjects meeting stability criteria (12 weeks) were randomised to ARI-IMD or placebo (52-week; Phase 4). Primary endpoint was time to impending relapse. Safety and tolerability were assessed.

**Results:** 710 patients entered Phase 2, 576 progressed to Phase 3 and 403 were randomised to Phase 4. The study stopped early because efficacy was demonstrated by pre-planned interim analysis. Time to impending relapse was significantly delayed in ARI-IMD compared with placebo in interim and final analyses (p < 0.0001, log-rank test). Rate of impending relapse was significantly lower with ARI-IMD than placebo at endpoint (10.0%, n = 27/269 vs. 39.6%, n = 53/134; HR: 3.51; 95% CI: 1.95–6.32; p < 0.0001). Improvements in PANSS total score were maintained with ARI-IMD, but showed significant worsening with placebo (mean change at Week 52: ARI-IMD = −1.4, placebo = −11.6, p < 0.0001). CGI-S scores showed significant differences favouring ARI-IMD (p < 0.0001). Most common treatment-emergent AEs (≥5% of aripiprazole-treated patients and greater than placebo) were insomnia (10.0% vs. 9.0%), tremor (5.9% vs. 1.5%) and headache (5.9% vs. 5.2%), respectively. Most AEs were mild or moderate. Incidence of injection site pain in Phase 3 was 5.9%, while in Phase 4 was 3.0% vs. 3.7% for ARI-IMD compared with placebo.

**Conclusion:** ARI-IMD significantly delayed time to impending relapse compared with placebo and was a well-tolerated maintenance treatment option in schizophrenia.

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**Policy of full disclosure:** John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Esai, Boehringer Ingelheim, Eli Lilly, Intracellular Therapeutics, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischacker has received research grants from Alkermes, Janssen, Lilly, BMS/Outuka, Wyeth, Janssen, Cilag Neurosearch, Amgen, Lundbeck, Endo, United Biosource, Targacept, MedAvante and AstraZeneca. Raymond Sanchez, Pamela Perry, Na Jin, Brian Johnson, Robert A Forbes, Robert D. McQuade and William H. Carson are all employees of Otsuka Pharmaceutical Development and Commercialization, Inc.

**SP-08-034** Medication prescribing patterns for patients with schizophrenia and related psychosis in a university psychiatric hospital

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**Objective:** Despite multiple therapeutic advances, especially in psychopharmacology, the treatment of schizophrenia has remained a major challenge. Surveys of prescribing in psychiatric services internationally have identified the relatively frequent and consistent use of antipsychotics polypharmacy (AP) with a prevalence of up to 50% in some clinical settings. The purpose of this study was to examine trends in the use of antipsychotic medications in an inpatient unit at a university mental health hospital in Korea.

**Methods:** This retrospective study was conducted in Severance Mental Health Hospital (SMH), a part of the unit of psychiatry, Yonsei University College of Medicine, which is a representative psychiatric facility offering comprehensive treatment to institutionalized patients.
with severe and persistent mental illness, in Korea. We reviewed all the psychiatropic medications prescribed to inpatients SMH, diagnosed as having schizophrenia or schizoaffective disorder (DSM-IV-TR, 4th edition) at time of discharge and 60 days after discharge in the year 2010.

Results: Of the 264 studied patients, 260 cases were treated with antipsychotics (Mean dose = 723 mg ± 519) chlorpromazine equivalent and 47.3% were discharged under AP treatment. The most prevalent combination of drugs was risperidone plus quetiapine (N = 20). Quetiapine was the most frequently used antipsychotic as adjuvant treatment (N = 64). Fifty-six cases (21.5%) received mood stabilizer 22 case received anticholinergics, 157 cases (60.3%) received benzodiazepines and 149 cases (57.3%) were prescribed anticholinergics.

Conclusion: Although, the controlled evidence for its efficacy and safety as a strategy remains inconclusive, AP is a common pharmacological strategy as it is shown in our study. Because of severe and patients in SMH, and using low dose quetiapine for sleep make the ratio of antipsychotic polypharmacy higher. And at some cases, polypharmacy was only used for short-term period (less than 60 days), the definition of antipsychotics polypharmacy. Clearly more controlled research is needed to evaluate the short-term and long-term effects of antipsychotic polypharmacy.

**P-08-035** Correlation between the left temporal lobe volume and the duration of untreated prodromal state in ultra-high risk for psychosis

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Objective: A longer duration of untreated psychosis (DUP) in schizophrenia is a common and complex psychiatric disorder. DUP plays a critical role in gene expression without altering DNA sequence. This is the first genome-wide methylation study using unmethylated samples with schizophrenia. Although previous studies have focused on methylation differences in schizophrenia at CpG sites within CpG islands around gene promoter regions, we demonstrated that aberrant DNA methylation in schizophrenia occurred across the genes. Our results also indicate that DNA methylation profiles can be used as a potential diagnostic biomarker for schizophrenia.

Methods: DUPS was defined as the duration in months from the first fulfillment of UHR criteria to the UHR screening. It was measured retrospectively by careful interview at the time of screening just before the MRI scan. The voxel based analysis tested the gray matter volume differences between the UHR and the control groups, and the regression analysis was conducted to examine if there was any gray matter region correlated with DUPS in UHR group with age and gender as covariates.

Results: The mean DUPS was 23.27 months (standard deviation: 22.45 months) in 34 ultra-high risk subjects. The left superior temporal lobe was ventral for acute schizophrenia patients.

Objective: The high use of long-term benzodiazepines (BZDs) with concomitant BZDs for at least 3 months were enrolled. Before and 4 weeks after tapering of daytime BZDs, the Brief Assessment of Cognition in Schizophrenia Japanese-language version (BACS-J) and the Schizophrenia Quality of Life Scale Japanese-language version (SQLS-J) were administered. Other clinical evaluations also included

Methods: Thirty schizophrenic patients who had received an SGA with concomitant BZDs for at least 3 months were enrolled. Before and 4 weeks after tapering of daytime BZDs, the Brief Assessment of Cognition in Schizophrenia Japanese-language version (BACS-J) and the Schizophrenia Quality of Life Scale Japanese-language version (SQLS-J) were administered. Other clinical evaluations also included
Objective: The examination of the effect of antipsychotic dosage on cognition and in particular memory in schizophrenia has produced contradictory findings. The aim of this study was to investigate the association of antipsychotic dose with memory performance in chronic schizophrenia using a cross-sectional design.

Methods: 107 patients (age = 42.3 years, SD = 10.12, range 18–64) with chronic schizophrenia from a psychiatric hospital were assessed with the Cambridge Automated Neuropsychological Test Battery (CANTAB) in tasks of pattern, spatial recognition and spatial working memory (PRM, SRM: per cent correct responses and SWM: between-search errors and strategy score). The Positive and Negative Syndrome Scale (PANSS) was used to measure symptomatology. Regression modeling was carried out to assess the effect of antipsychotic dose in chlorpromazine equivalents on memory performance, controlling for symptoms (PANSS), age, education and anticholinergic use.

Results: The patients' mean antipsychotic dose was 895.55 and their mean years of education 11.05 (SD = 3.46). Increased antipsychotic dose was significantly associated with worse PRM and SRM performance (B = −0.01, CI = −0.02, −0.004, t = −3.29, df = 93, p = 0.001 and B = −0.006, CI = −0.01, −0.002, t = −2.66, df = 93, p = 0.009, respectively). The correlations of antipsychotic dose with SWM measures SWM were not significant. The above results did not change after adjusting for atypical antipsychotic administration.

Conclusion: In conclusion, antipsychotic dose negatively correlated with recognition memory but not working memory performance in schizophrenia. Future prospective trials should further clarify the relationship of antipsychotic dose with specific memory deficits in patients with schizophrenia.

P-08-041

Association of antipsychotic dose with memory performance in chronic schizophrenia

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Objective: Four patients with resistant paranoid schizophrenia were included in this study. The patients were male, on the average 39.8 years old, diagnosed according to DSM-IV with schizophrenia from on the average 15.7 years, which had presented therapeutic resistance to some antipsychotics (haloperidol, clopixol, risperidone, olanzapine, clozapine). All subjects were treated with 3–12 mg paliperidone ER, according to the severity of symptoms. Patient’s Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), Adverse Events (AEs) were assessed at five timepoints: baseline, 1st, 2nd, 3rd, month of treatment. Personal and Social Performance (PSP) scale was assessed at every three month of treatment.

Results: Three patients completed the four month trial of paliperidone ER and one of them interrupted the medication (3 mg/day) after one month because of the noncompliance. One patient started and finished the treatment with paliperidone XR 6 mg/day, two patients started the treatment with 9 mg/day, but during the last month they received 12 mg/day for better improvement. The PANSS, CGI-S, AEs and PSP scales indicated that the treatment with paliperidone XR of three schizophrenic patients was effective and paliperidone did not produce adverse events. The treatment with this medication was noneffective only for one patient.

Conclusion: These data support results from recent studies that paliperidone ER is well tolerated and effective in patients previously unsuccessfully treated with other antipsychotics. Background: Paliperidone is a second generation antipsychotic medication approved for the treatment of schizophrenia. It is a useful option in the treatment of the acute symptoms of schizophrenia and may also be used in patients previously unsuccessfully treated with other antipsychotics.
P-08-042 Cost-effectiveness of asenapine in the treatment of schizophrenia and bipolar disorder in Canada

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Objective: Asenapine is a new antipsychotic approved in Canada for the treatment of schizophrenia and bipolar disorder (SCZ and BPD). Asenapine has shown a comparable efficacy profile to atypical antipsychotics. However, in contrast to most atypical antipsychotics, it is associated with a favourable (metabolic) profile. The objective of this study was to assess the economic impact of asenapine compared to atypical antipsychotics in the treatment of SCZ and BPD in Canada.

Methods: A combined decision tree and Markov model was constructed to assess the cost-utility of asenapine compared with atypical antipsychotics. The decision tree takes into account the occurrence of extrapyramidal symptoms (EPS), the probability of switching treatment due to EPS, and the probability of gaining weight. The Markov model compares the following strategies: long-term metabolic complications (diabetes, hypertension, CHDs (Coronary heart Disease), and stroke), fatal stroke, fatal CHD, and death by suicide or other causes. For SCZ, asenapine was also compared with olanzapine, quetiapine, ziprazidone and aripiprazole. For BPD, due to limited data on other antipsychotics, asenapine was compared with olanzapine only. Analyses were conducted from both a Canadian Ministry of Health (MoH) and a societal perspective. Compared to quetiapine, asenapine has a favourable economic impact compared to ziprazidone and aripiprazole in SCZ.

Conclusion: This economic evaluation demonstrates that asenapine is a cost-effective strategy compared to olanzapine and to most atypical antipsychotics used in Canada.

Policy of full disclosure: Jean Lachaine received research funds from Lundbeck. Dominique Gilbert, Maud Beillat and Helene Corson are employees at Lundbeck.

P-08-043 Glutamate levels in the associative striatum decrease with antipsychotic treatment in firstepisode of psychosis

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Objective: Schizophrenia is a mental illness in which both glutamatergic and dopaminergic systems are thought to be involved. Using proton magnetic resonance spectroscopy (1H-MRS), our group has demonstrated an increase of glutamate levels in the associative striatum (dopamine rich-region) of first-episode of psychosis (FEP) subjects. Nevertheless, it is unclear whether this increase persists after antipsychotic treatment. The aim was to compare glutamate levels in FEP patients, before and after antipsychotic treatment, with appropriate controls in the associative-striatum and the cerebellar cortex as a control region (negligible for dopamine).

Methods: Twenty-one antipsychotic-naïve FEP patients (age: 26.1 ± 8.5, 12-males), and 18 age and gender similar controls (age: 24.5 ± 5.1, 8-males) were included. Patients were treated with risperidone (3.45 ± 1.27 mg/day) for 4-weeks with doses adjusted based on clinical judgment (PANSS pre-treatment = 94.7 ± 13.3; post-treatment = 57.6 ± 9.1, p < 0.001). Participants underwent two 1H-MRS studies in a GE-3T scanner (PRESS TE = 30 ms, TR = 2000 ms, 128 averages, voxels = 8 ml) centred in the right dorsal caudate and right cerebellar cortex in all subjects. Concentrations were estimated with LCmodel and corrected for cerebrospinal fluid proportion.

Results: Patients showed higher levels of glutamate during the antipsychotic-naïve condition versus controls in the associative-striatum (T = -2.62, p = 0.01). After antipsychotic treatment, patients showed a decrease in glutamate levels (T = 2.18, p = 0.04) and no differences with controls. There were no differences in glutamate cerebellar levels between all groups.

Conclusion: Our results indicate an increase of glutamate in the associative-striatum in FEP patients, showing a decrease after clinically effective antipsychotic treatment. These preliminary results suggest that higher glutamate levels in the associative striatum can be reversed with appropriate antipsychotic treatment. Moreover, the lack of change in the cerebellum suggests that the increase of glutamate in psychosis is not ubiquitous within the brain and may be associated with dopamine rich regions.

Policy of full disclosure: This work was supported by an Investigator-initiated research by JANSSEN to A Graff-Guerrero and C de la Fuente-Sandoval. P. León-Ortiz, M Azcárraga, S Stephano, P. Alvarado-Alanis, and J Ramirez-Bermúdez and have no conflicts of interest to disclose. R. Favila is an employee of GE Healthcare. C. de la Fuente-Sandoval has received grant support from UC MEXUS-CONACYT, ICyTDF, professional services compensation from IMS Health, and speaker compensation from Eli Lilly. A Graff-Guerrero has received grant support from NIH, CIHR, and CONACyT, professional services compensation from Abbott Laboratories and Gedeon Richter Plc, and speaker compensation from Eli Lilly.
In the patient group we found 29 abnormal functional connections, including 19 hyper-connections and 10 hypo-connections. To interpret these aberrant functional connections in terms of brain functionalities, we divided the whole brain into ten functional networks/areas and ascribed each functional cluster to one of these networks. Changed connections between functional clusters were thereby interpreted as abnormal connections between functional networks.

**Results:** Hyperconnectivity was observed within the default mode network (DMN) and between the DMN and other cognitive networks, whereas hypoconnectivity was predominantly associated with sensory networks. The data collectively suggest that information processing related to the external world (i.e. connectivity involving sensory networks) is compromised in company with increased connectivity related to the internal world (i.e. connectivity involving the DMN), and communications between the internal and external worlds are impaired in schizophrenia.

**Conclusion:** These findings imply distorted sensory perceptions and undermined coordination between perception and cognitive functions in the patient, and should provide a new angle to understand several core features of schizophrenia such as sensory processing deficits and positive symptoms like hallucination.
P-08-045 Ahhl gene expression levels in mutant mice are directly correlated with levels of state anxiety and threat detection: Translational relevance to schizophrenia and autism

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Objective: Schizophrenia is characterized by substantial genetic contribution to its etiology. The Abelson helper integration site (AHI1) gene was previously shown by our group to be associated with schizophrenia in humans, with evidence for changes in its expression as the possible causative mechanism. Association with autism has also been reported. Therefore, we studied the behavioral consequences of expression alterations of this gene in various paradigms modeling different facets of schizophrenia, employing mice heterozygous (HET) for an Ahhl knockout mutation.

Methods: Open field (OFT), elevated plus maze (EPMT), social interaction in pairs (SIIPT) and light dark box (LDT) tests were conducted on HET mice compared to littermates wild type (WT) mice.

Results: A consistent finding of our experiments was significantly reduced levels of situational anxiety in HET mice compared to WT mice. In the OFT, HET mice spent significantly more time in the arena center compared to WT mice (p = 0.02). In the EPMT, HET mice, compared to WT mice, spent significantly more time in the maze open arms (p = 0.006) and less time in the closed arms (p = 0.009). In the SIIPT, pairs of unfamiliar HET mice spent significantly more time interacting with each other than corresponding pairs of unfamiliar WT mice, in the first, anxiety provoking encounter (p = 0.01). This finding probably reflects less anxiety in the HET mice when encountering a potentially hazardous situation such as an unknown animal. Finally, in the LDT, HET mice spent significantly more time in the open lightened zone (p = 0.02) than WT mice.

Conclusion: Our findings indicate that reduced expression of the Ahhl gene in mice is associated with a decrease in perception of threatening situations, which may arise from reduced connectivity between the amygdala and other forebrain areas, including schizophrenia and autism.

P-08-046 G72 protein expression in peripheral blood as a diagnostic biomarker of schizophrenia

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Objective: To date, there is no peripheral biomarker for schizophrenia. NMDA hypofunction is implicated in the pathophysiology of schizophrenia. D-serine, a potent NMDA co-agonist, is metabolized by D-amino acid oxidase (DAAO), which is activated by DAAO activator (DAAO, or named G72). Theoretically, DAAO overactivation leads to NMDA hypofunction. This study examined whether peripheral G72 protein expression is characteristic of schizophrenia.

Methods: G72 protein level was measured in peripheral plasma in patients with schizophrenia, patients with bipolar I disorder, and healthy controls. Receiver operating characteristic (ROC) curve was conducted to determine the optimal cutoff values of G72 protein level for schizophrenia patients vs. healthy controls and vs. bipolar patients.

Results: Among all subjects, the G72 protein level was higher in schizophrenia (mean = 2.726 ± 1.411, n = 119) when compared with healthy individuals (0.892 ± 0.415, p < 0.001, n = 42), but lower when compared with bipolar I patients (3.896 ± 2.103, p < 0.001, n = 51). The optimal cutoff value, 1.564, between schizophrenia and healthy subjects generated a sensitivity of 0.77 and specificity of 0.98 (area under curve [AUC] of ROC = 0.894). A cutoff of 4.318 differentiated all schizophrenia from bipolar I patients with a sensitivity of 0.41 and specificity of 0.87 (AUC = 0.659).

Conclusion: These findings provide the first peripheral diagnostic tool for schizophrenia. NMDA hypofunction as evident by over-activated G72 protein expression may serve as a common pathway for vulnerability of schizophrenia.

P-08-047 Effect of lurasidone on weight and metabolic parameters: Results from post-hoc placebo-controlled trials in schizophrenia

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Objective: To evaluate the effect of lurasidone treatment of subjects with schizophrenia on weight and metabolic parameters.

Methods: Data were pooled from 7 DB, placebo-controlled trials, including 4 with active comparators, of subjects who met DSM-IV criteria for schizophrenia with an acute exacerbation. The analysis sample consisted of subjects treated with lurasidone (dose range, 20–160 mg, total N = 1508); haloperidol 10 mg (N = 72); olanzapine 15 mg (N = 122); risperidone 4 mg (N = 65); quetiapine XR (N = 119); and placebo (N = 708).

Results: During 6 weeks of treatment, the mean change in weight, in kg at LOCF-endpoint, was +0.43 for lurasidone (pooled), +0.02 for haloperidol, +4.15 for olanzapine, +2.09 for quetiapine-XR, +0.20 for risperidone, and −0.02 for placebo. The proportion of patients experiencing ≥7% weight gain was 3.3% for placebo, 4.2% for haloperidol, 4.8% for lurasidone, 6.2% for risperidone, 15.3% for quetiapine XR, and 34.4% for olanzapine. Median endpoint changes in lipids were as follows: triglycerides (mg/dL), −4.0 for lurasidone, −3.0 for haloperidol, +25.0 for olanzapine, +4.0 for risperidone, +9.5 for quetiapine XR, and −6.0 for placebo; and total cholesterol (mg/dL), −5.0 for lurasidone, −8.0 for haloperidol, +9.0 for olanzapine, +6.5 for risperidone, +6.0 for quetiapine XR, and −5.0 for placebo. Median LOCF-endpoint change in glucose (mg/dL) were similar for combined lurasidone (0.0) and placebo (0.0), and somewhat higher for haloperidol (+2.0), olanzapine (+4.0), risperidone (+3.0), and quetiapine XR (+3.0).

Conclusion: In these pooled analyses of short-term studies, treatment with lurasidone was associated with minimal increases in weight and BMI. Decreases in median total cholesterol and triglycerides were also observed.
Policy of full disclosure: Dr. Pikalov, Silva, Cucchiaro, Hsu, Xu, and Loebel are full-time employees of Sunovion Pharmaceuticals Inc, Fort Lee, NJ, USA.

P-08-049 Effectiveness of lurasidone vs. quetiapine XR for relapse prevention in schizophrenia: A 12-month, double-blind study

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Objective: To evaluate the efficacy and safety of lurasidone (LUR) vs. quetiapine XR (QXR) in preventing relapse in subjects with schizophrenia.

Methods: After completing an initial DB, 6 week trial with LUR (80 mg; 160 mg) or QXR (600 mg), subjects received 12 months of DB, flexible once-daily doses of LUR (40–160 mg) vs. QXR (200–800 mg). The primary a priori time-to-relapse comparison was between subjects treated with LUR (n = 139) and QXR (n = 79) who were clinical responders after acute treatment, using a Cox proportional hazards model, with a pre-specified non-inferiority margin for the risk of relapse hazard ratio of 1.93.

Results: LUR was non-inferior to QXR in risk for relapse over the 12 month treatment period (hazard ratio 0.728, 95% CI [0.410, 1.295]). Risk of relapse in LUR treated subjects was reduced by 27.2% (hazard ratio 0.728) compared with QXR. The Kaplan-Meier estimate of the probability of relapse was lower for LUR vs. QXR (0.237 vs. 0.336). Rates of adverse events ≥5% in the LUR group were akathisia (12.6%), headache (10.6%), insomnia (7.9%), anxiety (6.0%), parkinsonism (6.0%), and weight increased (6.0%). At 12 months, treatment with LUR and QXR, respectively, resulted in a mean change in weight of +0.7 vs. +1.2 kg; a median change in cholesterol of 0.0 vs. +4.0 mg/dl; and a median change in triglycerides of -18.0 vs. -7.0 mg/dl. There were no clinically meaningful changes in other laboratory or ECG parameters on either drug.

Conclusion: This DB study demonstrated non-inferiority of lurasidone to QXR in prevention of relapse over a 12 month period, with a 27.2% reduction in relapse risk compared with QXR. Lurasidone was associated with minimal adverse effects on weight and metabolic parameters.

Policy of full disclosure: Dr. Loebel is a full-time employee of Sunovion Pharmaceuticals Inc, Fort Lee, NJ, USA.

P-08-050 Efficacy of lurasidone in schizophrenia: Factor analysis of pooled short-term trials

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Objective: To evaluate the efficacy of lurasidone across five previously validated PANSS factors (positive, negative, disorganized thought, hostility, and depression/anxiety).

Methods: A post-hoc factor analysis was performed on pooled data from 3 positive six-week, double-blind, placebo-controlled trials of subjects hospitalized with an acute exacerbation of schizophrenia who were randomly assigned to fixed, once-daily doses of lurasidone 40 mg (n = 290), 80 mg (n = 334), 120 mg (n = 290), 160 mg (n = 121), or placebo (n = 497). Data were analyzed using a mixed model repeated measures (MMRM) model with an unstructured covariance matrix. Effect sizes (ES) were calculated from an ANCOVA analysis (LOCF-endpoint) as the between-treatment group difference in LS mean change scores divided by the pooled standard deviation of the change scores.

Results: Baseline characteristics were highly similar in the pooled lurasidone (n = 1035; mean PANSS total score, 96.3) and placebo (n = 497; mean PANSS total score, 96.1) groups. At endpoint, treatment with lurasidone was associated with significantly greater improvement in the PANSS total score compared with placebo (22.6 vs. 12.8; P < 0.001; ES, 0.42). Significantly greater endpoint improvement (P < 0.001 for all comparisons) was observed for lurasidone versus placebo across all five PANSS factors. Changes for lurasidone vs. placebo were: -8.4 vs. -6.0 (ES, 0.35) in the PANSS positive factor; -5.2 vs. -3.3 (ES, 0.32) in the PANSS negative; -4.9 vs. -2.8 (ES, 0.40) for disorganized thought; 2.7 vs. -1.6 (ES, 0.34) for hostility; and -3.2 vs. -2.3 (ES, 0.29) on depression/anxiety factors. Lurasidone160 mg dose was consistently associated with the highest effect size for each factor.

Conclusion: In this pooled, post hoc factor analysis of placebo-controlled trials, treatment with lurasidone across the daily dosing range of 40–160 mg, was effective in improving all 5 PANSS factors, suggesting efficacy across the full spectrum of symptoms associated with schizophrenia.

Policy of full disclosure: Drs. Cucchiaro, Silva, Mao, Pikalov, and Loebel are all full-time employees of Sunovion Pharmaceuticals Inc, Fort Lee, NJ, USA.

P-08-051 An in vitro analysis of disintegration times of different formulations of orally disintegrating olanzapine

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Objective: Orally disintegrating tablet (ODT) forms of medication are sometimes used as alternatives to standard oral tablets for patients who have difficulty swallowing, those who need to have ingestion verified, and those who may resist other drug product forms (e.g. injection). ODTs are a tablet or wafer form of medication that disintegrate in the mouth, aided only by saliva. ODTs can disperse in as little as 1 to 2 seconds or as long as 2 to 3 minutes, depending on the different fast dissolve/disintegration technologies used to manufacture the tablets. Orally disintegrating olanzapine (ODO) is manufactured by several different companies, using different formulations and processes. The objective of the study was to investigate differences in disintegration time of these tablets which may potentially impact clinical parameters such as patient acceptance and adherence to treatment.

Methods: Six types of ODO, along with Risperdal M-Tab as an external comparator, were evaluated for formulation composition, manufacturing method, disintegration and dissolution characteristics, expiration dates, packaging and formulation differences in comparison with the freeze-dried Zydis/Velotab formulation of ODO. Automated dissolution test equipment, DISTEK DISBA0045 and DISBA0046 with an Opt-Diss UV fiber optic SPEC0088 attachment, was used to capture the various ODT dissolution rates by measuring real time release of the active ingredient. Additionally, a high speed video camera was used to capture disintegration times of ODO products in simulated saliva held at 37°C.

Results: Time required for initial and complete disintegration, with 95% confidence intervals, will be presented.

Conclusion: The in vitro disintegration test is a proxy for the disintegration process in a patient’s mouth. Differences found in formulation and manufacturing process of ODO may be associated with different disintegration times which may potentially impact their use in clinical practice.

Policy of full disclosure: Dr. McDonnell is a full-time employee of Eli Lilly and Company. Research reported was sponsored/funded by Eli Lilly and Company.

P-08-052 Patient satisfaction and caregiver burden related to olanzapine long-acting injection

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Objective: To assess patients’ attitudes toward and satisfaction with olanzapine long-acting injection (LAI) and determine effects on caregiver burden.

Methods: Data were analyzed from 2 long-term, open-label studies. Study 1 (N = 931) assessed long-term safety up to 6.5 years. Study 2 was a 2-year randomized study comparing the effectiveness of olanzapine LAI (N = 264) and oral olanzapine (N = 260). Measures included the Patient Satisfaction with Medication Questionnaire-Modified (PSMQ) in both studies and the Drug Attitude Inventory (DAI-10) and Burden Assessment Scale (BAS; a caregiver self-report measure) in Study 2, with assessments at 6- to 12-month intervals.

Results: In Study 1, 73% of patients were satisfied with olanzapine LAI at first assessment, 87% at 6 years, and 73% at patient’s endpoint.
In Study 2, 7.5% were satisfied at first assessment, 88% at 2 years, and 73% at patient’s endpoint (similar to oral-treated patients). On the DA1-10, >80% of LAI-treated patients endorsed positive statements at each time point, including 90% stating that “the good things about the medication outweigh the bad” at 2 years. On the BAS, caregivers reported statistically significant improvement in their overall burden at 2 years (p values <0.001).

**Conclusion:** Results suggest that olanzapine LAI is viewed positively by patients and caregivers.

**Policy of full disclosure:** Dr. McDonnell is a full-time employee of Eli Lilly and Company.

**P-08-055** Benefits of switching schizophrenic patients from olanzapine to aripiprazole

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**Objective:** It is well-known that olanzapine easily cannot be used in schizophrenic patients with hyperglycemia and is contraindicated for patients with diabetes in Japan. Aripiprazole has advantages compared to other antipsychotics regarding side-effects. Schizophrenic patients switching from an agent with an anticholinergic profile to another could have risk of cholinergic rebound symptoms. Therefore, longer taper of the anticholinergic agent may be necessary because of their different receptor-affinity profiles. The purpose of the present study was to evaluate if switching could be successful after switching from olanzapine to aripiprazole concomitantly with dipehenydra mine, an antihistaminergic agent.

**Methods:** Patients, diagnosed with schizophrenia (DSM-IV criteria) and required a change in olanzapine therapy because of persistent symptoms and troublesome side-effects, were included. Aripiprazole was given at a dose of 6 to 12 mg/day in addition to olanzapine, and then olanzapine was tapered down at a rate not exceeding 2.5 mg/week and aripiprazole was up-titrated after switching, after which aripiprazole was maintained between 6 and 24 mg/day through the evaluation period. Dipehenydramine was used between 0 and 150 mg/day. Clinical efficacy was assessed with PANSS, CGI-S, CGI-I and GAF at weeks 4 and 8 after switching.

**Results:** Of 14 patients, 9 patients (64.3%) successfully completed the study and continued aripiprazole treatment to 6-week after switching. Although 1 patient showed exacerbation in symptoms caused by rebound, discontinuations due to adverse events of aripiprazole were not observed.

**Conclusion:** Switching from olanzapine to aripiprazole generally resulted in retention of efficacy and improvements in tolerability across the evaluation period. Most notably, management of rebound effects by switching was achieved. This would be due to gradual discontinuation of the pre-switch medication and concomitant use of diphenydramine to avoid rebound symptoms.

**Policy of full disclosure:** Speakers: Otsuka, Eli Lilly, GSK, De-pharma.

**P-08-056** Altered levels of endocannabinoids in postmortem human brain of schizophrenic subjects

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**Objective:** Numerous studies have implicated the endocannabinoid (EC) system in the pathophysiology of schizophrenia. Some ECs have been measured in blood and cerebrospinal fluid of schizophrenic
We investigated the effects of aripiprazole on plasma levels of brain-derived neurotrophic factor (BDNF) and catecholamines treated with aripiprazole monotherapy. Twenty-nine were male and schizophrenia patients who met the DSM-IV-TR criteria and were sequence around the region. The study was approved by the Ethical ELISA. The genotyping (BDNF Val/Met) was determined by direct measured by HPLC-ECD. The plasma BDNF levels were measured by

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<td>p</td>
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<td>CB</td>
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<td>vs.</td>
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<td>HC</td>
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Conclusion: These results demonstrate that AEA and 2AG levels are altered in some brain areas in schizophrenia. Moreover, these data provide further evidence that the chronic antipsychotic treatment is able to modulate the EC brain levels.

P-08-057 Aripiprazole treatment and plasma levels of brain-derived neurotrophic factor (BDNF), BDNF gene Val66Met polymorphism, and catecholamine metabolites in first-episode untreated Japanese schizophrenia patients


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Objective: We investigated the effects of aripiprazole on plasma levels of brain-derived neurotrophic factor (BDNF) and catecholamine metabolites in first-episode untreated schizophrenia patients.

Methods: The subjects were 50 Japanese first-episode untreated schizophrenia patients who met the DSM-IV-TR criteria and were treated with aripiprazole monotherapy. Twenty-nine were male and 21 were female. The age was ranged from 21 to 42 yr (mean ± S.D.; 30.8 ± 5.3 yr). The plasma levels of catecholamine metabolites were measured by HPLC-ECD. The plasma BDNF levels were measured by ELISA. The genotyping (BDNF Val/Met) was determined by direct sequence around the region. The study was approved by the Ethical Committee of the UOEH.

Results: Treatment with aripiprazole for 8 weeks significantly increased plasma BDNF levels. It also changed plasma levels of homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG). A negative correlation was also observed between duration of psychosis (DUP) and plasma BDNF levels. No correlation was however observed between plasma BDNF levels and the dose of aripiprazole. In addition, twelve of 50 patients were longitudinally measured plasma levels of catecholamine metabolites and BDNF. Plasma HVA increased at week 2, and decreased at week 8 comparing to baseline. Plasma MHPG increased at week 8.

Conclusion: To the best of our knowledge, this is the first report showing that aripiprazole increases plasma levels of BDNF and MHPG in first-episode untreated schizophrenia patients, which might be related to the improvement of negative symptoms of schizophrenia and cognitive functions. Furthermore, the BDNF Val66Met polymorphism was independent of the response to aripiprazole.

P-08-058 Assessment of subjective well-being and safety in patients with atypical schizophrenia treated with blonanserin: One-year open-label trial

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Objective: Blonanserin is a novel atypical antipsychotic that exhibits a potent antagonist activity at dopamine D2, 3 and serotonin 5-HT2A receptors. The purpose of this study was to assess the subjective well-being and safety in patients with atypical schizophrenia first-episode schizophrenia treated with blonanserin for one year.

Methods: Twenty-four atypical schizophrenia patients with first-episode schizophrenia participated in this study. Blonanserin (2–24 mg/day) was given in an open label design for 12 months. Psychopathology, subjective well-being, and safety were evaluated at baseline, 2, 6, and 12 months. Psychopathology was assessed by Positive and Negative Syndrome Scale (PANSS). Subjective well-being was evaluated by the Subjective Well-being Under Neuroleptic Treatment Scale Short form-Japanese version (SWNS-J). Safety assessments included laboratory tests, body weight, Body Mass Index (BMI), and the Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS). This study was approved by the bioethics committee of St. Marianna University School of Medicine, and written informed consent was received from all participants.

Results: Thirteen patients (6 males and 7 females; mean age, 28.2 ± 5.6 years) completed the study. The mean blonanserin dose was 4.2 ± 3.0 mg/day at 12 months. Significant improvements from baseline to endpoint were reported for all items on the PANSS (p < 0.01) and SWNS-J (p < 0.05). In the laboratory tests, the values of alkaline phosphatase significantly increased from baseline (p < 0.05). In addition, high density lipoprotein cholesterol and fasting blood sugar significantly decreased (p < 0.05), but all of these data remained within the normal range. Although mean body weight and BMI increased from baseline, the rate of weight gain was only 6.1%. There was no significant change in the DIEPSS score.

Conclusion: Blonanserin produced favorable long-term outcomes and good safety profiles in patients with atypical schizophrenia first-episode schizophrenia. The results suggest that blonanserin may be useful in the management of first-episode schizophrenia.

Policy of full disclosure: Dr. Miyamoto has served as a consultant for Dai nippon Sumitomo Pharmaceutical. He has received advisory board honoraria from Chugai Pharmaceutical. No other authors have any conflicts of interest with any commercial or other associations in connection with this study.

P-08-059 Antidepressant and anxiolytic effects of quetiapine strongly correlate to neuropeptide Y increase and corticotropic-releasing hormone decrease in CSF from schizophrenic patients

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Objective: NPY and CRH play a role in the CNS physiology/pathophysiology and in the mechanisms of action of antidepressant/antipsychotic drugs. Early data showed increased NPY in CSF from schizophrenic patients and NPY changes by antipsychotics in rodent brain. In depression, NPY is decreased in CNS from depressed patients and animal models of depression, chronic stress and PTSD. Conversely, ECT, lithium and antidepressants increase NPY. In view of these findings we investigated if (1) quetiapine, an antipsychotic efficient also in affective disorders would modify NPY and CRH in CSF of schizophrenic patients, and (2) the effects on NPY and CRH will correlate to changes in depression and anxiety, symptoms that are common both in schizophrenia and affective disorders.

Methods: Twenty-two DSM-IV schizophrenics (age 35.9 ± 7.4 y; illness duration 20.3 ± 24.8 m), diagnosis confirmed with Structured Clinical Interview participated. Patients were assessed with PANSS at baseline and weekly thereafter. Lumbar puncture was performed at

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PANSS depression items (p < 0.001) of the Δ PANSS anxiety symptoms (p < 0.05) and Δ CRH-LI 42% of the Δ PANSS depression items (p < 0.05).

Conclusion: Quetiapine effects on NPY and CRH correlated strongly with the decrease in the depression and anxiety PANSS items. Since psychiatric diagnoses are generally clusters of symptoms of various durations and there are hardly any pathognomonic signs, our approach to focus on specific symptoms, regardless of diagnosis, would seem to be a more fruitful approach to elucidate the underlying neurobiology.

**P-08-060** Effects of discontinuation of long-term biperiden use on cognitive function and quality of life in schizophrenia

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Objective: The high use of long-term antiparkinsonian anticholinergic drugs with antipsychotics has been identified as an important issue in the treatment of schizophrenia in Japan. The aim of this study was to evaluate the effects of gradual discontinuation of biperiden, an anticholinergic drug, on cognitive function and quality of life (QOL) in schizophrenia.

Methods: Thirty-nine schizophrenic patients who had received one or two kinds of second-generation antipsychotics (SGAs) with concomitant biperiden for at least 3 months were enrolled. Before and 4 weeks after discontinuation of biperiden, the Japanese version of the Brief Assessment of Cognition in Schizophrenia (BACS-J) and the Schizophrenia Quality of Life Scale (SQLS-J) were administered. Clinical evaluation also included the Positive and Negative Syndrome Scale (PANSS). To compare the practice effect on BACS-J, 10 chronic patients with schizophrenia were assessed without tapering biperiden.

Results: Biperiden was discontinued safely in most patients receiving an SGA (N = 24), and no emergent extrapyramidal symptoms (EPS) were observed. Significant improvements were shown in attention, processing speed, and composite score, as measured by the BACS-J without practice effect. In addition, the psychosocial condition score on the SQLS-J and the general psychopathology score on the PANSS significantly improved after biperiden discontinuation. However, exacerbation in clinical symptoms and emergent EPS were observed in patients taking more than two kinds of SGAs (N = 5).

Conclusion: Discontinuation of long-term biperiden use may be warranted in patients with schizophrenia treated with a single SGA, as it may improve cognitive function, subjective QOL, and psychiatric symptoms with no significant adverse effects. However, caution should be paid when tapering biperiden in patients treated with more than two kinds of SGAs, since it may worsen psychotic symptoms or motor function.

**P-08-062** Multiple behavioral deficits reminiscent of schizophrenia in mice deficient in DISC-M (disrupted in schizophrenia matsuzawa), a gene encoding a transcriptional regulator

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Objective: We have recently reported a schizophrenic patient with a de novo mutation, a balanced chromosome translocation t(4;13)(p16.1;q21.31). We attempted to determine the break point within chromosome 4 and found that it locates at the upstream region of a gene encoding a putative transcriptional regulator protein, and we named the gene DISC-M (Disrupted_In_Schizophrenia, Matsuzawa). However, it remains unknown whether and how the functional loss of the gene really impacts on the etiology of schizophrenia in the patient.

Methods: To get insights into the question, we analyzed mice lacking the corresponding gene using multifaceted approaches in the current study. In addition, we have conducted a comprehensive gene expression analysis of the mouse brain from the KO mice.

Results: The homozygous mice were born in a mendelian ratio by the cross between heterozygous mice. Behavioral assessments showed that they are hyperactive in the open field test and other tests, and that they are highly sensitive to MK-801, an NMDA antagonist. In addition, the mice have a severe impairment in auditory fear conditioning test, suggesting deficits in learning/memory abilities. In contrast, we have found abnormalities in neither prepulse inhibition nor social interaction. Of interest, but neurogenesis in hippocampal dentate gyrus of the young adult mice was significantly decreased, although the tissue architecture seemed to be not different from the control mice. Furthermore, we identified DISC-M-regulated genes, many of which are related to neuronal function or development.

Conclusion: In conclusion, some of phenotypes of the mice seem to be reminiscent of schizophrenia. Since biological functions of the gene are still largely unknown, further investigation will be needed to reveal the mechanism of the abnormalities and the relationship between schizophrenia and this gene.

**P-08-063** Kynurenic acid in cerebrospinal fluid, plasma and urine of healthy male volunteers

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Objective: Kynurenic acid (KYNA) is a neuroactive tryptophan end metabolite, produced both in peripheral and brain tissues, with poor blood-brain crossing properties. Its precursor kynurenine however easily crosses the blood-brain barrier. KYNA is elevated in the brain and cerebrospinal fluid (CSF) of patients with schizophrenia and is currently being investigated for its possible role in schizophrenia pathophysiology. In the present study we compare the levels of KYNA in CSF, plasma and urine of healthy male volunteers and correlate these levels to putative confounders.

Methods: Plasma (collected at five time points over 24 hours starting/ending at 08:00 am), urine (24-hour) and CSF (collected at the end-point 08:00 am) from 30 healthy male volunteers were analyzed for KYNA content using HPLC with fluorescence detection.

Results: The mean 24-hour plasma and urine KYNA levels were positively correlated (r = 0.41, p = 0.03). No correlations were observed between CSF and plasma levels of KYNA. A trend towards significance was observed between CSF and urine KYNA levels (r = 0.33, p = 0.08). We found no correlations between the CSF, plasma or urine levels of KYNA and age, weight, height, body mass index or coffee consumption. However, there were negative associations between nicotine use and the urine KYNA levels (r = −0.45, p = 0.02) and CSF (r = −0.47, p = 0.01) levels of KYNA.

Conclusion: The plasma and urine levels of KYNA were positively correlated, while CSF KYNA levels did not correlate to plasma or urine KYNA content in healthy male volunteers. Interestingly, the use of nicotine was negatively associated with both CSF and urine levels of KYNA. In line with this, chronic exposure to nicotine reduces KYNA content in the rodent brain [1]. Nicotine use might thus be an important confounding factor in clinical studies investigating kynurenine metabolism.

Anhedonia as an influencing factor to social functioning and quality of life at patients with schizophrenia

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Objective: study the role of anhedonia in negative affect to social functioning and quality of life in patients with schizophrenia and postpsychotic depression.


Results: 205 patients were divided into comparable groups. 115 patients with negative syndrome of paranoid schizophrenia (NSH), 90 patients with postpsychotic depression (PPD). Men – 65.9%, women – 34.1%. The average age was 32.85 (±0.66) years. 58.93% of patients had anhedonia. NSH group observed anhedonia in 60 patients (52.17 %), PPD group – 60 patients (66.66 %). The anhedonia level in all groups reached moderate (22.16 ± 0.38). In all groups the disability level reached of severe. NSH-A group the disability level was significant (p<0.05). NSH group observed significant disturbances of cognitive functioning and “communication” (p < 0.05; r = 0.329), “family life” (p < 0.01; r = 0.285) compared with patients without anhedonia. PPD-A group the cognitive functioning was a considerable. In the “communication” (p < 0.01; r = 0.428) and “family life” (p < 0.01; r = 0.598) revealed moderate disturbance, but these disturbances were significant against groups of patients without anhedonia. In PPD and NSH groups observed a significant reduction in various areas of social and professional activities or teaching. Was found poor quality of life in patients with anhedonia in all groups of study. NSH-A group the quality of life was significantly (p < 0.05; r = –0.282). In patients without anhedonia in all groups was satisfactory quality of life.

Conclusion: anhedonia presence in the clinical picture of schizophrenia makes a favorable foundation for the impairment of cognitive performance, breach of communication and inability to perform their household and family responsibilities, and degrades the quality of life of patients.

The psychopharmacology algorithm project at the Harvard South shore program: An update on schizophrenia

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Objective: This is an update of the algorithm for schizophrenia from the Psychopharmacology Algorithm Project at the Harvard South Shore Program.

Methods: A literature review was conducted focusing on new data since the last published versions (1999–2001).

Results: For new-onset schizophrenia, the first-line antipsychotics, recommended with very slight preference, are amisulpride, aripiprazole, risperidone, or ziprasidone. If the trial of the first antipsychotic cannot be completed due to intolerance, try another until one of the four is tolerated and given an adequate trial of 4–6 weeks. There should be evidence of bioavailability. If there is an unsatisfactory response to this adequate trial, try a second monotherapy with any antipsychotic. If there is another unsatisfactory response, and at least one of the first two trials was with risperidone, olanzapine, or a first-generation antipsychotic (FGA), then clozapine is recommended for the third trial. If neither trial was with one of these three possibly slightly more effective antipsychotics, a third trial prior to clozapine should occur, using one of these options. If there is an unsatisfactory response to monotherapy with clozapine (with dose adjusted using plasma levels), consider adding risperidone, lamotrigine, or electroconvulsive therapy. If one of these augmentations is unsuccessful, possible options are to try another, try adding memantine or omega-3 fatty acid to clozapine, switch from clozapine to another antipsychotic not yet tried (especially aripiprazole), combine an FGA with mirtazapine, or combine risperidone with celscoxb. Finally, combinations of antipsychotics not including clozapine may be tried.

Conclusion: Though all recent major guidelines for the pharmacotherapy of schizophrenia propose that two monotherapy antipsychotic trials should occur followed by a trial of clozapine, there is variation in the manner in which clinicians are encouraged to accomplish these steps. The authors argue that the above is an evidence-supported approach.

Policy of full disclosure: Osser – no financial conflict of interest Jalali-Roudsari – no financial conflict of interest Manschreck – received research support from Pfizer in the past year.
A. Pereira, Y. Zhou, H. Raaijmakers, S. Sundram. 

Objective: Treatment of the positive psychotic symptoms of schizophrenia with standard antipsychotic drugs (APDs) is ineffective in about one third of cases. For these treatment-resistant patients the alternative is the ADP clozapine which is superior to other agents but carries serious side-effects. Why clozapine is uniquely effective is unknown, but may involve G-protein coupled receptor (GPCR) and epidermal growth factor (EGF) receptor (Erbb1) transactivation signaling to the MAPK-ERK cascade. This was based upon clozapine-induced initial down-regulation and delayed Erbb1 mediated activation of the cortical and striatal Erk response in vivo distinct from other APDs. The GPCR to which clozapine binds to induce EGF receptor (EGFR) phosphorylation is unidentified and thus we examined the dopamine D1 receptor (D1R) as a candidate given its association with dopaminergic transmission in the prefrontal cortex and regulation of locomotion and cognitive function.

Methods: The effects of the selective D1R agonist SKF38393, antagonist SCH23390 and EGFR inhibitor, AG1478 on clozapine-mediated EGFR-ERK phosphorylation in CHO-K1 cells stably expressing the EGFR and transiently transfected with the D1R were examined. A 10 nM GPCR antagonist (GPRCI) was included to assess GPCR involvement.

Results: Clozapine induced significant inhibition of ERK1/2 phosphorylation within 10 minutes of exposure to CHO-K1-EGFR D1R transfected cells, followed by a delayed maximal increase in ERK phosphorylation at 90 minutes which normalized by 120 minutes, a profile similar to that described in cortical neuronal cells. SKF38393 caused reversal of clozapine-induced ERK1/2 inhibition at 10 minutes; SCH23390 plus clozapine elevated ERK1/2 phosphorylation above clozapine treatment alone at 90 minutes while AG1478 dose-dependently inhibited clozapine-mediated ERK1/2 phosphorylation seen at 90 minutes. Parallel detection of EGFR (Tyr1068) phosphorylation indicated a time disconnect with ERK phosphorylation.

Conclusion: These data highlight complexity in the clozapine-induced D1R-EGFR transactivation mechanism that initiates downstream ERK effects and advocate disturbed D1R-EGF system signaling in refractory schizophrenia.


Objective: Schizophrenia is associated with deficits in higher order processing of visual information, steady state visual evoked potential responses recorded over the occipital cortex in patients with schizophrenia suggest a dysfunction of lower level visual pathways, which was more prominent for magnocellular than parvocellular biased stimuli. The magnocellular pathway helps in orienting towards salient stimuli. A magnocellular pathway deficit could contribute to higher level visual cognitive deficits in schizophrenia dysfunctions of the magnocellular pathway may also account for other well described aspects of neurophysiological dysfunction in schizophrenia, for example, the magnocellular pathway projects predominantly to dorsal cortical stream (i.e. parietal lobe), which codes motion perception and spatial localization. Our work aims at assessing the magnocellular pathway by VEP.

Methods: 30 schizophrenic patients were recruited randomly from Alexandria University Hospital. They scored 4 or higher on the Clinical Global Impression Scale for Severity CGI-S. Visual Evoked Potential VEP was done to them and compared to healthy control group.

Results: In the right eye the mean P100 was 104.5±5.62 and 95.85±8.10 microvoltage in schizophrenic and healthy control group respectively with statistically significant difference. A finding that has been replicated in the left eye where the mean P100 was 105.8±5.41 and 95.85±5.4 microvoltage in the same respective groups.

Conclusion: P100 in both right and left eyes are more prolonged in schizophrenic patients compared to healthy control groups.


Objective: Repetitive transcranial magnetic stimulation represents a promising therapeutic method for influencing negative symptoms of schizophrenia, thanks to its unique ability to modulate the neuronal activity of the cortical cerebral areas and neuronal spheres that are included in the pathophysiology of schizophrenia.

Methods: The Aim of Study to find out whether, under conditions of a double-blind, placebo coil controlled study, high frequency rTMS over the left DLPFC area, on working memory parameters and the respective changes of neuronal activation detected by fMRI was found. (2) rTMS seems to be a very well tolerated neurostimulation method for treatment of negative schizophrenia symptoms from the point of view of the effect on cognitive functions.


Objective: Does repetitive transcranial magnetic stimulation have a positive effect on working memory and neuronal activation in treatment of negative symptoms of schizophrenia?

Methods: Repetitive transcranial magnetic stimulation represents a promising therapeutic method for influencing negative symptoms of schizophrenia, thanks to its unique ability to modulate the neuronal activity of the cortical cerebral areas and neuronal spheres that are included in the pathophysiology of schizophrenia.

Methods: The Aim of Study to find out whether, under conditions of a double-blind, placebo coil controlled study, high frequency rTMS over the left DLPFC area, on working memory parameters and the respective changes of neuronal activation detected by fMRI was found. (2) rTMS seems to be a very well tolerated neurostimulation method for treatment of negative schizophrenia symptoms from the point of view of the effect on cognitive functions.

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Objective: To assess daytime cognitive performance and overall sedation in patients receiving quetiapine extended release (XER) versus quetiapine immediate release (IR).

Methods: Phase IV prospective, double-blind, crossover study (NCT01213836). Patients with stable schizophrenia were treated with XER or IR before enrolment. Study design comprised 2 stages; Periods 1 and 2 (10–18 days each). Patients were randomized to 2 groups: XER once-daily evening dose (Period 1), followed by IR dosed twice-daily (Period 2); IR twice-daily (Period 1), followed by XR once-daily evening dose (Period 2). Doses corresponded to quetiapine dose before enrolment (400–750 mg). Assessments from 3 post-dose visits (≥5 days following treatment in each Period), were analysed according to quetiapine formulation received. Daytime cognitive performance was measured by standardized Attentional Composite score, combining Detection and Identification domains of the CogState Battery Task. Sedation was assessed with the 0–100-point Bond-Lader VAS and 1–7-point Stanford Sleepiness Scale.

Results: 65 patients were randomised (69.2 % male; mean age 38.6 years); 51 included in per protocol analysis. Averaged across the real rTMS caused a statistically significantly higher reduction of severity of the negative, affective and total symptoms of schizophrenia. On the contrary, no difference was found with respect to the positive and common symptoms of schizophrenia.

Conclusion: (1) No positive impact of high frequency rTMS, administered over the left DLPFC area, on working memory parameters and the respective changes of neuronal activation detected by fMRI was found. (2) rTMS seems to be a very well tolerated neurostimulation method for treatment of negative schizophrenia symptoms from the point of view of the effect on cognitive functions.

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3 post-dose assessments, adjusted mean difference in Attentional Composite score in XR and IR patients was 0.005 (p=0.907). Patients receiving XR were more alert than those receiving IR, (Bond-Lader VAS score, mean [SD]: 23.5 [19.0] vs. 28.6 [21.4];) estimated overall treatment difference: 5.2 [95% CI: 2.3; 8.2] (p = 0.0009). Patients receiving XR also reported feeling less sedated than those on IR (Stanford Sleepiness Scale, mean [SD]: 2.4 [0.9] vs. 2.6 [1.0]); estimated overall treatment difference: 0.28 [95% CI: 0.12; 0.43] (p<0.0008).

Conclusion: Daytime cognitive performance was similar for the quetiapine IR and XR treatment groups. XR was associated with less daytime sedation than IR at approved doses for this indication.

Policy of full disclosure: M. Riedel has received research grants/ support or has served as a consultant for AstraZeneca, Pfizer, Otsuka Pharma, Jansen-Cilag. In the context of investigator initiated trials M. Riedel has received support from AstraZeneca and Pfizer.

P-08-072 Is it possible to improve the prediction of the psychotic chronic patients? An extension study after 60 months

Objective: To evaluate the clinical and functional progression of patients that have been treated with conventional antipsychotic medication in a previous comparative study vs. Risperidone Long Acting Inyectable(RLAI), accepted RLAI as a treatment choice for their illness.

Methods: We conducted the study with an initial sample consisting of 26 schizophrenic patients, treated with conventional antipsychotic treatment in the previous main study, and 14 of them voluntarily accepted the change to RLAI treatment. During a period of 12 months, follow-up visits were performed at 3, 6 and 12 months for all patients included in both treatment groups. The following scales and questionnaires were used for assessment and measurement : Global Illness Severity (Global Clinical Impression GCI), Treatment Satisfaction Scale, Insight (G12 PANSS), Remission Criteria (Andreassen Criteria), Quality of Life Scale, Compliance (PROMIS), Social Performance Scale (PSP). Global Activity Evaluation Scale (GAES). Personal and Social Performance (PSP). Also the following information was collected : hospitalization rates, treatment discontinuation and concomitant antipsychotic.

Results: We found statistical differences among patients treated with long acting atypical and typical antipsychotic. The RLAI group showed significantly higher remission rates and treatment satisfaction scores. Also an improvement in patient Insight, GCI, GAES, PSP and an increase of patients treated with antipsychotic monotherapy was observed. Regarding hospitalization and treatment discontinuation rates, no statistical differences were found in both groups at baseline and at endpoint.

Conclusion: Clinical and functional improvements observed following treatment with RLAI for one year in patients previously treated with conventional antipsychotic treatment, were similar to those showed in the main study, which this study is its extension.

P-08-073 Physical condition, functionality and cognition in patients with schizophrenia
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Objective: To evaluate the association between physical condition, mental cognition and functionality in patients with schizophrenia.

Methods: We conducted a epidemiological, retrospective and transversal study including a total sample of 90 patients diagnosed with schizophrenia, according to CIE 10. Patients were divided into 2 groups regarding the antipsychotic treatment received: conventional (typical) or atypical ones. Physical condition was assessed by evaluating the anthropometric, biochemical and clinical parameters and also by the analysis of the presence of metabolic syndrome (defined according to WHO) and cardiovascular risk (as determined by Framingham and waist/triglycerides scores). Cognitive impairment was assessed by the Screen for Cognitive Impairment Scale in Psychosis (SCIP) and functionality was evaluated with the Personal and Social Performance Scale (PSP). Clinical data also included years in the disease evolution and number of hospital admissions in the previous year.

Results: The following significant correlations were observed, all of them measured by the Pearson correlation coefficient: Inverse correlations: PSP endpoint score and SCIP total score, p<0.05. PSP endpoint score and number of hospital admissions, p<0.01. Direct correlation: SCIP total score and number of hospital admissions, p<0.05. Cardiovascular risk (Framingham) and disease progression years, p<0.05. The group of patients treated with atypical antipsychotics have better functionality, less deterioration cognitive and lower cardiovascular risk when compared to those patients treated with typical antipsychotics.

Conclusion: Lower functionality has been observed in patients with greater cognitive impairment and it is related to increased cognitive impairment, cardiovascular risk and number of hospital admissions. The group of patients treated with atypical antipsychotics demonstrated better functionality, less deterioration cognitive and lower cardiovascular risk when compared to those patients treated with typical antipsychotics.

P-08-074 Clinical outcome in outpatients with schizophrenia who switched their antipsychotic treatment due to suboptimal efficacy: Results from the ETOS study
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Objective: Schizophrenia is a chronic, severely disabling illness associated with poor treatment adherence and frequent treatment modifications. The ETOS study aimed to identify the reasons and evaluate the outcome of switching antipsychotic treatment in outpatients with schizophrenia.

Methods: ETOS was an observational 18-week study in outpatients, diagnosed with schizophrenia according to DSM-IV, who were initiated on a new antipsychotic monotherapy within the previous two weeks. A total of 574 patients were enrolled. Ethical approval was obtained prior to study initiation (NCT00999865).

Results: The final analysis included 568 patients, 53% male and 47% female and mean disease duration of 11.7 (± 12.3) years. In total 249 patients (43.8%) switched due to lack of efficacy and 50 patients (8.8%) switched due to the lack of both tolerability and efficacy. Patients who switched due to lack of efficacy were mainly (>10%) switched from aripiprazole (22.1%), risperidone (21.3%), olanzapine (16.5%) and ziprasidone (12.9%). PANSS and CGI-S scores at baseline were 92.9 (± 28.2) and 4.1 (±1.1) respectively. Following treatment switch, 86.9% of patients who switched due to efficacy reasons experienced meaningful clinical benefit by achieving a CGI-CB score of ≤ 4 at final visit [clinical benefit in all patients was 87.9% (n = 499)]. Total PANSS, CGI-I and CGI-S scores were significantly improved by the end of study, showing a mean decrease of 31.69, 0.70 and 1.14 respectively (all p < 0.0001). BARS was also significantly improved by the end of the study with a mean change of 9.73 (p = 0.0001).

Conclusion: Antipsychotic monotherapy switch due to lack of efficacy was shown to be beneficial in outpatients with schizophrenia, associated with significantly improved clinical benefit and significant increase of patients’ adherence to treatment in daily clinical practice.

Policy of full disclosure: Andreas Roussidis is an employee of AstraZeneca Hellas. This study was funded from AZ Hellas.
**P-08-075** Reasons for switching antipsychotic treatment in outpatients with schizophrenia: Results from the ETOS study with focus on tolerability

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**Objective:** The ETOS study aimed to identify the reasons and evaluate the outcome of switching antipsychotic treatment in outpatients with schizophrenia.

**Methods:** ETOS was an observational 18-week study in outpatients, diagnosed with schizophrenia according to DSM-IV, who were initiated on a new antipsychotic monotherapy within the preceding two weeks. A total of 974 patients were recruited. Ethical approval was obtained prior to study initiation (NCT00999895).

**Results:** The final analysis included 568 patients. 53% of participants were male and 47% female. The main reason for switching antipsychotic treatment was lack of tolerability (n = 369, 65.0%), followed by lack of efficacy (n = 249, 43.8%), while 8.8% of patients switched due to lack of both tolerability and efficacy. The main tolerability reasons (>5%) in descending order of prevalence were weight gain (40.4%), extrapyramidal symptoms (30.1%), lack of tolerance (11.4%), hyperprolactinemia (10.6%), hyperlipidemia and/or hyperglycemia (6.5%). Patients who changed treatment for tolerability reasons (n = 369) were mainly (>10%) switched from olanzapine (37.4%) and risperidone (24.7%). Of those patients switching due to lack of tolerability, 58.5% were switched to quetiapine/quetiapine XR, 10.8% to aripiprazole, 9.8% to olanzapine, 6.2% to paliperidone, 5.4% to ziprasidone, followed by other antipsychotics (<5%). A CGI-CB score of ≤4 was achieved by 89.0% of patients switching due to tolerability reasons. In patients switching due to weight gain (n = 149), extrapyramidal symptoms (n = 111) or hyperprolactinemia (n = 39), weight, SAS scores and prolactin levels were significantly decreased by 6.85 kg, 11.30 and 62.30 ng/ml respectively (all p < 0.0001).

**Conclusion:** The ETOS study identified lack of tolerability to be the main reason for switching antipsychotic treatment in outpatients with schizophrenia. Switching to antipsychotic monotherapy was accompanied by significantly improved tolerability for specific measures in daily clinical practice.

**Policy of full disclosure:** This study was funded from AstraZeneca Hellas. Andreas Roussidis is an employee of AZ Hellas.

**P-08-076** Effect of aripiprazole, risperidone and olanzapine, on the acoustic startle response in recent episodes of schizophrenia

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**Objective:** Studies have also shown that differences in the kind of the antipsychotics influence disruption of the sensorimotor gating system, including prepulse inhibition of the startle reflex (PPI). Atypical antipsychotics improve PPI more than typical, but little is known about the effects of aripiprazole on PPI. Aripiprazole, an atypical antipsychotic drug, is a D2 dopamine–receptor partial agonist, but also has affinity to several serotonin receptors (5-HT1A,2A,2C,7). We hypothesized that patients taking aripiprazole would show greater improvement in PPI than those patients with risperidone or olanzapine.

**Methods:** In the present study we investigated the influence on startle response in recent episodes of schizophrenia in 15 patients taking aripiprazole, 15 taking risperidone and 14 patients with olanzapine. Participants were on maintenance therapy with only one antipsychotic drug for 12 weeks. The startle measures used were prepulse inhibition percentages at 30, 60 and 120 milliseconds ( % PPI, % PPI-60 and % PPI-120 respectively), and PPI habituation.

**Results:** Aripiprazole improved PPI more than risperidone and than olanzapine at 30 and 60 milliseconds but not at 120 (p < 0.01). Risperidone improved %PPI-60 more than olanzapine (p < 0.01).

**Conclusion:** Aripiprazole, in subjects with recent episodes of schizophrenia improved PPI disruption more than risperidone and olanzapine at early attentional stages. These data suggest the role of the D2 Dopamine –receptor partial antagonist on sensorimotor gating system of patients with schizophrenia.

**P-08-077** First-episode psychosis: Factors influencing relapse over 1-year follow-up

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**Objective:** Describe which variables are related with relapse in patients diagnosed of first-episode psychosis over one-year follow-up.

**Methods:** Consecutive 129 first-episode patients treated in Institut de Neuropsiquiatria i Addicions from Barcelona from 2007 to 2011 were evaluated over 1-year follow up. We assessed sociodemographic and clinical variables, including cannabis use, duration of untreated psychosis (DUP), relapses, and several scales (PANSS, SUMD, GAF), at different timepoints: baseline, 1-month, 6-months and 1-year follow-up. We performed a multiple regression analysis. Number of relapses was the dependent variable, and DUP, gender, age, cannabis use over follow-up, PANSS positive and negative subscale, GAF, and SUMD at one-month follow-up were the independent variables.

**Results:** Gender (p = 0.014), PANSS positive symptoms at 1-month follow-up (p = 0.027), and cannabis use (p = 0.001), are associated with relapse in our sample.

**Conclusion:** Male gender, persistent positive symptoms at one-month follow-up and cannabis use, may predict independently relapse in first-episode psychosis.

**P-08-078** Dopamine D2 receptor occupancy and cognition in schizophrenia: Analysis of the CATIE data

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**Objective:** Antipsychotic drugs exert antipsychotic effects by blocking dopamine D2 receptors in the treatment of schizophrenia. However, effects of D2 receptor blockade on neurocognitive function still remain to be elucidated. The objective of this analysis was to evaluate impacts of estimated dopamine D2 receptor occupancy with antipsychotic drugs on several domains of neurocognitive function in patients with schizophrenia in the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) trial.

**Methods:** The dataset from the CATIE trial was used in the present analysis. Data were extracted from 410 subjects who were treated with risperidone, olanzapine, or ziprasidone, received assessments for neurocognitive functions (verbal memory, vigilance, processing speed, reasoning, and working memory) and psychopathology, and provided plasma samples for the measurement of plasma antipsychotic concentrations. D2 receptor occupancy levels on the day of neurocognitive assessment were estimated from plasma antipsychotic concentrations, using population pharmacokinetic analysis and our recently developed model. A multivariate general linear model was used to examine effects of clinical and demographic characteristics, including estimated D2 occupancy levels, on neurocognitive functions.

**Results:** D2 occupancy levels showed significant associations with the vigilance and the summary scores. Neurocognitive functions, including vigilance, were especially impaired in subjects who showed D2 receptor occupancy level of > 77%.

**Conclusion:** These findings suggest a non-linear relationship between prescribed antipsychotic doses and overall neurocognitive function and vigilance, which has an important clinical implication and may endorse the upper limit of the established antipsychotic therapeutic window of D2 occupancy (i.e., 80%) from the standpoint of neurocognition as well.

**Policy of full disclosure:** Dr. Bies has received NIH, CAMH, Lily and Indiana University based grant funding. Dr. Stroup has received grants from NIMH and the Foundation for the National Institutes of Health. He has received consulting income from Janssen and Lilly.
P-08-080 | NMDAR-mediated dysfunctional connectivity predicts cognitive impairments

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Objective: Disordered brain connectivity is a central pathophysiological hallmark of schizophrenia. The key mechanism for disconnection is thought to be disrupted N-methyl-D-aspartate receptor (NMDAR)-mediated synaptic plasticity. However, no study has yet experimentally investigated the contribution of NMDAR-mediated synaptic plasticity to psychotic symptom formation. The mismatch negativity (MMN) is an event-related potential (ERP) and has recently been interpreted as a prediction error (PE) signal during perceptual learning and has been shown to depend critically on NMDAR-mediated synaptic plasticity. Specifically, the NMDAR antagonist S-ketamine, which induces schizophrenia-like symptoms, reduces the MMN in healthy subjects comparable to those observed in schizophrenia. The key mechanism for dysconnectivity is thought to be disrupted N-methyl-D-aspartate receptor mediated effects on synaptic plasticity thus connects pharmacological, physiological and computational approaches in relation to the formation of the MMN. The key mechanism for dysconnectivity is thought to be disrupted N-methyl-D-aspartate receptor mediated effects on synaptic plasticity thus connects pharmacological, physiological and computational approaches in relation to the formation of the MMN.

Methods: We combined conventional statistical parametric mapping (SPM) with DCM modeling of ERP data to investigate effective connectivity within the MMN network in order to examine whether the known reduction of MMN under S-ketamine can be explained by changes in the plasticity of glutamatergic long-range connections among hierarchically related auditory areas, and if so, where these changes would be expressed.

Results: DCM analyses revealed that S-ketamine significantly perturbed bottom-up effective connectivity, the extent of which predicted significant S-ketamine-induced cognitive impairments.

Conclusion: Based on empirical data, we have described for the first time a pathophysiological mechanism underlying dysfunctional connectivity, which gives rise to specific symptom formation, namely to cognitive impairments. Our model-based characterization of NMDAR-mediated effects on synaptic plasticity thus connects pharmacological, physiological and computational approaches in relation to the formation of a specific psychotic symptom, suggesting high relevance for pathophysiological theories of schizophrenia.

P-08-08 | Patient-reported outcomes (PROs) with aripiprazole intramuscular depot (ARI-IMD) for maintenance treatment in schizophrenia


Objective: To characterise the adherence profile of ARI-IMD by examining PROs from long-term treatment.

Methods: Subjects were cross-titrated to oral aripiprazole (10–30 mg/day) during a 4–6-week oral conversion phase (Phase 1). Phase 2 was a 4–12-week oral aripiprazole stabilisation phase. Subjects meeting stability criteria (4 weeks) entered an IMD stabilisation phase (400 mg/injection) with co-administration of oral aripiprazole the first 2 weeks (Phase 3). Subjects meeting stability criteria (12 weeks) were randomised (2:1) to ARI-IMD or placebo (52-week: Phase 4). Mean changes in PROs were assessed from baseline to last visit in Phases 2-4 using the DAI, MAQ and PSMQ modified.

Results: 710 subjects entered Phase 2 (633 were titrated to oral aripiprazole in Phase 1); 576 Phase 3 and 403 Phase 4. The study stopped early because efficacy was demonstrated by pre-planned interim analysis. Between Phases 2–4, mean DAI scores remained similar (Phase 2: 21.5; Phase 3: 21.4; Phase 4: 21.1 ARI-IMD-depot vs. 22.2 placebo) indicating adherence to medication. Mean MAQ scores 0–1 indicated high adherence behaviour. PSMQ scale scores at last visit showed subjects had high levels of treatment satisfaction (Phase 3: 92.8%; Phase 4: 92.7%; Phase 4: 92.7%; Placebo: 85.7%). There were a sustained percentage of subjects reporting less to no side-effects at last visit (Phase 3: 86.9%; Phase 4 ARI-IMD : 88.9%; Phase 4 placebo: 89.0%).

Conclusion: ARI-IMD offers a new treatment option for the long-term management of schizophrenia with the potential to improve adherence to medication resulting from improved PROs and medication satisfaction.

Policy of full disclosure: John M. Kane has received honoraria for lectures and/or consulting from Alkermes, Amgen, BMS, Cephalon, Eisai, Boehringer Ingelheim, Eli Lilly, Intracelular Therapeutics, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, Sunovion and Targacept. He is a shareholder of MedAvante. Dr. Fleischhacker has received research grants from Alkermes, Janssen Citag, Eli Lilly, BMS/Otsuka and Pfizer. He has received honoraria for educational programs from Janssen, Pfizer and AstraZeneca, speaking fees from AstraZeneca, Pfizer, Janssen Citag and Roche. Dr. Suzuki has received grants and/or consultant fees from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Kansai Pharmaceutical, Otsuka Pharmaceutical, Pfizer, and speaker’s honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Kansai Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 5 years. Dr. Uchida has received grants from Pfizer, speaker’s honoraria from Eisai, Astellas Pharma, GlaxoSmithKline and Meiji, and received speaker’s honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Kansai Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 5 years. Dr. Pollock has served one time as a consultant for Wyeth (October 2008) and Takeda (July 2007). He was also a faculty member of the Lundbeck International Neuroscience Foundation (LINF) (final meeting was April 2010). Dr. Watanabe has received grants, or consultant fees from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, and Pfizer, and received speaker’s honoraria from Janssen Citag, Eli Lilly, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 5 years. Dr. Mimura has received grants, or consultant fees from Eisai, Astellas Pharma, GlaxoSmithKline and Meiji, and received speaker’s honoraria from Astellas Pharma, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Kansai Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 5 years. Dr. Mamo has received investigator-initiated grant support from Pfizer within the past 5 years. Dr. Suzuki has received grants and/or consultant fees from Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, and Pfizer, and received speaker’s honoraria from Janssen Citag, Eli Lilly, Dainippon Sumitomo Pharma, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Meiji, Otsuka Pharmaceutical, Pfizer, and Yoshitomi Yakuhin within the past 5 years.
Central interleukin-6 activation in patients with chronic schizophrenia

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Objective: Accumulating studies during the last decade indicate that schizophrenia is associated with immunological processes in the brain. For this reason, studies have been directed towards cytokines, proteins that directly initiate and control immunological responses. One of the most frequently reported cytokine in schizophrenia is interleukin (IL)-6, a cytokine involved in brain development, synaptic plasticity and behavior. The purpose of the present study is to analyze cytokine concentration in the cerebrospinal fluid (CSF) from well-characterized patients with respect to antipsychotic treatment and symptoms.

Methods: CSF cytokine concentrations were analyzed by an electrolychemiluminescence biosensor assay (Meso Scale Discovery, Gaithersburg, MD, USA). Patients were stable, chronically outpatients with schizophrenia (23 males and 14 females). Diagnosis was confirmed by clinical interviews by an experienced psychiatrist and the severity of symptoms was rated with Brief Psychiatric Rating scale (BPRS) and global assessment of functioning (GAF). All patients were medicated with olanzapine for at least one month before lumbar puncture. CSF concentrations of IL-6 from patients were compared with those of 37 healthy age matched volunteers (23 males and 14 females).

Results: Our results show that patients with schizophrenia display significant increased levels of IL-6 in CSF (3.2 ± 0.4 pg/ml) compared with healthy volunteers (1.8 ± 0.2 pg/ml). No correlation between IL-6 and symptoms rated with BPRS or GAF were found. Further, treatment with olanzapine did not influence IL-6 concentrations as no correlation between IL-6 and treatment with respect to prescribed dose, time of treatment or concentration of olanzapine in CSF were found.

Conclusion: Present data confirm that IL-6 is increased in the brain of chronic patients with schizophrenia and strengthen the idea that the disease is associated with brain immune activation. Cytokines, in particular IL-6 may hence serve as biomarkers of chronic schizophrenia.

The enhancing properties of modafinil in schizophrenia and early psychosis

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Objective: Modafinil is a central nervous system compound that has vigilance promoting properties as well as beneficial effects on cognitive and emotional functions in the healthy and diseased population. Our group showed that modafinil improved working memory, planning abilities, cognitive flexibility and emotional recognition in chronic schizophrenia and first episode psychosis. It is still unclear how modafinil affects these functions. We aimed at reviewing the literature that tested the neuropathways of modafinil in different areas of the brain. We also targeted the cognitive and emotional effects of modafinil in all the studies that tested the compound in patients with schizophrenia.

Methods: Two systematic reviews were carried out. One reviewed the neuropathways taken by modafinil and categorised studies according to the animal models used, the neurotransmitter systems and the brain regions activated by the compound. The other was a Cochrane review protocol that aims at meta-analysing the effects of modafinil in schizophrenia.

Results: Preliminary results from these two reviews show that modafinil acts mainly by inhibiting the GABAergic system, where as it activates the glutamatergic, dopaminergic, noradrenergic and serotonergic systems. These patterns of action have been shown particularly in the prefrontal cortex, hippocampus, hypothalamus, thalamus, striatum and substantia nigra both in animals and humans. These neuropharmacological effects of modafinil induce improvements in working memory, fluency, cognitive flexibility and problem solving in patients with schizophrenia.

Conclusion: These original findings allow us to better understand the neuromechanisms of modafinil and although the interaction between modafinil and antipsychotics – the most commonly prescribed medication in psychosis – has yet to be tested, results from these two reviews suggest that modafinil may be an adequate adjuvant treatment for psychosis. It may help patients cope with their cognitive impairments and improve their functional outcomes and quality of life.
Conclusion: The neurocognitive training showed itself as an effective method of correcting neurocognitive deficits. Using drugs with serotoninergic mechanism showed significant improvement in neurocognitive profile of schizophrenia patients. Serdolect showed statistically significant improvement in the basic neurocognitive parameters in comparison with Fevarin.

P-08-085 Service delivery improvement project for clozapine monitoring in assertive outreach team

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Objective: Clozapine plasma levels are broadly related to daily dosing. Despite different estimates of response thresholds, plasma levels can be useful in optimizing treatment. It has been observed that there needs to be a high quality service system, to aid the effective monitoring of the Clozapine levels in the Assertive Outreach Team, Halifax. Objectives: (1) To develop additional indications for Clozapine level monitoring in the Southwest Yorkshire Partnership Foundation Trust Policy (2007). (2) To develop Clozapine monitoring from the date of first initiation of Clozapine medication.

Methods: Clozapine monitoring form has been designed. Clozapine levels collected from the clinical notes/Kings pathology online system. Communication made with pharmacists of the Southwest Yorkshire Partnership Foundation Trust and Clozapine monitoring Policy discussed in Drug and Therapeutics Sub Committee Meeting in July 2011.

Results: The Policy now includes additional indications for clozapine level monitoring: "To monitor concordance with treatment particularly if there is a history of non-concordance with medication, which is linked with previous or likely hospital admission. Adherence can be measured over time with serial Clozapine assays, particularly when adherence is a critical part of the care plan, for example for maintenance of mental health that is essential for the patient's safety, adherence to a Community Treatment Order or other Section of the Mental Health Act 1983 (Amended 2007)". Clozapine monitoring form is designed and is available to the AOT.

Conclusion: The current system would help in a longitudinal analysis of the variation of levels with doses of Clozapine, also giving an opportunity to determine possible reasons for changes in clozapine levels. Clozapine levels can help monitor concordance with treatment for service users with a history of enduring mental illness and low compliance, including support with adherence to requirements for Community Treatment Orders. A Clinical Audit Project can be conducted in 1 year to make sure that the policy is being adhered to and Clozapine monitoring forms are being completed.

P-08-086 Effects of aripiprazole on autonomic nervous system activity in schizophrenia

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Objective: Schizophrenic patients have been reported to have an increased prevalence of cardiovascular diseases. Although treatment with second-generation antipsychotics (SGAs) have effects on positive and negative symptoms of schizophrenia, they also promote weight gain, may lead to metabolic syndrome that increases the risk of cardiovascular diseases. On the other hand, aripiprazole displays low affinity for H1-histaminergic, muscarinic, cholinergic, and adrenergic receptors. This profile is predictive of low propensity to weight-gain, metabolic disruption. We reported reduced autonomic nervous system (ANS) activity in schizophrenia. In the present study, we sought to replicate the reported positive association between low ANS activity and schizophrenia in a larger number of patients, and we...
investigated the influence of aripiprazole on ANS activity and compared with other antipsychotic drugs.

**Methods**: Subjects were 211 Japanese patients with schizophrenia and 44 healthy controls. All subjects received an explanation of our study and written informed consent was obtained. ANS activity was assessed by means of heart-rate variability power spectral analysis, which enables us to identify separate frequency components, i.e., total power (TP; overall ANS), low-frequency (LF: sympatho-vagal) power, and high-frequency (HF: vagal) power, during a resting condition. Statistical analyses were performed using t-tests to determine the presence of differences in the ANS activity.

**Results**: We found significantly lower ANS activity in schizophrenic patients than controls (TP; p < 0.001, LF; p < 0.001, HF; p < 0.001). Patients receiving amisulpride (n = 11) have higher ANS activity than the other patients (n = 196).

**Conclusion**: Our findings suggest that schizophrenic patients possess reduced ANS activity, which might be associated with increased cardiovascular mortality, and aripiprazole have less adverse effects on ANS activity compared with other antipsychotic drugs.

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**Prevalence of metabolic syndrome among schizophrenia patients treated with monotherapy atypical antipsychotics in Malaysia**

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**Objective**: The objective of this study was to determine the prevalence of metabolic syndrome (MetS), hypertension and diabetes mellitus (DM) among schizophrenia patients treated with monotherapy atypical antipsychotics.

**Methods**: The study was conducted at 4 mental institutions and 4 general hospitals in Malaysia. 527 patients were screened during study period and 485 patients fulfilled the DSM-IV criteria for schizophrenia. 325 schizophrenia patients agreed to be interviewed but only 274 consented for fasting blood investigations and metabolic syndrome profile. The definition of MetS was based on Modified National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III) with Asians values for waist circumference.

**Results**: Out of 325 patients, 186 patients (57.2%) received monotherapy atypical antipsychotics. 64/186 on risperidone, 61/186 patients were on olanzapine, 28/186 patients were on paliperidone, 14/186 were on clozapine, 8/186 on aripiprazole, 7/186 on quetiapine and 4/186 on amisulpride. The prevalence of hypertension and DM among schizophrenia patients after initiation of monotherapy antipsychotics was 5.7% (95% CI 1.9–15.4) and 5.7% (95% CI 1.9–15.4) in olanzapine, 7.5% (95% CI 3.0–17.9) and 5.3% (95% CI 1.9–15.4) in risperidone, 7.1% (95% CI 2.0–22.7) and 11.5% (95% CI 4.0–29.0) in paliperidone, 16.7% (95% CI 3.0–56.4) of DM in quetiapine and 14.3% (95% CI 2.6–51.3) of DM in aripiprazole. None of amisulpride patients developed hypertension and DM. 32.2% of overall patients had MetS. While 43.3% in clozapine, 66.7% in quetiapine, 53.8% in paliperidone, 52.8% in olanzapine, 43.4% in risperidone and 14.3% in aripiprazole developed MetS. None of patients on amisulpride has MetS.

**Conclusion**: The prevalence of MetS was high among schizophrenia patients treated with monotherapy atypical antipsychotics in Malaysia. Urgent measures are needed to address the issue.

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**Defining treatment-resistant schizophrenia and treatment response: A pragmatic proposal**

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**Objective**: To propose a pragmatic definition on treatment-resistant schizophrenia (TRS) and treatment response that was originated from a critical appraisal of the currently available evidence.

**Methods**: The authors previously presented comprehensive reviews on TRS and response status thereafter in TRS. They formed the basis of our proposal, with an updated literature search.

**Results**: Previous studies defined TRS with a failure to respond to adequate trials with antipsychotics. Treatment response has been defined mainly with improvements in the Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS). Other factors were somewhat variable, and the resultant response rates differed substantially across the TRS studies. Integrating past evidence and real-world feasibility, we propose that TRS be defined by at least two failed adequate trials with different antipsychotics (at chlorpromazine equivalent doses of ≥600 mg/day for ≥6 consecutive weeks) that could be retrospective or preferably include prospective failure to respond to ≥1 antipsychotic trials. In addition, our proposed criteria require both a score of ≥4 on the Clinical Global Impression (CGI)-Severity subscale and a score of ≤14 on the Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) or ≤30 on the Global Assessment of Functioning (GAF) scales to define TRS. Once TRS is established, we propose that subsequent treatment response be defined based on a CGI–Change score of ≤2, ≥20% decrease on the total PANSS or BPRS scores, and an increase of ≥20 points on the FACT-Sz or GAF.

**Conclusion**: Defining TRS, although challenging, is highly relevant given its personal and societal consequences and an agreement is desirable for the field. We propose an adoption of the CGI (global impression), PANSS/BPRS (classical psychopathology) and GAF/FACT-Sz (global functioning) for these purposes. These definitions should be further tested for reliability/validity and practicality.

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**Deficiency of schnurri-2, an MHC enhancer binding protein, induces mild chronic inflammation in the brain and confers molecular, neuronal, and behavioral phenotypes related to schizophrenia**

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**Objective**: Schnurri-2 (Shn-2), an NF-kB site-binding protein, tightly binds to the enhancers of major histocompatibility complex (MHC) class I genes and inflammatory cytokines, which have been shown to harbor common variant single nucleotide polymorphisms associated with schizophrenia. Although genes related to immunity are implicated in schizophrenia, there has been no study showing that their mutation or knockout results in schizophrenia.

**Methods**: As a course of our large scale screening to identify animal models of psychiatric disorders, Shn-2 KO mice were subjected to a comprehensive behavioral test battery.

**Results**: We showed that Shn-2 knockout mice have behavioral abnormalities that strongly resemble those of schizophrenics. The mutant brain demonstrated numerous schizophrenia-related phenotypes, including transcriptome/proteome changes remarkably similar to those of postmortem schizophrenia patients, decreased parvalbumin and GAD67 levels, increased theta power on electroencephalograms, and a thinner cortex. Dentine granule cell failures failed to mature in Shn-2 knockout mice, a previously proposed endophenotype of schizophrenia. Shn-2 mice also exhibited mild chronic inflammation of the brain.

**Conclusion**: These results suggest that genetically-induced changes in immune system may be a predisposing factor in schizophrenia.

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**Effects of chronic exposure of cariprazine on dopamine receptor subtypes**

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**Objective**: Cariprazine is a dopamine D3/D2 receptor partial agonist in development for the treatment of schizophrenia and...
bipolar mania. Long-term effects of cariprazine on expression of dopamine (DA) receptor subtypes in adult rat brain regions were quantified to determine regionally selective changes in tissue levels of DA receptors.

Methods: Rats (n = 8) received vehicle control (1 ml/kg, d) or cariprazine (0.06, 0.2, or 0.6 mg/kg) administered intra-peritoneally for 28 days. Brains were collected and dopamine receptor autoradiographic assays were performed on tissues from multiple regions. Mean values of nonspecific binding in each region were subtracted from the corresponding mean total binding to determine specific radioligand binding expressed as fmol bound/mg tissue; 2-way analysis of variance (ANOVA) analyzed overall changes across treatment and brain regions.

Results: Repeated treatment with cariprazine failed to alter levels of D1 or D2 receptors in all brain regions examined. Cariprazine 0.2 and 0.6 mg/kg dose-dependently increased D2 receptor concentrations in medial prefrontal cortex (27% and 43%, respectively), nucleus accumbens (40% and 45%), medial (41% and 53%) and lateral caudate putamen (52% and 65%): 0.06 mg/kg had no effect. Quantification of D3 receptors using [3H]-OH-DPAT showed that cariprazine 0.06, 0.2, and 0.6 mg/kg increased D3 receptor binding in olfactory tubercle (27%, 49%, and 67%) and Islands of Calleja (32%, 41%, and 57%); more increases in D3 receptor levels were also detected using the D3-prefering radioligand [3H]PHNO particularly in nucleus accumbens. Cariprazine (0.06, 0.2 and 0.6 mg/kg) increased D4 receptors in hippocampus (38%, 71%, and 98%).

Conclusion: Long-term administration of cariprazine induced regional and dose-dependent changes in DA receptor subtypes in different rat forebrain regions. Most changes were similar to other second generation antipsychotics; only cariprazine, and not any other antipsychotic agent, increased abundance of forebrain D3 receptors. These findings support the unique psychopharmacological properties of cariprazine.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc.
admission in 64.3%, and 89.8% showed thought disorder and only 54.8% perception disorder. 70.1% showed aggression, 25.2% were administered more than one antipsychotic at admission with 7.2% receiving long acting medications. After 3 weeks, 41.5% were on more than one antipsychotic. There was no statistically significant difference regarding the use of multiple drugs in patients with multiple admissions (over 5) compared to the rest of them.

Conclusion: Antipsychotic polypharmacy has been found to reduce the treatment compliance and to increase the relapses and the mortality compared to antipsychotic monotherapy, but it remains a usual practice which persists despite the doubtful clinical outcomes.

**P-08-094** The effect of antipsychotics on GABAergic interneurogenesis in adult brain

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Objective: Patients with schizophrenia display cognitive, behavioral disturbances and morphological abnormalities which might be caused by the progressive neurodegeneration. Although the mechanism of neurodegeneration in schizophrenia is still unclear, one of the current hypothesis is the relation to the altered GABA neurotransmitter system and density of GABA interneurons. In the previous study, we investigated the effect of recently developed atypical antipsychotics on the neural stem cell (NSC) function change especially focusing on the neuronal differentiation prepared from rat embryos. The atypical antipsychotics showed the suppressive effects on the non-competitive NMDA receptor antagonist MK-801-induced inhibition of NSC differentiation to neurons, indicating that atypical antipsychotic-induced alteration of neurogenesis could contribute to the neural network repair impaired in the schizophrenic brain.

Methods: In the present work, we examined the effect of atypical antipsychotics against MK-801/GABA antagonist-induced impairment of NSC differentiation to neurons those considered parallel observations in the pathophysiology of schizophrenia, using cultured adult hippocampal and subventricular zone (SVZ)-derived NSCs, and analyzed the suppressed effects on the GABAergic interneuron subtypes, such as somatostatin, parvalbumin, and calretinin.

Results: Several antipsychotics suppressed the MK-801/GABA antagonist-induced inhibition of neuronal differentiation of adult NSCs. Their promotions of each GABAergic subtype differentiation was different among tested antipsychotics.

Conclusion: The results suggested that the increase of adult interneurogenesis by antipsychotic might be involved in the mechanism of recovery of the neural network change in schizophrenia, and the different proportion of each antipsychotic-induced cell phenotype differentiation of NSCs might relate to its characteristic of clinical efficacy in the treatment of schizophrenia.

**P-08-095** Aminetpine treatment of chronic catatonia: A controlled study

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Objective: Data on the treatment response of catatonic phenomena accompanying chronic schizophrenia are limited. The objective of this study was to explore the therapeutic effects of add-on aminepine, a dopamine agonist antidepressant in chronic catatonic schizophrenia.

Methods: Fifteen subjects with DSM-IV schizophrenia with persistent catatonic features underwent a 15-week, double-blind, placebo-controlled cross-over trial; 6 weeks each for aminetpine and placebo with a 3-week wash-out period in-between. The primary outcome measure was the sum score of the Bush-Francis Catatonia Rating Scale. Changes in psychopathology and extrapyramidal side effects (EPS) constituted the secondary outcome measures.

Results: Aminetpine treatment augmentation treatment had no appreciable effect on catatonia ratings. Apart form a statistically significant but clinically negligible improvement of negative symptoms scores, there were no changes in the psychopathology and EPS ratings.

**P-08-096** Survey of prescription for 2nd generation antipsychotics in inpatients with schizophrenia in Japan: A nationwide multi-center survey on prescriptions in 2010

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Objective: Comprised mainly of pharmacists engaged in psychiatric care in adult hospitals, the Psychiatric Clinical Pharmacy Research Group (PCP Research Group) has been conducting nationwide studies on survey of prescription drugs on a continual basis since 2005, in order to understand the current state of pharmacotherapy in patients with schizophrenia. This article reports the study results of 2010 (n=25,346) from a view point of prescription 2nd generation antipsychotics (SGAs).

Methods: Among the schizophrenic patients (ICD-10: F20) hospitalized at one of the psychiatric clinics to which members of the PCP Research Group belonged, the names of drugs and doses were studied for the prescription given on the day of October in 2010, for the following types of drugs: antipsychotics, antiparkinsonians, anxiolytics/hypnotics, and mood stabilizers.

Results: The mean number and dose of drugs prescribed per day were 2.0 drugs at 802.8 mg/day (CP equivalents) for antipsychotics, 0.7 drugs and 1.9 mg/day (BP equivalents) for antiparkinsonians, and 1.3 drugs at 15.0 mg/day (DAP equivalents) for anxiolytics/hypnotics. The rates of prescriptions of SGAs were 58.2%, and that of SGAs were 84.0%, and the rates of monotherapy of each were 6.1% and 30.4%, respectively. The rates of concomitant therapy with SGAs were 57.3% for antiparkinsonians, 70.5% for anxiolytics/hypnotics, and 28.3% for mood stabilizers, respectively.

Conclusion: While the rates of prescription of SGAs have reached 84.0% of all prescriptions, the rates of monotherapy are limited in 30.4% and they are often used in combination with FGAs. It is suggested that pharmacists engaged in psychiatric care should actively conscientize themselves and control the rational use of SGAs by ensuring appropriate prescriptions in order to get maximum merits of SGAs, and hence improved adherence in patients.

**P-08-097** Pharmacological treatment of schizophrenia and schizoaffective disorder – focused on combinations of antipsychotics

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Objective: Acute treatment of schizophrenia and schizoaffective disorder is often carried out during hospitalization and its most important role is based on psychopharmacos, especially antipsychotics of the second generation. The most convenient is monotherapy but in clinical practice it is sometimes not possible.

Methods: The aim of our retrospective study was to focus on pharmacotherapy, especially combinations of antipsychotics, in our inpatients treated for schizophrenia or schizoaffective disorder during one-year period. Data were collected from medical records of inpatients treated for schizophrenia or schizoaffective disorder at the Department of Psychiatry in Brno, Czech Republic, during one-year period. We focused on therapy before patientdsicharge.

Results: During one-year period we treated 87 inpatients with schizophrenia (F20 according to ICD-10) and 35 inpatients with schizoaffective disorder (F25). One antipsychotic drug was used for
the treatment of 58.6% patients with schizophrenia and 74.29% patients with schizoaffective disorder. Two antipsychotic drugs were used in the treatment of 36.78% patients with schizophrenia and 17.14% with schizoaffective disorder. Three antipsychotic drugs were used in the treatment of 4.60% patients with schizophrenia and 2.86% with schizoaffective disorder. Remaining 57.1% patients with schizoaffective disorder were without antipsychotic medication, but no patient with schizophrenia. The most often combinations were: clozapine + amisulpride, clozapine + haloperidol and clozapine + aripiprazole. Mood stabilizers were used in 13.79% patients with schizophrenia and 17.14% with schizoaffective disorder. Three antipsychotic drugs were used in the treatment of 36.78% patients with schizophrenia and 17.14% patients with schizoaffective disorder.

Conclusion: In our retrospective study we found out, that most patients with schizophrenia and schizoaffective disorder are treated with one antipsychotic. Combinations were especially used in patients with treatment resistance, who are even resistant to monotherapy with clozapine. Just clozapine was very often combined with other antipsychotics, especially with amisulpride, haloperidol or aripiprazole.

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P-08-098 Cognitive effects of an anticholinergic challenge in healthy volunteers and drug-free patients with schizophrenia

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Objective: The importance of the cholinergic neurotransmission for cognitive processes is very well established. However, its role in the pathogenesis of schizophrenia is still not sufficiently explored. The purpose of this study was to investigate the effects of an anticholinergic challenge on cognition and attention in unmedicated patients with schizophrenia and healthy controls.

Methods: 12 medication-free patients with schizophrenia (29.3±8.8 years) and 12 healthy controls (29.8±9.6 years) were included. Psychopathology and cognitive performance were assessed twice: at baseline and after administration of a single dose of the subtype-nonselective acetylcholine receptor antagonist biperiden (5 mg intravenously). The following scales/tests were used: PANSS, Trail Making Test A and B (MTM-A/B), Regensburg Verbal Fluency Task (RVT), Digit Span from the Wechsler Memory Scale, Letter-Number Span, Digit-Symbol-Substitution Task and Continuous Performance Task-Identical Pairs version (CPT-IP).

Results: In almost all tests patients performed worse than controls in both conditions. Biperiden impaired the performance in the majority of the tests in both groups. Using a repeated measures ANOVA we found a statistically significant time*group interaction concerning the CPT-IP (p = 0.003), indicating a more pronounced impairment in patients than in controls. Analyzing the parameters verbal and spatial d-prime from the CPT-IP we found an effect that did not achieve statistical significance (p = 0.076 resp. p = 0.074). These results point to a slight improvement in attentional capacity in controls but not in patients. In the RWT the number of generated words after biperiden challenge increased in controls but not in patients (time*group interaction in phonemic category change: p = 0.016). The score increase showed a significant positive correlation with the observed increase in PANSS in controls (r = 0.688, p = 0.019).

Conclusion: Our results indicate a complex influence of anticholinergic intervention on different cognitive domains. The differences between controls and patients point to alternations in cholinergic systems in schizophrenia.

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P-08-099 Needs and QoL in schizophrenic hospitalized patients treated with risperidone or haloperidol

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Objective: Objective of this research is a discovery of the difference in most common needs and the QoL among patients of two groups of male paranoid schizophrenic hospitalized patients treated with risperidone or haloperidol.

Methods: Patients are classified in accordance with the diagnostic criteria of ICD X classification. First group of 20 patients was treated with risperidone in a dose of 2 mg to 6 mg. Second group of 20 patients was treated with haloperidol in a dose of 5 mg to 15 mg. Sample of paranoid schizophrenic patients were evaluated with the Camberwell Assessment of Need and the Lancashire Quality of Life Profile two months after admission to hospital treatment. Brief Psychiatric Rating Scale was used to assess the strength of psychopathological phenomena at the time of application of CAN and QLQOLP questionnaires. Research results obtained are processed using standard statistical methods.

Results: Patients treated with risperidone showed significantly higher subjective and objective quality of life in section of leisure & community participation and section of social relations. The same group of patients showed not significantly higher subjective quality of life in section of religion and section of family relations. Most often detected needs in the areas of accommodation, daytime activities, company, intimate relationships and sexual expression. Patients treated with haloperidol showed significantly higher mean number of unmet needs.

Conclusion: The results of this study indicate that risperidone may contribute to the socialization of male paranoid schizophrenic patients two months after admission to hospital treatment. Risperidone may also contribute to reducing unmet needs.

P-08-100 Daytime sleepiness and activity-rest rhythms in patients with schizophrenia during treatment with sedative and non-sedative antipsychotics

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Objective: Antipsychotics have variable effects on sleep and daytime sleepiness, sleep quality, and activity-rest rhythms in patients with schizophrenia during treatment with sedative and non-sedative anti-psychotics.

Methods: Hundred seventeen patients with paranoid schizophrenia (67 males, 50 females, mean age 27.4±6.9) were assessed with the use of the wrist actigraphy (Cambridge Neurotechnology AW4) throughout seven consecutive days. Daytime sleepiness was assessed with Epworth Sleepiness Scale (ESS), Athens insomnia scale (AIS), and sleep diaries were used for assessment of sleep quality. Analysis of variance (ANOVA) was used to test the differences between the patients and 40 healthy controls (HC) (20 males, 20 females, mean age 28.5±7.4) and between groups of patients with following monotherapy treatment options: aripiprazole n=13, olanzapine n=40, risperidone n=20, sertindole n=17. As the groups were not matched for gender the differences are reported separately for males and females.

Results: Male patients had longer time in bed (TIB) (p<0.001), longer total sleep time (TST) (p<0.001), lower average 24 h-activity (p<0.005) and lower daytime activity (p<0.05) than male HC. Female patients showed longer TIB (p<0.001), longer sleep latency (p<0.01), longer TST (p<0.001) lower 24 h-activity (p<0.001), and lower day-time activity (p<0.001) than female HC. Treatment with olanzapine and risperidone was related to longer TIB, longer TST, and higher sleep efficiency than treatment with aripiprazole and sertindole (p<0.05). The kind of antipsychotic treatment did not have significant
P-08-101 Valproic acid normalizes abnormal cellular proliferation, transcriptional changes and schizophrenia-related behaviors in Disc1 mutant mice

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Objective: Disrupted-In-Schizophrenia-1 (DISC1) is an established risk gene for schizophrenia. We sought to test potential preventative treatments in Disc1-L100P mutant mice, an animal model with schizophrenia-related behaviours.

Methods: We tested whether early valproate treatment would prevent behavioral abnormalities in Disc1-L100P mutants by counteracting aberrant expression of some genes, thereby normalizing brain development.

Results: Treatment with valproate before the onset of behavioral impairments in Disc1-L100P mutants corrected hyperactivity, and deficits in prepulse inhibition and latent inhibition. Disc1-L100P mutants also had increased glial cell proliferation in the subventricular zone, which was normalized by valproate pre-treatment. Genomic-wide transcription profiling showed that the Disc1-L100P mutation induced the largest changes in hippocampus, and some transcript changes were reversed by valproate.

Conclusion: Valproate treatment in adolescence may represent a type of preventative intervention for patients at risk for schizophrenia.

P-08-102 Association study of phencyclidine-responsive synapse-associated protein 97 (SAP97) gene in schizophrenia

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Objective: Disturbed neurotransmission via NMDA type glutamate receptor is thought to be involved in some molecular mechanisms of positive, negative and cognitive symptoms of schizophrenia. The synapse-associated protein 97 (SAP97) disc-like (DLG1) gene encodes the synaptic scaffolding PSD95 protein, which interacts with ionotropic glutamate receptors including the AMPA and NMDA receptors, and has been suggested to relate to the neural basis of the glutamate receptors-SAP97 protein signaling and/or the receptor trafficking might be involved in some of the etiology of schizophrenia and other psychoses.

Methods: We genotyped total 23 SNPs capturing the known common haplotype variations of the SAP97 gene in the samples from schizophrenic patients and healthy controls. The study was approved by the ethics committees of the institutes. All participants gave informed consent to participate in the study.

Results: In a single marker analysis, ten SNPs displayed nominally significant association with schizophrenia, although the p-values of these SNPs were not significant after the Bonferroni correction. We also compared haplotype estimates based on case-control genotypes and observed significant association of eight two- and three-SNP haplotypes with schizophrenia following permutation-based correction. Further examination of the above series of SNPs or haplotypes in each gender revealed significant associations between some of these SNPs or haplotypes and the disorder only in males.

Conclusion: The present findings suggest that the SAP97 gene may be a susceptibility factor in male schizophrenics. The modification of the glutamate receptors-SAP97 protein signaling and/or the receptor trafficking might be involved in some of the etiology of schizophrenia and other psychoses.

P-08-103 The satisfaction improved after switching to paripеридон ER mono-therapy among Japanese patients with schizophrenia

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Objective: Medication adherence is an important thing for continuation of schizophrenia medical treatment. The patient itself has satisfaction is important, in order to continue medical treatment and prevent a recurrence. The Paripеридон ER which put on the market in Japan in 2010 is expected stable blood concentration by OLOS system. This may affect to reduce the instability of symptoms or side effects, therefore may improve adherence. We investigated the patients' satisfaction by switching to Paripеридон ER mono therapy in Japanese patients with schizophrenia.

Methods: Design: A 24-weeks, open trial. This study approved by ethical committee in Fujita Health University. Setting: Inpatient (N=34) and outpatient (N=87) at eleven hospitals in Japan. Participants: Written informed consent patients with schizophrenia (N=121) age 20-78. Investigations: Switching to Paripеридон ER mono therapy and assessed GAF, CGI, side effects and satisfaction scale (POM) from patient and family in 0, 4, 12 and 24 weeks.

Results: Former antipsychotics were Risperidone (N=82), Olanzapine (N=11), Aripiprazole (N=9) and others (N=19). 109 patients completed 24 weeks. The median of CGI score changed from 4 to 3, the average GAF score changed from 42.7 to 59.9 and the median of patients' POM changed from "little well" to "well". And the EPS decreased among the study period.

Conclusion: We confirmed the Paripеридон ER mono therapy improved not only patients' symptoms but also satisfaction. This therapy expected to improve patients' QOL and reduce the distress among the life with schizophrenia.

Policy of full disclosure: Janssen Pharmaceutical K.K.

P-08-104 Cigarette smoking in male patients with chronic schizophrenia in a chinese population: Prevalence and relationship to clinical phenotypes

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Objective: A significantly high prevalence of smoking in schizophrenia may be linked to reduced clinical symptoms and side effects in subjects of European background. The aims of the present study were to examine the prevalence of smoking and its associations with clinical phenotypes in Chinese patients with schizophrenia, who were less well characterized than other populations.

Methods: The smoking prevalence and behaviors were evaluated by clinician-administered questionnaires and the Fagerstrom Test for Nicotine Dependence (FTND) in 776 male patients with schizophrenia and 560 control subjects. Patients also were rated on the Positive and Negative Symptom Scale (PANSS), the Simpson and Angus Extrapyramidal Symptom Rating Scale (SAES), and the Abnormal Involuntary Movement Scale (AIMS).

Results: Our results showed that compared to normal controls, patients had higher lifetime incidence of smoking (79% vs. 63%), and were more likely to be heavy smokers (61% vs. 31%), but had lower smoking cessation rates (4% vs. 9%) (all p < 0.001). In schizophrenia patients, the prevalence of smoking increased with age, with the particularly greater prevalence than controls in age cohorts of 55-75 years: 73% vs. 46% (p < 0.0001). Of the smokers with schizophrenia, 73% started to smoke an average of 7.6 years before the onset of their illness. Current smokers scored significantly lower on the PANSS negative symptom subscore (p < 0.005), and on the SAES symptom scale (p < 0.04; Bonferroni corrected p > 0.05), compared to non-smokers in patients.
P-09. Antidepressants

Conclusion: These results suggest that male schizophrenia patients of Chinese descent smoke more frequently than the general population. Further, smokers with schizophrenia may display fewer negative symptoms and, possibly less parkinsonism than non-smokers with schizophrenia.

P-08-105 Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls

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Objective: Studies suggest that the functional polymorphism of brain-derived neurotrophic factor gene (BDNF Val66Met) may mediate hippocampal-dependent cognitive functions. Few studies have reported its role in cognitive deficits in schizophrenia and whether peripheral BDNF levels may be useful to assess cognitive measures in schizophrenia.

Methods: Six hundred and fifty-seven schizophrenia inpatients and 445 healthy controls were included in this study. Performance on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), presence of the BDNF Val66Met polymorphism and serum BDNF levels were compared between groups. Patient psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS).

Results: Our results showed that visuospatial/constructional abilities significantly differed by genotype but not genotype x diagnosis, and the Val allele was associated with better visuospatial/constructional performance in both schizophrenia patients and healthy controls. On attention performance, there were significant genotype and genotype by diagnosis effects. Met allele-associated attention impairment was specific to schizophrenia patients but not healthy controls. In patient group, partial correlation analysis showed a significantly positive correlation between serum BDNF and the RBANS total score. Furthermore, BDNF levels x genotype interaction on RBANS total score was statistically significant.

Conclusion: Our findings demonstrate the association between the BDNF Met variant and poor visuospatial/constructional performance. Furthermore, the BDNF Met variant may be specific to attentional decrements in schizophrenic patients. The association between decreased BDNF serum levels and cognitive impairment in schizophrenia is dependent on the BDNF Val66Met polymorphism.

P-09. Antidepressants

P-09-001 Antidepressant-like activity of water-soluble curcumin formulations in behavioral paradigms of despair

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Objective: Curcumin is the active principle of Curcuma longa, one of the widely used components in traditional system of medicine in India. Despite its efficacy in experimental studies aiming neuronal disorders like depression, curcumin’s poor water solubility challenges its therapeutic formulations. This study investigates the antidepressant-like activity of novel water soluble curcumin formulations, dispersed in three different concentration levels. Further, the study comparatively evaluates St. John’s Wort (SJW), another herbal preparation.

Methods: These compounds were evaluated in the forced swimming test in mice and the corresponding changes in the neurotransmitter levels were measured.

Results: Three water soluble curcumin formulations, C-5, C-20, C-50 (50–200 mg/kg, p.o.) decreased the immobility period, increased serotonin and dopamine levels in the brain tissues. A sub-effective dose (50 mg/kg) of these formulations enhanced the antidepressant-like effect of various antidepressant drugs like desipramine (tricyclic antidepressant), fluoxetine (selective serotonin reuptake inhibitor (SSRI)) or venlafaxine (dual (5-HT and NE) reuptake inhibitor (SNRI)). However, no significant change in the anti-immobility effect with tranylcypromine (non-selective MAO inhibitor) was observed.

In addition, 25 mg/kg dose of SJW showed significant antidepressant-like effect in all the behavioral studies and also significantly increased brain neurotransmitter levels, especially that of serotonin.

Conclusion: The effects produced by C-5 were comparable with that of SJW and fluoxetine, respectively. Besides, in all these observations the water soluble formulation, C-5 showed significant antidepressant-like effect, including enhancement of neurotransmitter levels as compared to the similar dose of conventional curcumin preparation. Thus, this formulation may be a novel treatment option in the management of mental depression.

P-09-002 Transcriptional modulation of serotonin transporter as a new antidepressant strategy

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Objective: Identifying the factors contributing to the etiology of anxiety and depression is critical for the development of more efficacious therapies. Serotonin (5-HT) is linked to both disorders. Current antidepressants, which block the serotonin transporter (SERT), show limited efficacy and slow onset of action. Here, we used a small interference RNA (siRNA) strategy to examine the biochemical consequences of reducing SERT expression, as previously reported for 5-HT1A-autoreceptors.

Methods: Adult mice were locally infused with vehicle, nonsense-siRNA and SERT-siRNA into dorsal raphe nucleus (DR). The functional effects of SERT-siRNA knockdown were compared with those produced by chronic fluoxetine treatment.

Results: Local SERT-siRNA infusion for 4-days decreased SERT expression in the DR (40%). This was accompanied by a widespread reduction of SERT-binding sites throughout the brain. Moreover, a 4-day regimen with intra-DR SERT-siRNA modified brain variables considered to be key markers of antidepressant action, such as: (a) reduced expression and sensitivity of 5-HT1A-autoreceptors, (b) augmented extracellular 5-HT in DR-projecting areas such as striatum and hippocampus, (c) increased hippocampal neurogenesis, and (d) increased expression of plasticity-associated genes (BDNF, VEGF and ARC). In contrast, a 4-day regimen with fluoxetine did not alter any of these variables and only started to modify them after 15-day treatments.

Conclusion: These findings highlight the critical role of SERT in the control of serotonergic function, including neural plasticity. They also support the use of siRNA targeting serotonergic genes (SERT, 5-HT1A autoreceptors) as a new generation of antidepressant therapies with a potential greater efficacy faster onset of action than current treatments.

P-09-003 Prevalence and pattern of sexual dysfunction in females receiving antidepressants

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Objective: To study the prevalence and pattern of sexual dysfunction in female patients receiving antidepressants. Eighty married female patients with a diagnosis of depressive disorder, currently in remission, and receiving a single antidepressant at least for 3 months, were assessed for sexual dysfunction on Female Sexual Function Index (FSFI) scale.

Methods: Eighty married female patients with a diagnosis of depressive disorder, currently in remission, and receiving a single antidepressant at least for 3 months, were assessed for sexual dysfunction on Female Sexual Function Index (FSFI) scale.

Results: It was found that 95% of patients had decreased desire, 60% had decreased arousal, 37.5% had decreased lubrication, 63.8% had decreased orgasm, 55% had decreased satisfaction and 25% had pain during sexual activity.

Conclusion: Sexual dysfunction is quite prevalent in married female patients receiving antidepressants and all the domains of sexual functioning are impaired by antidepressants.
**P-09-004** Antidepressant activity of curcumin: Involvement of serotonin and dopamine system

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**Objective:** Curcumin is a major active principle of Curcuma longa, one of the widely used preparations in the Indian system of medicine. It is known for its diverse biological actions. The present study was designed to investigate the involvement of monoaminergic system(s) in the antidepressant activity of curcumin and the effect of piperine, a bioavailability enhancer, on the bioavailability and biological effects of curcumin.

**Methods:** Behavioral (forced swim test), biochemical (monoamine oxidase (MAO) enzyme inhibitory activity), and neurochemical (neurotransmitter levels estimation) tests were carried out.

**Results:** Curcumin (10–80 mg/kg, i.p.) dose dependently inhibited the immobility period, increased serotonin (5-hydroxytryptamine, 5-HT) as well as dopamine levels (at higher doses), and inhibited the monoamine oxidase enzymes (both MAO-A and MAO-B, higher doses) in mice. Curcumin (20 mg/kg, i.p.) enhanced the anti-immobility effect of subthreshold doses of various antidepressant drugs like fluoxetine, venlafaxine, or bupropion. However, no significant change in the anti-immobility effect of imipramine and desipramine was observed. Furthermore, combination of subthreshold dose of curcumin and various antidepressant drugs resulted in synergistic increase in serotonin (5-HT) levels as compared to their effect per se. There was no change in the norepinephrine levels. The co-administration of piperine (2.5 mg/kg, i.p.), a bioavailability enhancing agent, with curcumin (20 and 40 mg/kg, i.p.) resulted in potentiation of pharmacological, biochemical, and neurochemical activities.

**Conclusion:** The study provides evidences for mechanism-based antidepressant actions of curcumin. The co-administration of curcumin along with piperine may prove to be a useful and potent natural antidepressant approach in the management of depression.

**P-09-005** Abuse antidepressant use

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**Objective:** The number of antidepressants has grown exponentially and its indication has been changing over time. Initially mainly used as a treatment for mood disorders, while in recent decades, used to treat anxiety, eating disorders, obsessive-compulsive disorder, substance abuse, personality disorders, schizoaffective disorder, chronic neuropathic pain, etc. No conclusive data on long-term risks of these drugs, but they continue to prescribe indiscriminately by the firm belief of its safety. OBJECTIVE: Conduct a descriptive study to reflect how many patients started antidepressant treatment on admission to a Brief Hospitalization Unit (UHB) of Psychiatry during 2000. After 10 years of monitoring, evaluating the effectiveness-ineffectiveness, continuity-discontinuation of it.

**Methods:** Select medical records of patients who are discharged from a antidepressant medication. Collect the following data: age, sex, diagnosis and previous antidepressant treatments, family history of antidepressant treatment, reason for admission and establishment of antidepressant treatment, type of antidepressant, average stay, discharge diagnosis, continuity of treatment/discontinued (reason discontinuation), current clinical status.

**Results:** After 10 years found that 40% patients continue antidepressant treatment. Most did not have the diagnosis of Mood Disorder.

**Conclusion:** Antidepressants have a clear potential for abuse and dependence that is attributed to its anticholinergic action. The reasons for treatment discontinuation: clinical stability, abandonment, powerlessness, turn, side effects.

**P-09-006** Low-trapping NMDA channel blocker AZD6765 increases gamma-band EEG without dissociative side-effects: A comparison with ketamine in healthy volunteers

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**Objective:** Ketamine has demonstrated robust antidepressant activity in small clinical trials. However, ketamine’s side-effects may limit its therapeutic utility. AZD6765, a low-trapping NMDA channel blocker in development for major depression, is predicted to have an improved tolerability profile compared to ketamine. Preclinically, NMDA channel blockers increase gamma-band EEG – a potential therapeutic biomarker of cortical disinhibition. The object of this study was to use quantitative EEG to determine whether AZD6765 in humans causes electrophysiological changes comparable to ketamine without the occurrence of dissociative side-effects.

**Methods:** A four-way, placebo-controlled, crossover study in healthy volunteers compared i.v. infusion of AZD6765 (75 and 150 mg) with an antidepressant dose of ketamine (0.5 mg/kg). Baseline and post-drug EEGs were obtained under controlled conditions and composite brain EEG maps were analyzed using Standard Decision Tree methods. Changes in gamma (35–55 Hz) band power served as the primary endpoint. Secondary endpoints included Clinician Administered Dissociative Status Scale (CADSS), electro-nystagmography, and pupill size.

**Results:** Significant increases in gamma-band EEG were observed at 1 hour for ketamine and AZD6765, and baseline-corrected gamma-band EEG following AZD6765 150 mg was statistically indistinguishable from that observed following ketamine. In contrast, AZD6765 caused no dissociative symptoms, whereas ketamine produced a moderate yet significant increase in CADSS and was associated with an increase in supine systolic blood pressure. No significant changes in nystagmus or pupil size were observed with AZD6765.

**Conclusion:** Consistent with preclinical findings, this study supports the utility of gamma-band EEG as a biomarker for NMDA channel blockade and provides evidence that differentiates ketamine from AZD6765 across multiple tolerability endpoints including cardiovascular and psychotomimetic liability. AZD6765 demonstrated NMDA channel blockade and an improved tolerability profile compared to ketamine.

**Policy of full disclosure:** Author is employed by Forenac, the CROI conducting the study on behalf of AstraZeneca.

**P-09-007** Clinical predictors of antidepressant response and remission in treatment resistant depression

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**Objective:** Few studies investigated clinical predictors of antidepressant response-remission in treatment resistant depression (TRD). The present has been performed in the context of a European multicenter project. Its aim was to identify predictors of antidepressant response/remission in a sample of TRD prospectively assessed patients and to compare results to ones obtained on another sample of TRD patients retrospectively assessed.

**Methods:** 514 patients who failed to respond to a previous antidepressant were firstly included in a 6-week treatment with venlafaxine; secondly, those who failed to respond were treated for a 6-week treatment with escitalopram. MINI was administered at baseline. HIRSD, MADRS, CGI-S and CGI-I scales were administered from baseline to week 12. Other information has been collected at baseline.

**Results:** Completers have been included in the analyses. In the first phase, non responders and non remitters to venlafaxine reported lower rate of inpatients, higher rate of psychiatric antecedents, lower benzodiazepine use at baseline, higher rate of side effects, higher CGI-S and lower CGI-I scores, and higher treatment doses. Moreover, non responders showed lower age and lower episode number while non remitters showed higher current suicidal risk level. In the second
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phase, non responders and non remitters to escitalopram reported higher duration of current episode, higher treatment dose, and higher CGI-S and lower CGI-I scores. Moreover, non remitters showed higher rate of current suicidal risk and higher current suicidal risk level, higher rate of comorbid anxiety disorders, in particular panic disorder and generalized anxiety disorder, and higher rate of antidepressants of second degree affected by bipolar disorder.

Conclusion: Some clinical variables have been identified as associated with treatment non response/non remission in TRD. Specifically, current suicidal risk and comorbid anxiety disorders, in particular panic disorder, seem to be predictors of treatment non remission/resistance in two sample of TRD patients. Further clarification of the role of other clinical variables should be explored.

P-09-008 Effects of pharmacodynamic properties of antidepressants on central autonomic regulation in young women with recurrent depression

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Objective: Recurrent depression is often associated with alterations of central autonomic regulation. Pharmacodynamic properties of antidepressants may cause changes in central autonomic function. We examined the relationship between autonomic status of women with recurrent depression and pharmacodynamic properties of antidepressants.

Methods: Resting RR intervals and respiratory signals were simultaneously obtained from 38 euthymic women with recurrent depression receiving escitalopram (n=19) or venlafaxine monotherapy (n=19) and 38 matched and healthy women. Linear measures of heart rate variability were extracted to assess cardiac autonomic control. Sample Entropy (SampEn) was computed to assess the complexity of heart rate and respiratory signal, and Cross-SampEn were calculated to measure a nonlinear interaction of both signals.

Results: Women with recurrent depression receiving venlafaxine showed significant decreases in cardiac vagal activity and interaction between heart rate and respiration when compared to women with recurrent depression receiving escitalopram or healthy controls. Effect sizes for these differences in autonomic control were large between women receiving venlafaxine and healthy controls. Compared with healthy controls, women with recurrent depression receiving escitalopram showed tendencies toward decreased cardiovagal tone and reduced cardiorespiratory coupling. A significant association between venlafaxine and autonomic dysregulation, the current study suggests that altered autonomic modulation in euthymic women with recurrent depression may be associated with pharmacological properties of antidepressants.

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P-09-009 Tianeptine in treatment of depression in cancer with deep vein thrombosis on anticoagulant medication

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Objective: Patients undergoing major abdominal surgery for malignancy are at particularly high risk of developing deep vein thrombosis (DVT). Studies show that half of all cancer patients have a psychiatric disorder, usually a depression. The antidepressant given to prevent recurrent risk for DVT can cause bleeding but this adverse event was reported also at more antidepressants classes like selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. The aim of this study was to investigate the tianeptine effect, used for treatment of depression, on anticoagulation during the anti-coagulant medication in patient with cancer and DVT.

Methods: We included 11 patients, 7 women and 3 men with age between 30-42 years, with diagnosis of depression by DSM IV criteria, who were suffered DVT >1 times during the last month after a surgery intervention for cancer. All patients received anticoagulants daily with high intensity of international normalized ratio (INR) settings (around 3.7-4.0 INR) and tianeptine 12.5 mg three times on day. The combination of tianeptine with anticoagulants was monitored by measurements of INR to avoid overanticoagulation.

For measurement the depressive symptoms we used Hamilton Depression Rating Scale (HDRS) 17 items. Period of study it was 3 month, with one visit per week in the first month and at 2 weeks to the endpoint.

Results: We didn’t found risk for overanticoagulation during anti-coagulant treatment in combination with tianeptine. The patients tolerated very well the treatment and at the endpoint we obtained the remission of depressive symptoms. It wasn’t necessary to adjustment the doses of anticoagulant on the period of the study.

Conclusion: There was no increase in risk for overanticoagulation in subjects treated with tianeptine and anticoagulants. This medication can be take in consideration in treatment of depression at patients with recurrent DVT on anticoagulant medication.

P-09-010 Antidepressant usage after bariatric surgery

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Objective: To examine antidepressant medication usage in a retrospective study of 439 patients who had Roux-en-Y gastric bypass surgery for weight loss.

Methods: A retrospective chart review identified 170 patients on antidepressant medications presurgery and 180 patients not on antidepressant medications presurgery. Average age of the sample was 47 years old, most were female, and average BMI was 47.

Results: Of the 170 patients who were on antidepressant medications presurgery, 40% had no change in their antidepressant medications, 23% had an increase in antidepressant medications, 18% changed antidepressants, and only 16% decreased or stopped their antidepressant medications.

Conclusion: Many patients seeking to have bariatric surgery are prescribed antidepressant medications, but there is little documentation regarding antidepressant usage after having bariatric surgery. In this retrospective medical chart review few patients were able to reduce or discontinue their antidepressant medications after having bariatric surgery. These results highlight the need for careful monitoring of mood after having bariatric surgery. These results have been accepted for publication.

P-09-011 Agomelatine treatment normalized anxiety behaviour, Period 1 and Period 2 expression in a rat model of posttraumatic stress disorder

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Objective: Post-traumatic stress disorder (PTSD) is a chronic anxiety disorder defined by the co-existence of three clusters of symptoms: re-experiencing (flash-backs, recurrent and distressing recollections and dreams, intense physiological reactivity after reminders exposure), avoidance/numbing (persistent avoidance of trauma’s reminders) and hyperarousal (anxiety, insomnia, concentration difficulties, exaggerated startle response, irritability). Moreover, abnormal circadian rhythms are observed in PTSD patients. Agomelatine is a melatonergic agonist (MT1/MT2) and 5HT2C antagonist with antidepressant, anxiolytic and re-synchronizing effects in animals and humans. Here, we evaluated the effect of agomelatine on behavior and clock genes Period1 and Period2 expression in the predator scent stress (PSS) rat PTSD model.

Methods: Adult male Sprague-Dawley rats were exposed to PSS for 10 min, and 1 h later treated for 3 days with vehicle or agomelatine (50 mg/kg i.p.). Rats were assessed in the Elevated Plus Maze (EPM) model.
and acoustic startle response (ASR) on Day 8 and sacrificed 24 h after (ZT19) for Per1 and Per2 immunohistochemistry evaluation.

Results: In the EPM, agomelatine antagonised (p < 0.035) the time spent in the open arms decrease observed in PPS vehicle-treated rats. In the ASR, agomelatine (p < 0.002) reversed the mean startle amplitude increase observed in PPS vehicle-treated rats. Moreover agomelatine induced decreases in the prevalence rates of individuals displaying extreme behavioural responses (EBR) (PTSD-like). As regards clock genes expression, agomelatine normalized Per1 increases observed in the CA3 (p < 0.05), DG (p < 0.015) and SCN (p < 0.0002) of PPS rats. Agomelatine also normalized the Per2 increases observed in the CA1 (p < 0.00025), CA3 (p < 0.0008), DG (p < 0.05) and SCN (p < 0.0035) of PPS rats.

Conclusion: These results suggest that agomelatine normalized anxiety-like behavior in this animal model of PTSD and normalized the Per1 and Per2 clock genes expression changes observed in this model suggesting that these clock genes are involved in the neurobiological response to anxiety in this PTSD model.

P-09-013 PharmacoMRI and cognitive effects of the low-trapping NMDA channel blocker AZD6765 compared with ketamine in untreated major depressive disorder

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Objective: To determine the immediate effects of AZD6765 and ketamine on neural activity in the subgenual cingulate cortex (SGC) and its relationship with subsequent change in depressive symptoms and emotion processing using pharmaco- and functional magnetic resonance imaging (phMRI, fMRI).

Methods: Sixty treatment-naive males or females aged 18 to 45 years with major depressive disorder were randomly assigned to three groups to receive (i.v.) ketamine, AZD6765, or placebo during a 60 min phMRI scan. Twenty-four hours later, behavioural and fMRI responses to emotional stimuli were recorded. Baseline and follow-up Montgomery-Asberg Depression Rating Scale (MADRS) scores were recorded.

Results: Both AZD6765 and ketamine increased SGC BOLD signal responses; no decreases were seen in any brain region. The SGC responses correlated with improvement in MADRS scores 24 hours and 7 days post-infusion. Following administration of AZD6765, inter viewer-rated psychotic and dissociative symptoms were minimal and not statistically significant. In contrast, ketamine produced a moderate statistically significant increase in dissociative symptoms. Both drugs reduced amygdala responses to fear and sadness in the emotional faces task 24 hours post-infusion.

Conclusion: Activation of the SGC was seen following both drugs and this effect was associated with improvement in depressive symptoms 24 hours and 7 days post-infusion. The results suggest that AZD6765 and ketamine both have antidepressant-like effects on emotion processing in the brain and that diminished NMDA glutamate neurotransmission in the SGC is a likely proximal mechanism.

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**P-09-015** Serotonergic antidepressants and hypoaemia in aged psychiatry

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**Objective:** To investigate the incidence and risk factors for antidepressant induced hypoaemia in elderly people treated with serotonergic antidepressants.

**Methods:** In a retrospective chart analysis depressed patients aged $>63$ years were investigated for change in serum sodium levels in two samples separated by a median period of 45.5 days and with the first specimen taken prior to treatment. Patients were grouped into three cohorts; treated with an antidepressant other than an SSRI or SNRI ($n=54$) and not treated with an antidepressant ($n=128$).

**Results:** For change in sodium level between measurements and total number of patients with hypoaemia, there was no significant difference between cohorts. Moreover, the rate of reduction of serum sodium levels between time points was significantly greater for SSRI and SNRI treated patients ($p<0.001$) and patients treated with other antidepressants ($p=0.03$) compared to patients not treated with antidepressants. Moreover, the distribution of values of change in serum sodium was skewed towards reduced serum sodium in patients treated with SSRI or SNRIs (skew $=0.43$) and patients treated with other antidepressants (skew $=-0.09$) but not for patients not treated with antidepressants (skew 0.25).

**Conclusion:** These data suggest that hypoaemia is associated with antidepressant treatment that effects some individuals only. Generalized linear modelling showed that the risk of hypoaemia increases with increased age, female gender, and particularly the antidepressant agents sertraline and escitalopram. The findings are of clinical significance as they demonstrate that hypoaemia can occur rapidly in patients treated with these antidepressants.

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**P-09-016** Difference between morning and evening thyrotropin response (delta TSH) and prediction of antidepressant treatment outcome in major depression

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**Objective:** About 50% of major depressed patients have inadequate response to an individual antidepressant trial. Early predictors of response are needed to improve effectiveness of antidepressant treatment. This study sought to determine whether the thyroid function evaluation at baseline and after 2 weeks of treatment could predict antidepressant response in hospitalized patients.

**Methods:** Serum levels of thyrotropin (TSH), free triiodothyronine (FT3), free thyroxine (FT4) were measured before and after 08:00 h and 23:00 h (proteolipid challenge) (thyrotropin-releasing hormone [TRH]; 200 µg intravenously), on the same day, in 30 medication-free DSM-IV euthyroid major depressed inpatients and 30 healthy hospitalized controls. After 2 weeks of antidepressant treatment (tianeptine, n = 15; extended-release venlafaxine, n = 15) the same TRH tests were repeated in all inpatients. Antidepressant response was evaluated after 6 weeks of treatment.

**Results:** At baseline, serum 23:00 h-TSH basal values, 23:00 h maximum increment in TSH level (delta TSH) and the difference between 11 Pm-delta TSH and 8 AM-delta TSH (delta delta TSH) were significantly lower in patients compared to controls (p=0.03, p=0.001, and p<0.001, respectively). Twenty patients showed reduced delta TSH values (i.e. $<2.5$ mIU/l; sensitivity, 67%; specificity, 97%). Pretreatment thyroid function tests were not associated with clinical outcome (full response rate 57%). After 2 weeks of treatment, patients with reduced delta TSH values (n=14 [47%]) showed poor clinical outcome, while those with normal delta TSH values showed full response on day 42 (p<0.0006). A logistic regression on delta delta TSH values on day 14 predicted endpoint clinical response (odds ratio 3.30; 95% confidence interval, 1.35-8.08; p=0.009).

**Conclusion:** Our results suggest that the delta TSH TST performed early during antidepressant treatment could be used to predict eventual outcome and guide treatment decision.

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**P-09-017** Pharmacodynamics of Org 26576, an AMPA positive allosteric modulator, in patients with major depression: an exploratory, randomized, double-blind, placebo-controlled Phase I trial

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**Objective:** This study explored the safety, tolerability, pharmacokinetics, and pharmacodynamic (PD) of Org 26576 in depressed patients; PD included QEEG endpoints, cognition, and treatment response on the MADRS.

**Methods:** Part I (N = 24) evaluated maximum tolerated dose (MTD) and optimal titration schedule using a 10 to 16-day multiple rising dose paradigm in depressed subjects. Part II (N = 30) followed a parallel-group design, in which subjects received either 100 or 400 mg Bid of Org 26576 or placebo for 28 days. The QEEG-based endpoint Antidepressant Treatment Response (ATR; Coviiden) was assessed at baseline and Week 1. MADRS and a computerized cognitive battery were administered at baseline and endpoint.

**Results:** Part I: The MTD study determined a safe starting dose of 200 mg Bid with an MTD of 450 mg Bid. Part II: Both doses of Org 26576 showed a small numeric advantage over placebo on the MADRS at Day 28 (Change from baseline 100 mg Bid: $-15.40$ (95% CI: $-20.39$) to $-13.51$ (95% CI: $-18.55$); 400 mg Bid: $-14.78$ (95% CI: $-20.43$) to $-12.67$ (95% CI: $-18.39$); and $-16.24$ (95% CI: $-21.78$) to $-13.51$ (95% CI: $-18.85$); $p<0.05$). Org 26576 was associated with improvements on computerized tests of executive functioning (Eff size 100 mg Bid vs. placebo: 1.01; 400 mg Bid vs. placebo: 0.77) and speed of processing (Eff size 100 mg Bid vs. placebo: 0.88). The ATR at Week 1 was able to significantly predict symptomatic response at endpoint in the active treatment group, as was early improvement in social acuity, as measured by a face emotion recognition task (POET; CNS-Vital Signs).

**Conclusion:** Org 26576 was well tolerated in patients. Exploratory pharmacodynamic endpoints suggested that it may show promise as an antidepressant in future well-controlled, adequately powered proof of concept trials. Further study is also warranted to assess the use of markers such as ATR and social acuity as response surrogates in small Phase I patient studies.

**Policy of full disclosure:** Ereshefsky, Gertsik, Kim, and Unabia are employees of PAREXEL, recipient of grant support from Merck, USA. Nations was an employee of Merck. Dogterom, Bursa, and Schipper were employees of Merck. Starpe and Dohme, The Netherlands. Greenwald and Zraik are employees of Coviiden recipients of grant support from Merck.
**P-09-018** Lymphoblastoid cell lines as models for pharmacogenomics in psychopharmacology
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Objective: Epstein-Barr virus (EBV) immortalized human lymphoblastoid cell lines (LCL) serve as models in personalized medicine to understand the genetic variability underlying drug effects. Different cohorts of LCLs are existing that so far have been mainly used to study genomic influences on the phenotype of cytotoxic drug effects in cancer therapy. Recently, other than anticancer drugs have been used to study transcriptional regulation in modulation of drug effects.

We use this method to study the genetics of antidepressant drug effects and see if this method may serve as a surrogate parameter for antidepressant drug response. The aim of this project was first, to study if the cell toxic effects of different antidepressant drugs are specific to the drug class, and second, to correlate the findings of drug induced cell-toxicity with clinical data.

Methods: We used LCLs from patients who have been treated with antidepressant drugs and characterized for the clinical course of drug response in the Munich Antidepressant Response Signature (MARS) study by the Max Planck Institute of Psychiatry. We examined the effects of mirtazapine, imipramine and paroxetine in different concentrations and epigallocatechin gallate (EGCG), the main component of green tea that has known antiproliferative effects as a control for a different antiproliferative substance class. The experiments were repeated three-times in each cell line.

Results: The drug concentration that inhibited the cell growth by 50% (IC50: imipramine 80 μM, paroxetine 15 μM, mirtazapine 300 μM, EGCG 15 μM) correlated significantly between the three antidepressant drugs (imipramine versus paroxetine r = 0.55, p = 0.017; imipramine versus mirtazapine r = 0.48, p = 0.045). EGCG also inhibited cell growth but it did not correlate with the cell toxicity of the antidepressant drugs (r = 0.13, p = 0.47 for imipramine, r = 0.23, p = 0.23 for paroxetine, r = 0.1, p = 0.57 for mirtazapine).

Conclusions: Correlations between cell growth inhibition and clinical antidepressant therapy outcome will then be tested in these patient cohorts from Munich.

**P-09-019** Differential regulation of FADD protein content by electroconvulsive seizure and classic antidepressants in rat brain
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Objective: Major depression has been linked with genetic abnormalities of Apaf1, suggesting a role for enhanced cell death or apoptosis. Light deprivation in rats, a behavioral model of depression-like behavior, was recently shown to increase apoptosis and apoptotic-related markers. Conversely, the antidepressant drugs desipramine and tianeptine induced antinotic effects in an animal model of depression. Fas-Associated protein with Death Domain (FADD), the adaptor protein of the extrinsic apoptotic pathway, is essential in Fas receptor-induced apoptosis. Moreover, FADD is a unique regulator of cell life and death and plays a critical role in many essential cellular processes. In fact, phosphorylated FADD (pSer191 FADD) mediates non-apoptotic actions such as cell growth and differentiation.

Methods: The current study investigated the effects of acute and chronic electroconvulsive seizure (ECS) and classic antidepressant treatments (desipramine and fluoxetine) on total FADD and pFADD protein contents in brain regions associated with depression in the rat.

Results: A single session of ECS (95 mA, 0.6 s, 0.6 ms, 100 pulses/s) increased FADD in the hippocampus (22%, p < 0.01) and cortex (30%, p > 0.05), without altering pFADD content. Repeated sessions of ECS (5 days) were not associated with alterations in FADD (induction of tolerance) or pFADD in the hippocampus and cortex. Contrarily, desipramine (10–30 mg/kg, 2–4 h) and fluoxetine (10 mg/kg, 2 h) decreased FADD in cortex (20–30%, p > 0.05; 10–15%, p > 0.05; respectively), without altering pFADD content. Notably, two weeks treatment with desipramine (10 mg/kg) or fluoxetine (3 mg/kg) stimulated pFADD in the cortex (desipramine: 23%, p < 0.05; fluoxetine: 59%, p < 0.01). These chronic treatments were not associated with alterations in FADD content.

**P-09-020** Potential benefits of slow titration of paroxetine treatment in elderly population
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Objective: Approximately 15% among over 65-years individuals suffers from depression. Particularly in this population, SSRIs could lead to an early exacerbation of anxiety and a very gradual titration is usual in clinical practice. The aim of this study is to compare efficacy and tolerability of gradual versus rapid titration of paroxetine in the elderly.

Methods: 50 non-demented elderly (≥ 60 years old) outpatients with Major Depression or Anxiety disorders (≥ 13 total score at Hamilton Depression Rating Scale –HAM-D– or Hamilton Anxiety Rating Scale –HAM-A) were randomized to paroxetine 10 mg or to gradual tapering (2.5 mg on alternate days up to 10 mg in 7 days). Then dosage could be adjusted according to clinical response.

Results: During the first 3 days of treatment a significant worsening in psychic anxiety was observed in patients treated abruptly with 10 mg of paroxetine (difference in HAM-D psychic anxiety subscale from baseline: 110.61% vs. 89.38% with rapid and slow titration respectively; p = 0.03). Overall a significantly greater improvement in depressive and anxious symptoms favored gradual titration (HAM-D Core cluster and HAM-D psychic anxiety cluster respectively repeated misure ANOVA = 0.014 and p < 0.001, also when controlling for confounders). At 8th week slightly higher drop outs in patients administered with abrupt dosage was observed (15.38% vs. 39.13%, p = 0.06; respectively for slow and rapid titration).

Conclusion: Our results suggest that a gradual titration of paroxetine could avoid the initial treatment anxiety worsening and drop out at the beginning of the treatment. Open issues are possible concomitant somatic treatments and difference in long-term tolerance.

**P-09-021** Fluvoxamine boosts duloxetine plasma levels in depressed patients
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Objective: Duloxetine (DLX) is a serotonin-norepinephrine reuptake inhibitor (SNRI) that is effective for major depressive disorder and generalized anxiety disorder (GAD). The drug is metabolized by CYP1A2 and to a lesser extent by CYP2D6. Fluvoxamine (FLX) is a serotonin reuptake inhibitor (SSRI) and known to be a potent inhibitor of the cytochrome P450 isoenzyme CYP1A2. It should therefore not be co-administered with DLX in the first place. There are nevertheless rare clinical situations when a combination might be advantageous, for example in cases when plasma levels of DLX remain low despite individuals taking high doses.

Methods: In this study the plasma levels of DLX as well as the clinical and adverse effects were retrospectively analyzed in thirteen patients treated with a combination of the two substances. Steady state DLX levels were measured in patients before taking FLX and under different daily doses of FLX within the same subjects.

Results: Adding 25 mg of FLX per day to a steady-state treatment with 30 mg of DLX in 8 patients led to an average increase of DLX plasma levels that was 3-fold with a magnitude of 50–506%.

Conclusion: Our findings indicate that DLX plasma levels can be boosted by the potent CYP1A2 inhibitor FLX. However, the co-administration of duloxetine with potent CYP1A2 inhibitors should not be used in clinical routine without extreme precaution and under continuous control of plasma-levels.
P-09. Antidepressants

**P-09-022** Progesterone withdrawal-induced depression-like behavior is differentially sensitive to the effects of direct serotonin receptor modulation in comparison to selective serotonin reuptake inhibition

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**Objective:** Background: Long-term progesterone administration followed by abrupt withdrawal induces depression-like and anxiety-like behavior in female rats, similar to symptoms in women with premenstrual dysphoric disorder (PMDD). However, few studies have compared efficacy of antidepressants with different mechanisms of action in women, or in animal models of hormonally induced depression-like behavior. Objective: The progesterone withdrawal (PWD) model was used to compare the efficacy of an SSRI (fluoxetine), specific serotonin (5-HT) receptor modulators, and a novel multimodal antidepressant, LuAA21004. LuAA21004 is a 5-HT3 and 5-HT7 receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist and an inhibitor of the 5-HT transporter in vitro.

**Methods:** PWD was induced in a multiple withdrawal paradigm by i.p. injection of progesterone in oil (30 mg/kg) for 3 weeks. Depression-like behavior was assessed using forced swim test, and brain 5-HT levels were measured using HPLC. Results: Fluoxetine did not reduce depression-like behavior when administered either chronically (2 weeks) or acutely (2 days). In contrast, LuAA21004 reduced depression-like behavior after both acute and chronic administration. Acute administration of 5-HT3 receptor antagonist ondansetron or 5-HT1A receptor agonist flesinoxan also reduced depression-like behavior. However, these effects were not additive in combination with fluoxetine. Brain serotonin levels were not altered after PWD.

**Conclusion:** These data indicate that antidepressants with 5-HT3 antagonist and/or 5-HT1A agonist activity are more efficacious than an SSRI after PWD in female rats. Furthermore, 5-HT receptor modulation is not additive with SSRI administration, consistent with data indicating no primary deficit in serotonin levels in this model.

**Policy of full disclosure:** This project is supported by H Lundbeck A/S and Takeda.

**P-09-023** Effect of the multimodal antidepressant LU AA21004 on rat hippocampal plasticity and recognition memory

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**Methods:** Field excitatory postsynaptic potentials were recorded in the CA1 area of dorsal hippocampus before and after high frequency stimulation (HFS) of the Schaffer’s collaterals in 5-HT-depleted rats (with PCPA), stressed rats placed on an elevated platform, and controls. The novel object recognition (NOR) test (24 h retention) in a novel environment was used to assess episodic memory. Hippocampal cell proliferation was measured by immunohistochemistry.

**Results:** In controls, HFS provoked a stable long-term potentiation (LTP) of ~30%. Lu AA21004 (10 mg/kg i.p.) reduced LTP to ~ 10%. The multimodal antidepressant Lu AA21004 is a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and 5-HT transporter inhibitor in vitro [Merk A, et al., J Pharmacol Exp Ther 2011. jpet.111.189008.]. From these results, we conclude that Lu AA21004 induced an increase in cell proliferation in the dentate gyrus after 1, 3 and 14 days of treatment.

**Conclusion:** Lu AA21004 produced an effect on LTP similar to that of serotonergic antidepressants, but prevented the suppressant effect of acute stress. Lu AA21004 also enhanced episodic memory, an effect mediated, at least partly, by its 5-HT3/7 receptor antagonism. Finally, Lu AA21004 induced a surprisingly rapid increase of hippocampal cell proliferation. Together, these preclinical data suggest that the antidepressant, Lu AA21004, may have a beneficial effect on cognitive processes.

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**P-09-024** The efficacy of paroxetine in treating chronic subjective dizziness

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**Objective:** To investigate the antidepressant paroxetine in the treatment of chronic subjective dizziness efficacy and indications.

**Methods:** 53 cases of chronic subjective dizziness were divided into two groups, integrated treatment group received Paroxetine (Seroxat 20-40 mg/d), the control group received conventional medical treatment (strong Dunguan films, etc.), both groups with supportive psychotherapy, the treatment period of 4 weeks. Before treatment, after Hamilton Depression Scale respectively (HAMD), Hamilton Anxiety Scale (HAMA), 90 Symptom Checklist (SCL-90) and self-vertigo symptom questionnaire score.

**Results:** 53 patients with chronic subjective dizziness with HAMD. HAMA score and the SCL-90 part of the factor scores were significantly higher than the norm, the difference was significant (P<0.05). After 4 weeks of integrated group therapy HAMD, HAMA and SCL-90 score was significantly lower than the control group, the difference was significant (P<0.05). Patients with chronic subjective dizziness antidepressants (paroxetine) reduce vertigo symptoms after treatment was significantly greater than the control sub-consolidated group, the difference was significant (P<0.05).

**Conclusion:** The prevalence of chronic subjective dizziness in patients with emotional problems, antidepressants for the treatment of patients with chronic subjective dizziness, vertigo can improve symptoms but also improve mood symptoms. Keywords: chronic subjective dizziness, anxiety, depression, paroxetine, treatment.

**P-09-025** Efficacy of agomelatine in elderly patients with major depressive disorder (MDD). Arandomised, double-blind study vs. placebo

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**Objective:** This 8 weeks multiethnic international double-blind randomized study evaluated the efficacy of the antidepressant agent agomelatine, a MT1/MT2 receptor agonist and a 5HT2c receptor antagonist, in elderly patients suffering from MDD compared to placebo using the Hamilton Depression Rating Scale 17 items (HAMD-17).

**Methods:** 222 out-patients MDD aged of at least 65 years were randomised to receive agomelatine 25-50 mg (151) or placebo (71) for 8 weeks.

**Results:** In the total population, the mean HAM-D total score significantly decreased from baseline to endpoint with agomelatine (from 26.9±2.8 to 13.4±7.5) vs. placebo (from 26.8±3.2 to 16.1±7.6) with a significant difference in favor of agomelatine of 2.67 (SE=1.06), p=0.013. In the more severe patients (HAM-D total score >25 and CGI-S>5 at baseline), the clinical benefit was reinforced with a significant difference in favor of agomelatine of 3.79 (SE=1.37), p=0.007. The response rate to treatment (decrease in HAM-D total score from baseline of at least 50%) was significantly higher with agomelatine than with placebo: 59.46% vs. 38.57% respectively in the total population (p=0.004) and 64.95% vs. 36.59% respectively in the more severe patients (p=0.002) The proportion of patients at least one Emergent Adverse Event (EAE) related to treatment was of 26.5% in the agomelatine group and 19.7% in the placebo group. A similar proportion of patients discontinued the treatment due to EAE.
in the agomelatine group (79%) and in the placebo group (85%). Most common reported adverse events and more frequent on agomelatine were somnolence, diarrhoea, dry mouth and constipation.

Conclusion: This study shows that agomelatine is an efficient antidepressant treatment in the elderly patients.

Policy of full disclosure: I received speaker honoraria from AstraZeneca, Bayer, BMS, Eisai, Pfizer, Janssen-Cilag, Novartis and Servier, and was international scientific coordinator of the study.

P-09-026 The combination of cognitive-behaviour therapy and antidepressants in the treatment of depression

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Objective: Cognitive Behavioral Psychotherapy constitutes a major treatment for Depression. Nevertheless, there are forms of depression that resist treatment, both with cognitive-behavioral therapy in monotherapy, and with a combination of antidepressants. Cognitive Behavioral anti-depression Treatment requires 20-25 sessions and is mainly based on the principles of Collaborative Empiricism, as well as on the doctrines of the ancient Greek philosopher Epictetus.

Methods: 15 patients (9 female, and 6 male) were studied. The patients were selected among the patients treated in the inpatient facility and the outpatient setting of the Psychiatric Department of “Konstantopoulio” General Hospital, Nea Ionia, during the years 2009 and 2010. All patients, without exception, were taking a combination of antidepressants. Furthermore, the above patients were given the MADRS (Montgomery-Asberg Depression Rating Scale) for Depression, and CGI-S (Clinical Global Impression of Severity) Scales. The cut-off value for Depression in MADRS scale is 12. All 15 patients were treated with a cognitive-behavioral treatment of 25-30 sessions, along with medication treatment.

Results: From 15 patients, 2 (male) abandoned cognitive behavioral treatment due to a lack of motivation, and free time. The 13 patients (7 female, and 6 male) that remained in treatment received a combination of antidepressant medication and cognitive behavioral therapy, and showed a significant improvement at their MADRS and CGI-S scores, proving that their depressive symptomology improved. It should be noted that all 15 patients suffered from moderate to severe depression. Anyhow, all 13 patients submitted to Cognitive Behavioral Therapy did not satisfactorily respond to the antidepressant medication combination.

Conclusion: Cognitive Behavioral Therapy, combined with antidepressant treatment, the latter being adequate in dosage and with a low side-effect profile, helps to treat treatment-resisting Depression. Research shall extend beyond the completion of Cognitive Behavioral Therapy, with a follow-up of these particular patients every six months, for a period of two years.

P-09-027 Efficacy and tolerability of paroxetine, fluvoxamine and milnacipran in depression: A result of two pooled open label randomized controlled trial

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Objective: To compare efficacy and tolerability of paroxetine(PAX), fluvoxamine(FLV) and milnacipran(MIL) in Japanese patient with major depressive disorder.

Methods: A total of 200 Japanese patients suffering from major depression were allocated to flexible dosage of PAX (n = 100), FLV (n = 50) or MIL (n = 50) in two randomized 6-week study. The clinical response was evaluated using the Hamilton Rating Scale for Depression (HAM-D) assessed at each visit. Tolerability was assessed by dropout rate caused by side effect. Involvement of anxious or depressive treatment in efficacy or tolerability was also evaluated. A repeated measures analysis of variance, analysis of covariance and Cox regression analysis were applied.

Results: HAM-D percent change among three treatment group was significantly different (p = 0.005, endpoint HAM-D % changes; PAX: 63.8%, FLV: 62.0% and MIL: 44.6%) by LOCF procedure (n = 168). Subsequent analysis between two treatment groups showed significantly better improvement in PAX compare to MIL (p = 0.004) and no significant differences were seen between PAX and FLV and also FLV and MIL. While in per protocol analysis (n = 143), PAX showed significantly better improvement than FLV (p = 0.033) and MIL (p = 0.012). Cox regression analysis showed significantly different side effect induced dropout rate among three antidepressants (p = 0.029, MIL: 29.4%>PAX:18.8%, FLV: 61%). In both anxious depression and delusional depression subgroup, FLV showed significantly greater improvement than MIL. Anxious depression was also associated with high side effect-induced dropout rate (p = 0.026).

Conclusion: PAX showed greater improvement than MIL and FLV with moderate risk of drop out. FLV showed lower dropout risk and subsequent favorable improvement only in LOCF procedure, in which fewer side effects medication tends to produce better result also in treatment efficacy. Greater efficacy of FLV in anxious and delusional depression might be related to its 5-HT1A receptor affinity. Higher efficacy, as well as the importance of dropout, should be considered as the important factor of dropout.

P-09-028 Antidepressant selective gynecomastia

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Objective: Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) indirectly result in decreased dopamine neurotransmission. Adverse effects (AE) associated with dopamine blocking agents have been reported with both SSRIs and SNRIs, including movement disorders and galactorrhea. Further, mammaplastia and gynecomastia have been reported which may be associated with altered dopamine neurotransmission or perturbations in sexual hormones. Whereas movement disorders can be objectively noted by the treating psychiatrist and galactorrhea is an AE which the patient readily volunteers, increased breast mass is less frequently directly reported by patients and rarely directly questioned of patients receiving antidepressants. This case report addresses selective gynecomastia in a patient having received multiple antidepressants.

Methods: Case analysis with literature review.

Results: A 67-year-old male with major depression, dysthymia, obsessive-compulsive disorder, social anxiety, hypertension, diabetes, and hyperlipidemia presented with new onset gynecomastia and breast tenderness. Mammography revealed bilateral gynecomastia without suspicious mass, cluster of calcification, or other abnormalities. These new symptoms developed after sertraline was added to his stable medication regimen (duloxetine, alprazolam, rosuvastatin, metoprolol, hydrochlorothiazide, sitagliptin). When sertraline was discontinued, gynecomastia and breast tenderness rapidly resolved. Though the patient had been treated with multiple psychotropics during 13 years (fluoxetine, sertraline, paroxetine, fluvoxamine, citalopram, escitalopram, mirtazapine, duloxetine, bupropion, nortriptyline, alprazolam, pregabalin and modafinil), gynecomastia and breast tenderness only occurred when sertraline was combined with duloxetine.

Conclusion: Gynecomastia is an AE associated with antidepressants but is rarely addressed. Gynecomastia can be antidepressant selective. Clinicians are advised to question patients regarding this potential AE.

P-09-029 Effect of duloxetine on chronic tension-type headache in patients with major depressive disorder

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Objective: A wide variety of antidepressants have been used to treat tension headache in patients with major depressive episode. Alterations in noradrenergic and serotonergic neurotransmitter systems have been implicated in the pathophysiology of major depressive disorder and chronic pain. So the newer antidepressant, duloxetine acting on both noradrenergic and serotonergic neurotransmitter systems is expected to be more effective in pain management in major depressive disorder than selective serotonin reuptake
Objective: It is well recognized that major depressive disorder (MDD) is associated with significant impairment in occupational functioning. However, there is still little information about gains in work productivity with effective treatment of MDD, in part because the intensive nature of standard clinical trials makes it difficult for working patients to participate. In this study, we used a novel clinical trials methodology (telephone raters, telephone administered psychotherapy, on-line questionnaires) to examine work productivity outcomes in treatment of MDD.

Methods: The WORKER Study was a 12-week randomized controlled trial of escitalopram plus cognitive-behaviour therapy (CBT) in employed patients with MDD. Patients were randomized to open-label treatment with escitalopram 10–20 mg with 8 sessions of a validated CBT program administered by trained therapists over the telephone (Tel-CBT), or to escitalopram with adherence reminder telephone calls. Outcome assessments included several work productivity questionnaires (e.g., Lam Employment Absence and Productivity Scale [LEAPS], Sheehan Disability Scale [SDS], Health and Work Performance Questionnaire [HPQ]) completed on-line over a secure web-site.

Results: A total of 98 evaluable patients were randomized to treatment. There were significant gains for both conditions on all measures after 12 weeks of treatment. However, some measures showed greater sensitivity to change and larger effect sizes for one treatment arm.

Conclusion: The novel methodology used in this study may provide better demonstration of productivity gains in clinical trials of depression treatment. Sensitivity to improvement in productivity varies by scale, so productivity scales must be validated in clinical trials.

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The antidepressant effectiveness of agomelatine in severely depressed and elderly depressed patients: Subgroups of the non-interventional study VIVALDI

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Objective: The antidepressant efficacy of agomelatine, a melatonergic agonist and 5-HT2C antagonist, has been demonstrated in clinical trials. The aim of this non-interventional study was to evaluate the effectiveness of agomelatine on depressive symptoms, sleep-wake rhythm and its acceptability in routine practice. Data of 2 subgroups, severely depressed and elderly depressed patients, are presented.

Methods: Within the VIVALDI study 3317 outpatients with MDD were treated by 665 German psychiatrists over 12 weeks. Patients received 25 mg agomelatine once daily (od) at bedtime, with possible dose increase to 50 mg od if needed. Antidepressant effects were evaluated by short-version MADRS (svMADRS) and CGI, the effects on sleep and daytime functioning by a patient questionnaire (modified CircScreen). Adverse drug reactions (ADR) were documented at weeks 2, 6 and 12. Subgroups with severely depressed (svMADRS ≥ 30; n = 1882) and elderly patients ≥ 65 years (n = 446) were analysed.

Results: In the total population, svMADRS total score decreased from 30.6 at baseline to 12.8 at final visit, in severely depressed from 36.7 to 14.7, in elderly depressed patients from 29.0 to 12.2. In total 65.8% of patients could be classified as responders (≥ 50% decrease in svMADRS) and 54.8% as remitters (svMADRS < 12). In the subgroups of severely depressed and elderly depressed patients 67.8% and 65.0% were responders, 47.8% and 59.3% were in remission, respectively. Daytime sleepiness was ameliorated in 78.2% of total population, 80.6% of the severely ill and in 68.0% of the elderly depressed patients. Agomelatine was well tolerated in all groups. ADR were reported for 10.0%, 8.9% and 10.1% of patients in total population, severely ill and elderly depressed patients, respectively.

Conclusion: In this study agomelatine demonstrated the antidepressant effects, improvement of daytime functioning and good tolerability in unselected depressed patients, including multimorbid elderly and severely depressed patients in daily practice.


Investigating nitric oxide synthase as an up-stream mediator of the antidepressant action of ketamine

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Objective: Excessive glutamate transmission at N-methyl-D-aspartate receptors (NMDA-R's) may underlie a primary mechanism in the physiology that leads to depression, and ketamine, an NMDA-R antagonist, rapidly alleviates depression in humans. Several downstream mechanisms are suggested to mediate the antidepressant action of ketamine, including the activation of extracellular-signal-regulated kinases 1/2 (ERK1/2), protein kinase B (or Akt) and the mammalian target of rapamycin (mTOR). However, the mechanism(s) that are affected immediately downstream of NMDA-R's remain unclear. Neuronal nitric oxide synthase (nNOS) couples to and is activated by NMDA-R's, and the uncoupling of the nNOS-NMDA-R complex prevents NMDA-R-mediated excitotoxicity. Therefore, we investigated whether the antidepressant mechanism of ketamine involves the inhibition of nitric oxide (NO) signalling.
Methods: We used a genetic rat model of depression, the Flinders Sensitive Line (FSL) rats, and their control, the Flinders Resistant Line (FRL) rats, to investigate whether l-arginine, a precursor of NO, attenuates the behavioural antidepressant-like effect of ketamine in FSL rats in the forced swim test (FST), and whether l-arginine can prevent the phosphorylation of ERK1/2, Akt and mTOR by ketamine in the frontal cortex in these rats. We also measured the activity of nNOS activity in this region. Four groups of FSL rats received vehicle (saline, i.p.), ketamine (15 mg/kg, i.p.), l-arginine (250 mg/kg, i.p.) or ketamine + l-arginine, and assessed in the FST 1 hour later, whereas their brains were dissected for molecular assays. One vehicle-treated group of FRL rats was used as validation.

Results: Behavioural results showed that l-arginine significantly attenuated the antidepressant-like action of ketamine in the FST. Western blotting and nNOS activity experiments are on-going and these results are imminent.

Conclusion: Results from the FST suggest that ketamine’s antidepressant activity may involve a reduction in NO signalling.

P-09-035 Regulation of biological rhythms with agomelatine in patients with major depression

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Objective: Disruption of circadian function is a cause of neuropsychiatric disorder. Ageing and stress are also associated with a weakened responsiveness of the circadian clock to environmental stimuli. Agomelatine shows chronobiologic effects, it has resynchronization properties. Agomelatine is an agonist of MT1 and MT2 and antagonist 5HT2c receptors, it desinhibits the release of noradrenaline and dopamine in the prefrontal cortex via GABA interneurons. Agomelatine promotes slow wave sleep, increases hippocampal neurogenesis, cell survival, neurotrophic factors BDNF, neuroplasticity and cell survival. It decreases stress induced glutamate release. Activates intracellular signaling involving kinases Erk, GSK3 beta, and Akt. The objective is to regulate the altered circadian rhythms with Agomelatine and also to evaluate its efficacy in the treatment of depression.

Methods: We administered to 150 patients, with moderate major depression, Agomelatine 25 mg, 1 hour before bedtime, during a period of 6 months. We evaluated HAM-D score, HAD for anxiety, Epworth for sleep.

Results: Experienced at least 50% reduction in HAM depression score and improvement in the other parameters. There was decreased depression, prevented relapse, adverse and discontinuation symptoms.

Conclusion: Agomelatine potentiates the effects of melatonin. It restores the circadian rhythm, resetting the suprachiasmatic nucleus, starts a new reorganization of neurotransmitters and hormones. It has the potential to balance all the biological rhythms of hormones producing an improvement in general health,because it helps to reinstate the balance of the PNIE system. It demonstrated efficacy in the management of major depression, anxiety and in the resynchronization of circadian rhythms.

P-09-036 A 6 month cross sectional study of antidepressants use in the first visits in our center for mental health between July and December 2011

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Objective: To evaluate the characteristics of the first 150 new patients and to determine the use of antidepressants in our Center for Mental Health between July and December 2011 and to determine the characteristics of the patients that were prescribed the use of antidepressants.

Methods: Subjects: The population study were one hundred and fifty patients that were first time visited in our Center for Mental Health between July and December 2011. Procedure: This is a cross-sectional study -Independent variable were sex and age. Patients were diagnosed according to DSM’s criteria-IV of Unipolar disorder, Bipolar affective disorder/Psychotic disorders/Substance use disorder/or comorbidity among axis II.

Results: From the selected sample of 150 patients 58 were male and 92 were female. The 82% were treated with antidepressants in the first visit. The 59% of the selected sample were diagnosed of Unipolar Depression disorder, the 21.3% of Anxiety disorders and only a 6% of Psychotic disorder and 5.3% of substances abuse disorder. The mean age of patients treated with antidepressants was 46 years old. The 18% of the patients that were treated with antidepressants had diagnosis of personality disorders. To be women aged between 24th-55th years old were the main variables associated to be prescribed the use of antidepressants (p-value <0.005).

Conclusion: From our selected one hundred and fifty patients visited from the first time in our Adults Center for Mental Health 123 were treated with antidepressant, the 70% of these patients were diagnosed of unipolar depressive disorder (86 patients) and the 22% of the patients treated with antidepressants were diagnosed of anxiety disorders. Antidepressives were most frequently used in that time period by people between 24 and 55 years old. The study shows that 80% of patients visited in our Cente between 24 and 35 years old take antidepressants, more than in any other age-sex group.

P-09-037 Dysthymia treatment with agomelatine

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Objective: Use of agomelatine in patients with dysthymia (DSM-IV-R), to evaluate efficacy and tolerance.

Methods: In 21 patients with dysthymia (14 women and 7 men) we have used for three months agomelatine as basic medication. 7 patients were treated with adjunctive benzodiazepines. We have Assessed the effectiveness of treatment by HAM-D (17 items) on days 0 and 90, also a complete haematological analysis was performed on these small RNAs may be critical for the pathophysiology of mental disorders and may influence the effectiveness of psychotropic drugs. In this work, we wanted to investigate a possible involvement of miRNAs in the mechanism of action of the AD escitalopram (SSRI).

Methods: We conducted a whole-miRNome quantitative analysis with qRT-PCR of the changes in the blood of 10 depressed subjects after 12 weeks of treatment with escitalopram. To get a global interpretation of the possible biological functions of the modulated miRNAs, we conducted a bioinformatic analysis of the 3'UTRs human sequences for the prediction of target genes and a functional survey of the KEGG pathways involved.

Results: Thirty miRNAs were significantly differentially expressed after the treatment: 28 were up-regulated and 2 were strongly down-regulated. The analysis of target genes and related KEGG terms showed a significant enrichment in several pathways associated with neuronal brain functions.

Conclusion: The results of this study represent the first evidence in the blood of MD patients of a possible involvement of miRNAs in AD action. The 12 weeks treatment with escitalopram modified the expression profiles of miRNAs that potentially target a multitude of genes implicated in outstanding neuronal functions in the adult brain.
all patients, including liver enzymes, and recorded the presence of side effects when reported by patients. In 11 patients, we tappered off previous antidepressant treatment because of insufficient therapeutic response, and 10 were new patients, being agomelatine their first treatment.

Results: The mean baseline HAM-D was 14 points and decreased at 3 months to 8 points, almost normal. There were no notable side effects, being Agomelatine well tolerated. The patients improvement was quite rapid.

Conclusion: We believe that agomelatine due to its special mecha-nism of action (melatonergic receptor agonist MT1 and MT2, and antagonist of 5HT2C receptors), and in the regulation of biological clock, as well as depressed mood, should occupy a notable place in the treatment of dystmic Depression.

**P-09-038** Comparison of the effects of agomelatine and the 5HT2C antagonists SB242084 and S32006 on suprachiasmatic nucleus cell firing rates in vitro

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Objective: Agomelatine is a melatonergic agonist and a 5HT2C antagonist with antidepressant activity in animal models and humans. Several preclinical studies have demonstrated that its antidepressant activity depends on synergy between its melatonergic agonist and 5HT2C antagonist properties. We previously showed that both agomelatine and melatonin can cause dose-dependent suppression of firing rates of suprachiasmatic nucleus (SCN) cells in Syrian hamsters in vivo. The aim of this study was to investigate in vitro the mechanism by which agomelatine decreases SCN neuronal activity by comparing its effects to those of two 5HT2C antagonists (SB242084, a neutral antagonist, and S32006, an inverse agonist).

Methods: Coronal slices 500 \(\mu\)m thick containing the SCN were prepared from male Wistar rats, and single-unit recordings of SCN neurons were made using glass microelectrodes. After establishment of baseline firing rates, slices were perfused with vehicle (DMSO) or agomelatine (3.75 mg/100 ml) in one study, or with vehicle (DMSO), SB242084, or S32006 (0.3 mM) in another study.

Results: For agomelatine, 90% of SCN neurons showed \(>20\%\) suppression of firing rates, with decreases averaging 37.3 \(\pm\) 32.3% (SEM) (n=25, p<0.001). For SB242084, 73.8% of neurons showed \(>20\%\) suppression of firing rates, with average decreases of 32.1 \(\pm\) 8.9% (n=45, p<0.01). For S32006, 66.7% showed \(>20\%\) suppression of firing rates, with average decreases of 31.0 \(\pm\) 8.0% (n=20, p<0.01).

Conclusion: These results demonstrate that the two 5HT2C antagonists decrease spontaneous firing rates of SCN neurons in vitro and that their effects are somewhat weaker than those observed with agomelatine. The findings suggest that the melatonergic agonist properties of agomelatine in synergy with its 5HT2C antagonist properties could be involved in immediately its effects on SCN neurons. Studies using a melatonergic antagonist (S22153) are ongoing to further clarify agomelatine's mechanism of action.

**P-09-039** Pioglitazone as an adjunct to citalopram for moderate to severe major depressive disorder: Randomized double blind placebo-controlled trial

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Objective: Major depressive disorder (MDD) is associated with immune and metabolic disturbances, neuroinflammation, and impaired neuroprotection. Thiazolidinediions(including pioglitazone) have important immunoregulatory, neuroprotective, anti-inflammatory, and anti-neuroinflammatory properties. Moreover, these drugs have shown antidepressant effect in animal models of depression as well as open-label human studies of concurrent MDD and metabolic syndrome. We aimed to evaluate the antidepressant effect of add-on pioglitazone in patients with MDD in the absence of metabolic syndrme and diabetes.

Methods: This was a randomized double-blind placebo-controlled study (NCT01109030). Forty patients with MDD (DSM-IV-TR) who had Hamilton depression rating scale-17 (Ham-D) score \(>22\), were randomized to pioglitazone (15 mg every 12 hours) (n=20) or placebo (n=20) in addition to citalopram for six weeks. Evaluation was done using Ham-D at baseline and, second, fourth and sixth weeks. Fisher's exact test was used for comparison of early improvement (\(>20\%\) score reduction by second week), treatment response (\(>50\%\) score reduction), and remission(score \(\leq 7\)) between the two groups. Two-factor analysis of variance (ANOVA) with repeated measures, and analysis of covariance were used for comparison of scores between placebo and pioglitazone groups.

Results: More patients in pioglitazone group achieved early improvement, response at sixth week, and remission than placebo group. (95.95%, 45% in pioglitazone group versus 30%, 40%, 15% in placebo group, \(P<0.001, 0.001, 0.04\) respectively). Repeated measure ANOVA showed significantly better results in pioglitazone than placebo group during the course of the study [F(1,38)=9.483, p=0.004] [Figure 1]. Subjects in pioglitazone group showed significantly lower scores at all time-points (aexcept baseline) than placebo group (\(P<0.01\)). Frequency of side effects was similar between the two groups.

Conclusion: Pioglitazone is an effective and safe add-on treatment in patients with moderate to severe MDD, even when metabolic syn-drome and diabetes are not present.

**P-09-040** Risk factors of drug interaction between warfarin and antidepressant in a clinical setting

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Objective: Patients with cardiovascular or cerebrovascular diseases are at increased risk of developing depression and when depression develops, vascular risk is exacerbated further (Lett H., 2004; Frasure-Smith N., 2009). Patients with treatment-resistant depression after an acute coronary syndrome are at an even greater risk for cardiovascular accidents (Carney R., 2009). Treatment of depression in these pa-tients should be emphasized not only to improve quality of life but also to acquire a better prognosis of vascular disease. Information concerning antidepressant use concurrently with warfarin is scarce. A study evaluating the risk factors for INR change in respect with warfarin and antidepressants would be very helpful.

Methods: In this study, we evaluated the risk factors for INR in-crease after addition of an antidepressant in a total of 312 patients who used warfarin. Patients' sex, age, BMI, AST, ALT) creatinine, indica-tion of warfarin use, dose of warfarin, type of added antidepressant were assessed for investigating possible risk factors with INR increase \(\geq 15\%\) after adding an antidepressant.

Results: Among 312 patients, 106 patients (34.0%) showed an elevation of \(\geq 15\%\) after adding an antidepressant. We selected 12 antidepressants which were used in more than 5 patients. These 12 antidepressants were used in 300 patients. Univariate analysis showed level of creatinine, indication of warfarin use, dose of warfarin, type of used antidepressants are potential risk factors for INR increase in respect to antidepressant and warfarin interaction.
Among the antidepressants, imipramine showed statistically significant increase of INR in warfarin users.

**Conclusion:** The results of this study suggest that level of creatinine, indication of warfarin use, dose of warfarin, adding imipramine are risk factors for INR increase with respect to the interaction of antidepressant and warfarin. The small number of patients is a limitation of this study. A large-scale study comparing multiple antidepressants will be needed.

**P-09-041** Effect of a single dose SSRI on serotonin levels in the non-human and human primate brain

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**Objective:** Despite widespread use of selective serotonin reuptake inhibitors (SSRIs) for treatment of depression and anxiety disorders, the exact mechanism underlying the clinical effect remain unclear. We previously demonstrated that the newly developed 5-HT1B-receptor specific radioligand [11C]AZ10419369 is sensitive to changes in endogenous serotonin concentrations in monkey. The primary aim of the present study was to examine whether a single dose of a SSRI (escitalopram) affects endogenous serotonin levels in serotonergic projection areas.

**Methods:** The study was performed in 3 monkeys and 9 human subjects. All subjects were examined with PET and [11C]AZ10419369 at baseline and post-dose conditions (monkey n=7, human n=9). Escitalopram was administered intravenously (2 mg/kg) to monkeys, and per orally (20 mg) to humans. The binding potential (BPND) of [11C]AZ10419369 in serotonergic projection areas (e.g. cortical regions, caudate nucleus, putamen and thalamus) were defined by means of the simplified reference tissue model (SRTM) and an equilibrium method (monkeys only). The difference in BPND between pre- and post-dose PET measurements was the primary outcome.

**Results:** In monkeys the BPND decreased post-dose in all examined brain regions. The decrease reached statistical significance in occipital cortex, midbrain, dorsolateral prefrontal cortex and thalamus (p < 0.05). In humans, there was on the contrary no decrease in BPND post-dose. Across examined areas there was rather a small increase in BPND, which reached statistical significance in occipital cortex (5±3 %; p<0.05).

**Conclusion:** A single dose of escitalopram generated a small, but significant, decrease in BPND in monkey, consistent with elevated serotonin levels. In humans, no evident effect was found at a 7-fold lower dose level. The study does not support a major effect on serotonin levels after administration of a single dose escitalopram in clinically relevant doses in either species.

**Policy of full disclosure:** The radioligand [11C]AZ10419369 has been developed in a cooperation between Karolinska Institutet and AstraZeneca. Lars Farde also holds a position as Chief Scientist, iMed CNS/Pain, AstraZeneca, Sweden.

**P-09-042** Chronic fluoxetine treatment increases neurogenesis in the cortex of adult mice

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**Objective:** Adult neurogenesis in the hippocampal subgranular zone (SGZ) and the anterior subventricular zone (SVZ) is regulated by various factors including neurotransmitters, hormones, stress, aging, voluntary exercise, environmental enrichment, learning, and ischemia. Chronic treatment with selective serotonin reuptake inhibitors (SSRIs) modulates adult neurogenesis in the SGZ, which is hypothesized to mediate the antidepressant effect of these substances. Layer 1 inhibitory neurons progenitor cells (L1-INP cells) were recently identified in the adult cortex, but it remains unclear what factors other than ischemia affect the neurogenesis of L1-INP cells.

**Methods:** FLX solution was intraperitoneally injected into mice at a certain dose per day for 3 weeks. FLX concentrations were determined for individual mice. For FLX pellet treatment, the mice were subcutaneously administered either FLX or control pellets (Innovative Research of America) in the dorsal interscapular region. To label L1-INP cells and new neurons with the retrovirus vectors that express a fluorescence protein Venus under the enhanced synapsin I promoter, the virus solution was stereotaxically injected into the cortical layer 1 of mice.

**Results:** Immunofluorescence and genetic analyses revealed that FLX treatments increased the number of L1-INP cells in all examined cortical regions in a dose-dependent manner. The virus labeling showed that Venus-expressing GABAergic interneurons were generated from retrovirus vector-labeled L1-INP cells.

**Conclusion:** This study indicates that FLX treatment can control the production of GABAergic interneurons in the cortex. The cortical neurogenesis of L1-INP cells would also account for some of the therapeutic effects of antidepressants.

**P-09-043** Compliance of depressed patients treated with specific serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs)

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**Objective:** Current data confirms previous estimates that depression will become in the near years one of the most important causes of social disability. Given the importance of the problem, patient adherence to an antidepressant treatment that has clinical efficacy, tolerability and functional rehabilitation is essential in the management of depression. The objective of this comparative study between the two classes of antidepressants was to evaluate the dynamic predictors that might influence the therapeutic adherence.

**Methods:** As a working method we carefully selected two groups of patients so that were no significant differences in the demographic, socio-professional, economic and family status. The study was designed with six evaluation visits at significant intervals, thus allowing us to obtain statistically significant data. Instruments used: MADRS to assess the severity of depression, Sheehan Disability Scale (SDS) as a global functionality scale, tolerability evaluation through direct interview and by spontaneous reporting of adverse reactions.

**Results:** The dynamics in MADRS score for the two groups of patients treated with two classes of antidepressants was comparable. Both classes proved to be effective as of 3 months and there were no statistically significant differences between the two classes in terms of therapeutic remission. Patients in both groups showed improvement in quality of life already noticeable at first evaluation (probably due to a lower acute depressive symptomatology), the patients treated with SSRIs having a better socio-occuopational functioning (p = 0.001). There was a significant difference between the percentages of patients who
abandoned the study because of side effects, a significantly higher proportion of patients in the group treated with TCAs presenting side effects severe enough to warrant withdrawal from research.

Conclusion: Although part of different generations of antidepressants, both SSRIs and TCAs are effective and retain the long-term effectiveness, the only obvious difference being therapy discontinuation due to adverse reactions.

**P-09-044** Experimental medicine model shows no depressogenic effects of varenicline

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Objective: To assess the effects of varenicline on emotional and non-emotional cognition. Varenicline is a partial agonist at α4β2 nicotinic acetylcholine receptors (nAChRs) and also binds at several other nAChRs; the drug is used clinically as an aid to smoking cessation. Post marketing data suggested an association between varenicline and depression and suicide, leading to a black box warning. By contrast, animal studies indicated a potential antidepressant effect. There is also evidence to suggest that varenicline may benefit non-emotional cognition, in particular working memory. Healthy volunteer models of emotional processing have the potential to detect both antidepressant and depressogenic effects of drugs (e.g. Horder et al., 2012).

Methods: We randomized 41 non-smoking healthy volunteers to receive varenicline (final dose 1 mg) or placebo for seven days. On the seventh day emotional processing (facial expression recognition, emotional memory and dot probe) and non emotional cognition (working and declarative memory) were assessed.

Results: 38 volunteers were included in the analysis. Varenicline did not affect subjective ratings of mood. There were no specific effects of the drug on facial expression recognition or the dot probe. Varenicline did, however, speed responses (p = 0.02) to positive words in the emotional recognition memory test. Varenicline also affected non-emotional memory with positive effects on recall memory (p = 0.02) and working memory (p = 0.03).

Conclusion: These results suggest that varenicline does not have a depressogenic effect in a healthy volunteer model, in fact the emotional recognition memory finding is more in keeping with the preclinical data in suggesting an antidepressant-like effect of the drug. These data also provide further evidence to support the involvement of nAChRs in non-emotional memory. Horder et al. (2012) J Psychopharmacol 26: 125–32.

Policy of full disclosure: C HJ has acted as a consultant for the following companies: Servier, GSK, Astra-Zeneca. Lundbeck and Pfizer. She also holds shares in Pfizer and is on the advisory board. PJF has been a paid member of advisory boards of Eli Lilly, Lundbeck, Servier and Wyeth and has been a paid lecturer for Eli Lilly, Servier, and GlaxoSmithKline. He has received remuneration for scientific advice given to legal representatives of GlaxoSmithKline. AP, EP, RJM, CPP and SFNCT report no conflicts of interest.

**P-09-045** Effects of low-trapping NMDA channel blocker AZD6765 on gamma-band EEG and psychotomimetic liability: A comparison to ketamine in freely behaving rats

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Objective: NMDA channel blockers increase gamma-band (~ 40 Hz) EEG – a potential biomarker of cortical disinhibition. Cortical disinhibition is believed to contribute to the antidepressant properties of the NMDA antagonist, ketamine. However, changes in spontaneous gamma-band EEG have been hypothetically linked to ketamine’s psychotomimetic adverse effects. Based on in vitro and behavioural studies, AZD6765, a low-trapping NMDA channel blocker, in clinical development for major depression, is predicted to have an improved tolerability profile compared with ketamine. The object of the current study was to test the hypotheses that gamma-band EEG activity can be separated from preclinical measures of psychotomimetic liability and evaluate the adverse effect profile of AZD6765 relative to ketamine.

Methods: EEG and behaviour were monitored simultaneously following administration of AZD6765 or ketamine to rats chronically implanted with skull surface electrodes and trained to perform an auditory detection task for food reward. Pharmacokinetic-pharmacodynamic modeling related EEG power within the gamma-frequency band (35–55 Hz) to free plasma and brain concentrations.

Results: Both ketamine and AZD6765 produced concentration-dependent elevations in gamma-EEG. Based on free brain exposures, the in vivo potency of AZD6765 (relative to in vitro MK-801 site-binding affinity) was greater than that of ketamine. At high plasma concentrations and high gamma-EEG, ketamine and AZD6765 produced transient reductions in attention; however, for comparable levels of gamma-band EEG, AZD6765 produced significantly less performance impairment and less hyper-locomotion than ketamine.

Conclusion: This study explored gamma-band EEG measurement as a translational, pharmacodynamic biomarker of NMDA channel blockade. Based on its ability to elevate gamma-band EEG without producing the same degree of behavioural disruption as ketamine, AZD6765 may deliver antidepressant benefits comparable with ketamine but with reduced psychotomimetic liability.

Policy of full disclosure: Full-time employee of AstraZeneca.

**P-09-046** Mode of action of agomelatine: Synergy between melatonergic and 5-HT2C receptors

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Objective: Agomelatine is a novel and clinical effective anti-depressant drug with melatonergic (MT1/MT2) agonist and 5-HT2C receptor antagonist properties. Both receptorial components are widely expressed in the central nervous system and, although the role of the different receptor activities of agomelatine in relation to its antidepressant action has not been fully elucidated, it seems that this compound could act synergistically on both the melatonergic and the 5-HT2C receptors. Aim of this poster is to highlight the available preclinical evidence suggesting that the molecular/cellular effects of agomelatine and, in turn its antidepressant activity, are the result of a synergic action between its agonism at MT1/MT2 and antagonism at 5-HT2C receptors.

Results: Indeed, it was found that survival of newborn hippocampal cells is stimulated only when both receptorial actions of agomelatine are present. In the same way, only agomelatine but not the two individual components attenuated the circadian rhythm of BDNF transcript in prefrontal cortex, resulting in significantly higher expression level in the morning, and increased Arc expression. Moreover, agomelatine showed a typical effect of antidepressants, blockade of acute stress-induced increase of glutamate release in cortical areas, which was not replicated by treatments with either mela
ton or a selective 5-HT2C receptor antagonist. This synergic action was shown to be responsible for agomelatine effects on neurogenesis, BDNF, Arc and glutamate release. Even if traditional antidepressants also modulate these parameters, this effect is not optimized as in the case of agomelatine, which is able to resynchronize these effectors at distinct circuital and intracellular levels.

Conclusion: Taken together, these findings strongly suggest that agomelatine effects at the cellular level result from a synergistic interaction between its action on MT1/MT2 and 5-HT2C receptors. This interaction underlies the efficacy of agomelatine in terms of restoring circadian rhythms and relieving depressive symptoms.

Policy of full disclosure: GR has scientific collaboration with and is member of scientific board for Eli Lilly, Innova Pharma, and Servier. MAR has received honoraria or research support from AstraZeneca, Bristol-Myers Squibb, Dainippon Sumitomo Pharma Co. Ltd, Eli Lilly, Innova Pharma, Merck Sharp & Dohme, Servier and Takeda. MP has received research support and/or has been consultant for Albiogen, GlaxoSmith-Kline, MerckSharp & Dohme, Servier and Fidia. The other Authors declare no conflict of interest. All authors did not receive any support for this paper from Servier.
P-09-047 Treatment of major depressive disorder in epilepsy

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Objective: In epileptic subjects often appears Major depressive disorder. Clinically experience suggest that low doses of SSRI are the measure better than other antidepressants agents. In this study we confirm the findings in controlled design.

Methods: The total of 67 adult patients of both genders (28 females) with Grand-mall epilepsy (clinically and EEG verified) and depression was treated either with sertraline p.o. 50 mg qd (n=35) or with psychotherapy, particularly supportive approach (n=32).

Conclusion: Diagnosis of epilepsy was confirmed clinically and by EEG. Diagnosis of depression was established with DSM-IV criteria and severity of illness was assessed with the use of HAM-D scale at baseline, after 2, 4, 6 and 8 weeks.

Results: The total HAM-D scores for sertraline group at baseline, 2, 4, 6, and 8 weeks were 22.36±5.35, 16.89±4.64, 13.97±3.12, 11.99±3.05 and 9.02±1.64, respectively (p<0.05). The total HAM-D scores for control group at baseline, 2, 4, 6, and 8 weeks were 22.96±5.11, 19.65±4.03, 19.12±4.07, 17.81±4.14 and 17.23±4.76, respectively (p<0.05). HAM-D scores of sertraline group was significantly lower than that ones in supportive psychotherapy group (p<0.05). There were no differences in number of seizure episodes in study groups (1 vs. 1, p>0.05).

Conclusion: Sertraline was significantly effective in ameliorating of Major depressive episode in epilepsy, with no additional risk for seizures.

P-09-048 Aripiprazole adjunctive pharmacotherapy in depression: Probable drug-drug interaction

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Objective: Aripiprazole is a third generation antipsychotic with partial dopaminergic activity. In addition to its proven antipsychotic effects, it has become more widely accepted at the clinical level. It is FDA-approved as an adjunctive therapy for depression with or without psychotic features. This case report concerns the development of severe Parkinsonian features in a depressed psychotic patient following the addition of aripiprazole to his sertraline treatment.

Methods: Irrelevant (case report).

Conclusion: The occurrence of extrapyramidal side effects of aripiprazole in the case reported here is likely attributable to multiple drug interaction. This may be explained by hepatic cytochrome P450-dependent metabolism of aripiprazole, in particular the enzyme sub-

Results: The total HAM-D scores for sertraline group at baseline, 2, 4, 6, and 8 weeks were 22.36±5.35, 16.89±4.64, 13.97±3.12, 11.99±3.05 and 9.02±1.64, respectively (p<0.05). The total HAM-D scores for control group at baseline, 2, 4, 6, and 8 weeks were 22.96±5.11, 19.65±4.03, 19.12±4.07, 17.81±4.14 and 17.23±4.76, respectively (p<0.05). HAM-D scores of sertraline group was significantly lower than that ones in supportive psychotherapy group (p<0.05). There were no differences in number of seizure episodes in study groups (1 vs. 1, p>0.05).

Conclusion: Sertraline was significantly effective in ameliorating of Major depressive episode in epilepsy, with no additional risk for seizures.

P-09-049 Augmenting ssris with an alpha2beta2nachr partial agonist: Lack of efficacy on major depressive disorder with insufficient response

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Objective: An nAChR Partial Agonist (PA) was tested in a proof-of-concept study to investigate its efficacy, safety, and tolerability in the augmentation of SSRIs therapy in MDD with insufficient clinical response.

Methods: An OL 8 week SSRIs treatment was followed by a 6-week, DB phase where subjects were randomized to adjunctive nAChR PA or placebo, while continuing on ADT. The primary efficacy endpoint was the change from DB baseline (week 8) in the MADRS total score at week 14. Independent remote interviews were utilized to confirm eligibility at screening and at week 8.

Results: In the OL phase, 297 subjects were treated with SSRIs, of whom 162 (54.5%) subjects were qualified to be randomized in the DB phase. When 113 of 198 planned subjects in double-blind phase (57%) either completed or discontinued the study, a Sponsor unblinded interim analysis for efficacy and safety was conducted. The stopping rule for futility was met and the study was terminated early. In the final analysis, the treatment difference presented in LS mean ± S.E. of the nAChR PA vs. PBO was −1.30 ± 1.565 with 2-sided 80% confidence interval (−3.32, 0.71). (2-sided p=0.4062). Placebo response rate (MADRS change from DB baseline at Week 6 of the DB phase; LS mean ± S.E = –8.30 ± 1.088) was not a factor in the lack of drug effect. Exploratory post-hoc analyses are currently ongoing.

Conclusion: The lack of a treatment effect of nAChR PA vs. placebo was demonstrated. Interim analysis with a futility rule allowed for early termination. Placebo response rate was not a factor in the lack of drug effect. The drug was safe and well tolerated in this study.

Policy of full disclosure: Pfizer, Inc.

P-09-050 Combined use of selective serotonin reuptake inhibitor drugs with other CNS active drugs during early pregnancy. Consequence on congenital malformation risk

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Objective: Many studies have shown that pregnant women who use selective serotonin receptor inhibitors (SSRI) also use several other drugs in excess compared with other pregnant women. The present study aimed to identify women with combined use of SSRIs and other CNS-active drugs in early pregnancy and to study the possible impact of such combinations on teratogenicity. It has been suggested that the combined use of SSRI and benzodiazepines should represent a higher teratogenic risk than either of the two drug categories.

Methods: Data from the Swedish Medical Birth Registry was used. Women giving birth between July 1, 1995 and December 31, 2008 (n =1,290,672) were interviewed in early pregnancy by midwives. Use of any CNS active drug was reported by 26,511 and 12,050 of them reported the use of SSRI. Data was adjusted for year of birth, maternal age, parity, smoking in early pregnancy, number of previous miscarriages, and body mass index. The teratogenicity risk analyzes were performed in two steps: (1) for each single category of drugs: Opioids (except dextromethorphan and codeine), Dextropropoxyphene or codeine, Anticonvulsants, Antipsychotics (except lithium, dixyrasine and proclorperazine), Lithium, Benzodiazepines, Hypnotic benzodiazepine receptor agonists, and Other sedatives or hypnotics, and (2) for concomitant use of an SSRI and one or more of the listed drug categories.

Results: Use of anticonvulsants, antipsychotics, or lithium alone was associated with an increased risk for any relatively severe congenital malformation and the use of opioids with an increased risk for a cardiovascular defect. The most common drug combination was SSRI and a benzodiazepines; n =509. No risk increase for any congenital malformation or for a cardiovascular defect was found.

Conclusion: The suggested synergistic action of SSRI drugs and benzodiazepines with respect to teratogenesis could not be supported.

P-09-051 Effect of antidepressants on serum sodium levels – a prospective study

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Objective: Antidepressants especially Selective Serotonin Reuptake Inhibitors have been associated with hyponatremia, though literature is mainly in the form of case reports. Considering paucity of literature this study aims to establish the incidence, risk factors, time of detection of hyponatremia complicating treatment with antidepressant therapy. Also, to objectively assess the causality, severity and preventability of hyponatremia.

Methods: A Prospective study with 74 patients in the Psychiatric outpatient setting. All patients evaluated by Psychiatrist, initiated on antidepressant therapy, with normal serum sodium concentration at

(57%) either completed or discontinued the study, a Sponsor unblinded interim analysis for efficacy and safety was conducted. The stopping rule for futility was met and the study was terminated early. In the final analysis, the treatment difference presented in LS mean ± S.E. of the nAChR PA vs. PBO was −1.30 ± 1.565 with 2-sided 80% confidence interval (−3.32, 0.71). (2-sided p=0.4062). Placebo response rate (MADRS change from DB baseline at Week 6 of the DB phase; LS mean ± S.E = –8.30 ± 1.088) was not a factor in the lack of drug effect. Exploratory post-hoc analyses are currently ongoing.

Conclusion: The lack of a treatment effect of nAChR PA vs. placebo was demonstrated. Interim analysis with a futility rule allowed for early termination. Placebo response rate was not a factor in the lack of drug effect. The drug was safe and well tolerated in this study.

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baseline and meeting eligibility criteria were conducted into the study with a follow up of more than 6 months.

Results: Overall incidence of hyponatremia [c < 135mEq/L] was 32.4% [24/72]. Time to detection of hyponatremia was 224.71 ± 117.79 days [Mean ± SD]. We found a moderately strong positive correlation between the use of mirtazapine (p value of 0.089) and venlafaxine (p value of 0.097) with hyponatremia. Though not statistically significant we identified 3 cases of hyponatremia with use of Milnacipran which has not been reported so far. No risk factors could be isolated as significant on multivariate regression analysis. Of the cases 85.7% were identified as “probable” with Naranjo’s Algorithm of causality assessment, 91.7% were identified as “moderate severity – level 3” on Hartwig and Siegel’s scale and all the cases were “probably preventable” on Schumock and Thornton scale.

Conclusion: Hyponatremia is an under-recognized and potentially serious complication of antidepressant therapy. There is a need for awareness and routine monitoring especially during the initial weeks of therapy and stratification of patients based on risk factors such as co morbid medical conditions and concomitant medications. Our results provide the foundation of a model for prevention, early detection and treatment of hyponatremia there by reducing the mortality, morbidity and health care costs associated with preventable adverse medical events.

P-09-052 Similarities in the biochemical modulation of DARPP-32, CREB, CamKII and AMPA receptors by lurasidone and fluoxetine

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Objective: Some atypical antipsychotics have antidepressant properties and are used as adjuvant therapies in depression. Lurasidone, a novel atypical antipsychotic, acts as an antagonist at D2, 5-HT2A and 5-HT7 receptors, but agonist at 5-HT1A receptors, a binding profile indicative of antidepressant properties. This study therefore aimed at comparing the biochemical actions of lurasidone with that of the fluoroxetine, risperidone and the selective 5-HT7 receptor antagonist, SB-258741.

Methods: Male adult C57Bl6 mice received daily oral gavage for 3 weeks with vehicle, lurasidone (3 mg/kg), fluoxetine (20 mg/kg), risperidone (1 mg/kg) or SB-258741 (10 mg/kg). One hour after the last drug administration, mice were killed by decapitation and their brains were rapidly snap frozen. Cortices, hippocampi and ventral striata were processed for immunoblotting to measure the phosphorylation states of proteins implicated in actions of antidepressants.

Results: Fluoxetine and lurasidone, but not risperidone and SB-258741, shared the ability to decrease P-Ser845-GluR1 and P-Ser133-CREB in hippocampus. Previous work has indicated that fluoroxetine increases the phosphorylation states of Glur1 and CREB. This discrepancy is likely due to differences in probe selectivity (P vs. subcutaneous or intraperitoneal) and/or treatment duration between studies. Fluoxetine and lurasidone, but not risperidone and SB-258741, also increased P-Thr286-CamKIIbeta in ventral striatum. Finally, fluoxetine and lurasidone decreased P-Thr34-DARPP-32 in ventral striatum, an effect shared with risperidone and SB-258741.

Conclusion: These data demonstrate similarities in the biochemical modulation of several important signaling molecules by lurasidone and fluoxetine. Future studies will evaluate whether co-administration of lurasidone will augment biochemical effects of fluoxetine and study behavioral paradigms of antidepressant efficacy.

Policy of full disclosure: Dainippon Sumitomo.

P-09-053 Enhanced memory for reward cues following acute buprenorphine administration in humans

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Objective: The mu-opioid system has been implicated in the preferential processing of reward cues in rodents, but no such data are available in humans. The happy facial expression is a pivotal reward cue in humans, and it has been shown that impaired memory for facial happiness is associated with self-reported and hormonal measures of depression. We investigated whether a single 2 mg administration of the mu-opioid agonist, buprenorphine, would change short-term memory for happy, angry or fearful expressions relative to neutral faces.

Methods: Healthy human subjects participated in a randomized placebo-controlled within-subject design, in which they performed an emotional face relocation task after administration of buprenorphine and placebo.

Results: Compared to placebo, buprenorphine resulted in a significant enhancement of the memory for happy faces relative to neutral faces.

Conclusion: Our data demonstrate, for the first time in humans, that acute up-regulation of the mu-opioid system increases the processing of reward cues, and thus points at potential antidepressant properties of mu-opioid agonists in humans.

P-09-054 SERT and NET occupancy by serotonin and norepinephrine reuptake inhibitors in non-human primates in vivo

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Objective: The monoamine systems are key targets for antidepressant drugs. The combined serotonin and norepinephrine reuptake inhibitors (SNRIs), a subgroup of antidepressants, have been reported to show a large variability in relative affinity in vitro for the serotonin transporter (SERT) and norepinephrine transporter (NET), respectively. For instance, the calculated affinity ratio is about 30 for venlafaxine, and 1.6 for milnacipran. However, in vitro data do not completely predict in vivo conditions. In this study in nonhuman primates, the in vivo occupancy of SERT and NET of the two SNRIs, venlafaxine and milnacipran was examined by PET.

Methods: PET measurements with [11C]MADAM, a PET radioligand for SERT, and [18F]MeNER-D2, a PET radioligand for NET, were performed in two female cynomolgus monkeys using the High Resolution Research Tomograph (HRRT) system at baseline conditions and after intravenous administration of venlafaxine or milnacipran, respectively. The relationship between dose, plasma concentration and transporter occupancy was examined by using the hyperbolic function developed for saturation analysis and a binding affinity (Kd) was expressed by the dose or plasma concentration corresponding to 50% occupancy of the transporter.

Results: After administration of venlafaxine and milnacipran SERT and NET were occupied in a dose and plasma concentration dependent manner. The affinity ratio between SERT and NET was 1.9 for venlafaxine and 0.6 for milnacipran.

Conclusion: In this PET study in nonhuman primates, the affinity in vivo was similar at SERT and NET after administration of any of the two test-drugs venlafaxine and milnacipran. This observation is not consistent with in vitro data in the literature and illustrates the need for in vivo studies when characterizing antidepressants.

P-09-055 Antidepressants as putative seizure-precipitating factors in Taylor's dysplasia

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Objective: This is a case report of a patient with depressive symptoms and a history of Taylor’s dysplasia (an epileptogenic cerebral cortical dysplasia) who demonstrated late-onset epilepsy.

Methods: We reviewed the patient’s case notes and the literature on Taylor’s dysplasia and the association of antidepressants with epileptic seizures.

Results: The patient is a 42 year old Greek woman who presented at the Emergency Department following a suicide attempt by drug overdosing and coexisting depressive symptoms. The patient had a history of Taylor’s dysplasia, which is associated with epilepsy, but had not experienced seizures until 5 years ago. At that time she...
was first prescribed mirtazapine for the treatment of anxiety and depressive symptoms. Following mirtazapine administration she developed focal seizures associated with aura. Thereafter, she experienced 5–6 seizures per year and was treated with oxcarbazepine. Depressive symptoms proved resistant to mirtazapine and she sequentially received venlafaxine and several specific serotonin reuptake inhibitors with moderate results. Since the first appearance of seizures she has always been under treatment with antidepressants. At psychiatric assessment she exhibited depressive mood, fatigue, loss of energy, inability to cope with stress but was free from active suicidal ideation. Her medication comprised Paroxetine 20 mg, oxcarbazepine 600 mg and lorazepam 5 mg daily. Following admission to psychiatric ward and due to the potential association of paroxetine with seizures, paroxetine was discontinued and oxcarbazepine was increased to 900 mg daily. Despite paroxetine discontinuation, her psychiatric symptoms improved. After three months of follow up she remains free of seizures and no longer demonstrates depressive symptoms.

Conclusion: This case report suggests that antidepressants could precipitate seizures in a patient with depressive symptoms and Taylor’s dysplasia. We conclude that antidepressants should be used with caution in patients suffering from brain disorders predisposing to epilepsy.

P-09-056 Efficacy of paroxetine compared to fluoxetine in the elderly patient with major depressive disorder
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Objective: Depression is a common problem in older adults. The symptoms of depression affect every aspect of your life, including energy, appetite, sleep, and interest in work, hobbies, and relationships. There are many antidepressants for the effective treatment of depression in elderly people. To compare fluoxetine vs. paroxetine in terms of efficacy and time of starting effect.

Methods: The efficacy of paroxetine and fluoxetine and their effects on cognitive and behavioural function were compared in a 6 week, randomly assigned study of 60 elderly depressed patients (aged 61 to 75 years). Antidepressant efficacy was assessed using the Hamilton Depression Rating Scale (HAMD), Beck Depression Inventory and Clinical Global Impression (CGI) scale. The Mini-Mental State Examination (MMSE), and HAMD cognitive factor scores were used to assess cognitive and behavioural function.

Results: Paroxetine demonstrated comparable efficacy to fluoxetine in the treatment of elderly depressed patients, but at the end of treatment, there was a significantly higher proportion of responders to paroxetine than to fluoxetine. Both treatments produced improvements in all measures of cognitive and behavioral function.

Conclusion: Paroxetine was significantly superior to fluoxetine from Week 3, indicating a possible early effect. There was no difference between the two agents in either the tolerability or safety of treatment.

P-09-057 Polypharmacy in major depressive disorder
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Objective: Major Depressive Disorder (MDD) is a disorder, that causes interpersonal disfunctioning. Although monotherapy is usually recommended in the initial phase of treatment, the results of STAR*D show, that <30% of the patients gain remission with monotherapy. The goal of this study is to investigate the incidence of antidepressant combination therapy against monotherapy between patients with severe depression, who are hospitalized in acute treatment departments in the Psychiatric Hospital of Attica.

Methods: The participants (47 patients) were randomly selected among the patients of the 9 acute treatment departments in the Psychiatric Hospital of Attica. Statistic program SPSS was used in the analysis.

Results: The participants (47 patients) had average age of 51.3 years (SD = 13.7). 44.7% of them were men, 10.6% were in involuntarily admitted in hospital, 66% had suicidal ideation or/and attempted suicide, only 23.4% of them had their first episode, 25.5% used also illegal substances. The average age of onset for their disorder was 35.7 years (SD = 16.6). 34% of these patients were treated with only one antidepressant, while the rest of them were treated with a combination of anxiolytics and/or mood stabilizers. After 3 weeks of treatment 23.4% of them were treated with only one antidepressant, when combination therapy with more than 3 medications was more complex and frequent. We were not able to find any statistically significant differences between the beginning of involuntary admission and the discharge in terms of combination treatment.

Conclusion: Due to development study of psychopharmacology treatment for Major Depressive Disorder a new tendency has appeared: increased polypharmacy – the concurrent use of many medications – for the treatment of depression.

P-09-058 Selective serotonin reuptake inhibitors inhibit glycoprotein vi-mediated platelet aggregation through the influence of the interaction between FCRY and syk
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Objective: Platelets are recognized as a peripheral model for central serotoninergic neurons because they share similarity in structure, function, and storage and metabolism of serotonin. The antidepressants selective serotonin reuptake inhibitors (SSRIs) block the reuptake of serotonin through serotonin transporter in neurons as well as platelets. We currently reported that an SSRI, citalopram, exerts an agonist dependent role in inhibiting the aggregation in response to collagen and convulxin, indicating that the transport of serotonin regulates the activation of glycoprotein (GP) VI-mediated pathways. Therefore, we further clarify the mechanism of the inhibitory effect of SSRIs on GPVI-mediated pathway of platelet aggregation.

Methods: Blood from healthy donors was collected by venipuncture into sodium citrate (9:1) and centrifuged to prepare platelet-rich plasma. The antplatelet effect of SSRIs was determined by platelet aggregometer. The expression of GPIIb/IIIa and P-selection on platelets was examined by flow cytometry. The influence of SSRIs on the molecules of GPVI-dependent signal transduction pathways was determined by Western immunoblot.

Results: SSRIs inhibited convulxin-induced platelet aggregation in a concentration-dependent manner. SSRIs inhibited the expression of GPIIb/IIIa and P-selection induced by convulxin. In addition, SSRIs concentration-dependently inhibited the phosphorylation of signaling molecules including Akt and Syk, but there was no inhibitory effect on the phosphorylation of FcRy, indicating that the target site of SSRIs in the inhibition the GPVI dependent activation pathway is downstream of FcRy and upstream of Syk. FcRy was co-immunoprecipitated with Syk under the stimulation of convulxin. Pretreatment of platelets with SSRIs reduced the amount of FcRy co-immunoprecipitated with Syk.

Conclusion: In platelets, the transport of serotonin through serotonin transporter during GPVI stimulation regulated the interaction or the recruitment of Syk to FcRy. This study partially explains the mechanism of the antplatelet effect of SSRIs.

P-09-059 Comparative analysis of agomelatine and selective serotoninergic reuptake inhibitors in major depressive disorder with severe anxiety features
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Objective: To evaluate the comparative medium term efficacy and tolerability of agomelatine versus selective serotoninergic reuptake inhibitors (SSRIs) in patients diagnosed with major depressive disorder and significant anxiety symptoms.

Methods: We included in our study 42 patients, 28 female and 14 male, age mean 41.5, diagnosed with major depressive disorder, according to DSM IV TR criteria, who also presented a Hamilton Anxiety Rating Scale (HAMA) score of at least 25, corresponding to...
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Severe anxiety. Mean duration of hospitalization was 12.7 days and both the depressive and anxiety symptoms were treated using either agomelatine 25–50 mg daily, flexible dose or an SSRI (fluoxetine 20–40 mg daily, paroxetine 20–40 mg daily or escitalopram 10–20 mg daily). Patients were monitored every 4 weeks for 6 months with psychometric instruments- Hamilton Depression Rating Scale (HAMD) 17 items, HAMA, Clinical Global Impressions- Severity/Improvement (CGI-S/I), Global Assessment of Functioning (GAF).

**Results:** Depressive symptoms responded well to agomelatine (mean endpoint HAMD value was 12.1) and SSRIs (mean endpoint HAMD value 10.7), with significant inter-group difference (p = 0.032) and both psychological and somatic components of the anxiety decreased significantly during the agomelatine administration (overall HAMA decrease 77.6 % – somatic 68.3 % and psychological 86.9 % at endpoint). Patients treated with SSRIs showed a similar evolution, with a 78.9 % overall HAMA decrease (somatic 77.1 % and psychological 80.7 %). CGI-S/I and GAF decreased significantly in both groups, without significant differences. Agomelatine was better tolerated than SSRIs (6 mild and moderate adverse events reported in the first group versus 11 in the second group). No drop out was recorded throughout the study due to adverse events.

**Conclusion:** Agomelatine has a similar efficacy to the SSRIs in the treatment of major depression associated with severe anxiety features. Agomelatine was better tolerated than SSRIs during the 6 months of this study.

**P-09-060 Quality of life assessment in fibromyalgia during duloxetine treatment**

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**Objective:** To assess the quality of life in patients diagnosed with fibromyalgia during medium-term treatment with duloxetine.

**Methods:** A group of 25 patients, 16 female and 9 male, mean age 53.2, diagnosed with fibromyalgia were evaluated for physical symptoms severity, depressive and anxiety symptoms, daily functioning and quality of life, using Hamilton Depression Rating Scale (HAMD), Fibromyalgia Impact Questionnaire (FIQ), Clinical Global Impressions-Severity/Improvement (CGI-S/I) and Quality of Life Inventory (QOLI). Patients included in this trial received duloxetine 60–90 mg daily, flexible dose, for 24 weeks and were monitored every 4 weeks. Inclusion criteria: age between 18 and 65, no personal history of major depressive disorder. Exclusion criteria: other severe organic diseases, comorbid axis I or II diagnosis, HAMD over 18.

**Results:** Patients responded well to duloxetine therapy, as the final normalized FIQ score decreased with 3.4 points (p < 0.01). Also, the HAMA scores improved significantly (~71.3 %, p < 0.001), with insomnia and psychological anxiety being more responsive than other items (~82.2 % and ~75 % at week 24). Reduction of insomnia correlated highly with improvement in quality of life (51), followed by decreased lombar pain (43) and overall HAMD score (40). The CGI-I scores improved, from mean baseline values of 4.8 to 2.1 at week 24. The quality of life scales regarding health, family relations and social relations from the QOLI registered significant improvement compared to baseline (+25.3 %, +39.2 % and +26.5 % respectively, p < 0.01). Patients who had the higher response rate to the treatment also had the higher rate of quality improvement (r = 0.63). There were 4 drop-outs registered, due to adverse events (nausea, sedation, n = 2) or non-compliance (n = 2).

**Conclusion:** Treatment of fibromyalgia with duloxetine determined improvements in pain, anxiety and depressive symptoms and, consequently, improved patients quality of life.

**P-09-061 Serotonin transporter gene-linked polymorphic region influences discontinuation of pharmacotherapy with paroxetine**

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**Objective:** Discontinuation of antidepressant is critical for the outcome of pharmacotherapy for depression and anxiety disorders, however, factors affecting discontinuation of antidepressants have been unknown. We investigated the association between discontinuation of selective serotonin reuptake inhibitor, paroxetine (PAX) and genetic variants of serotonin (5-HT) transporter gene-linked polymorphic region (5-HTTLPR), ~1019C/G promoter polymorphism of the 5-HT1A receptor in Japanese patients with panic disorder.

**Methods:** Subjects were 65 patients who fulfilled DSM-IV-TR criteria for a diagnosis of panic disorder. Subjects were administered PAX 10 mg/day for 2 weeks. Plasma concentration of PAX after the initiation of pharmacotherapy was determined by high performance liquid chromatography, and the patients were identified as being non-adherent for pharmacotherapy when their plasma levels were under the lowest limit of detection (0.5 ng/ml). 5-HTTLPR and ~1019C/G 5-HT1A genotypes were determined by polymerase chain reaction techniques. A multiple logistic regression was performed to analyze the relationships between gender, comorbidity of agoraphobia, comorbid major depressive disorder, comorbid physical illness, smoking, habitual use of alcohol, use of drugs for internal medicine, 5-HTTLPR and ~1019C/G gene variants (independent variables) and total discontinuation rate, discontinuation rate due to non-adherence, discontinuation rate due to adverse effects (dependent variables).

**Results:** Multiple logistic regression revealed significant relationship between 5-HTTLPR genotype (L/L, L/S vs. S/S) and total discontinuation rate (46.2 % vs. 21.1 %, p = 0.034). There were not significant relationships between independent variables and discontinuation rate due to non-adherence (26.9 % vs. 10.5 %) and, due to adverse effects (19.2 % vs. 10.5 %). The odds ratio for L allele carrier subjects who discontinued medication was 3.21 (95 % confidence interval, 1.07 to 9.62).

**Conclusion:** L allele carrier of 5-HTTLPR might predict discontinuation of pharmacotherapy with PAX.

**P-09-062 The importance of rigor in post-baseline assessments in CNS clinical trials**

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**Objective:** Inappropriate subjects may be enrolled in a study when enrollment pressures cause inflated baseline severity scores. An increasing number of studies now include methods such as blinded independent centralized ratings (CR) to ensure that appropriate subjects are entered into the trial. Post-baseline factors such as functional unblinding, expectation bias and rater drift can also affect outcomes. Independent raters, blind to study visit, can minimize functional unblinding and expectation bias. Continuous calibration of CR can minimize rater drift.

**Methods:** Studies with both site ratings (SR) and CR can be evaluated to determine how critical post-baseline blinding and continuous calibration are. A trial of acute schizophrenia used CR for the PANSS and SR for the BPRS on the same subjects. A Parkinson’s psychosis study used CR in the US and SR ex-US to assess subjects using the SAPS. A GAD trial used CR of subjects enrolled by SRs’ SIG-A evaluations.

**Results:** In the schizophrenia trial, CR separated the active comparator and one of two test arms. SR separated the active comparator but neither test arm. In the Parkinson’s psychosis study, pinemavirsen showed greater separation with CR than SR. In the GAD trial, CR had lower placebo response than SR, independent of subject selection.

**Conclusion:** Data from several studies support the continued importance of rater blinding and independence, post subject selection. Results suggest that precision of ratings beyond baseline can increase the sensitivity of findings in a clinical trial, decrease placebo response rates and potentially eliminate Type II errors.

**Policy of full disclosure:** MedAvante, Inc.

**P-09-063 The power of expectation bias**

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**Objective:** Expectation bias occurs when an individual’s expectations about an outcome influence perceptions of one’s own or others’ behavior. In clinical trials, both raters and subjects may enter trials with
Isolation rearing prevents the antidepressant effects of carbamazepine to vehicle (2% tween 80) treated rats. However, these effects were not (decreased immobility time and increased struggling time) compared to socially reared rats significantly induced the antidepressant effects of carbamazepine (10, 20 and 40 mg/kg i.p.) 24, 5 and 1 h after administration of carbamazepine in the rats of the forced swimming test than socially reared rats. Sub-chronic administration of carbamazepine or following sub-chronic administration of carbamazepine in the rats of the forced swimming test.

**Methods:**

Isolation and socially reared rats were compared for their response in the two aversive situations, either without drug pretreatment or following sub-chronic administration of carbamazepine or vehicle (2% tween 80). Beginning at 21 days of age, male Wistar rats were raised either in social isolation (one rat/cage) or in groups of five rats/cage (social rearing) for six weeks before behavioral testing.

**Results:**

The results demonstrated that untreated isolation reared rats showed significantly less immobility time and more struggling in the forced swimming test than socially reared rats. Sub-chronic administration of carbamazepine (10, 20 and 40 mg/kg i.p.) 24, 5 and 1 h before socially reared rats significantly induced the antidepressant effects (decreased immobility time and increased struggling time) compared to vehicle (2% tween 80) treated rats. However, these effects were not observed in carbamazepine treated isolation reared rats.

**Conclusion:**

These results indicate early life stress such as social isolation rearing prevents the antidepressant effects of carbamazepine in the rat forced swimming test, but mechanisms of action remain unknown.

**Objective:**

Affective disorders are highly debilitating diseases whose treatment is still unsatisfactory because of poor efficiency and unwanted side effects of drugs. The most successful approaches in drug development are those that demonstrate preclinical antidepressant and/or antipsychotic activity and target the unmet clinical needs.

**Method:**

Continuing our research with long-chain arylpiperazines as mixed ligands of serotonergic and dopaminergic receptors, a new series of quinoline- and isoquinoline-sulfonamide with 2,3-di- chlorophenylpiperazine moiety (PZ-380, PZ-381, PZ-387, PZ-389, PZ-508, PZ-547, PZ-548, PZ-549, PZ-599) were synthesized and evaluated in vitro for their affinity for dopamine D2 and serotonin 5-HT1A, 5-HT2A, 5-HT6, 5-HT7 receptors. Selected compounds with the most promising receptor profile, i.e. PZ-380, PZ-387, PZ-508, PZ-599, were examined in vivo models towards their potential antidepressant and antipsychotic activity in mice.

**Results:**

All compounds displayed high-to-moderate affinity for D2 (Ki = 8–54 nM), 5-HT1A (Ki = 13–88 nM), 5-HT2A (Ki = 57–200 nM) and 5-HT7 (Ki = 12–83 nM) and low affinity for 5-HT6 receptors (Ki = 121–13310 nM). The four selected to study compounds produced antidepressant-like effects in the forced swim test in mice with effective doses of 10 and/or 20 mg/kg. PZ-380 displayed antagonistic activity toward D2 receptors examined in the apomorphine-induced climbing model in mice. However, the remaining compounds proved to be partial agonists of these sites. None of the tested compounds attenuated locomotor hyperactivity induced by MK-801 in mice.

**Conclusion:**

The obtained results indicate that new synthesized compounds targeting the aforementioned receptor systems could yield an exciting antidepressant action. Unfortunately, in contrary to Aripiprazole containing 2,3-dichlorophenylpiperazine moiety, potential antipsychotic effects of evaluated compounds have not been proven in the hyperlocomotion induced by MK-801 in mice. Study supported by: MNiSW (No. N N405 378 437), Funds for Statutory Activity (UJCJ), Polish-Norwegian Research Fund (No. PNRF-103-AI-1/07).

**Objective:**

We have previously reported that a delta opioid receptor (DOP) agonist, SN80, produces potent antidepressant-like effect in rodent. However, SN80 also produced convulsions. Recently, we succeeded in synthesizing a novel DOP agonist called KNT-127. In this study, we have examined the antidepressant-like and the possible convulsive effects of KNT-127 in mice.

**Method:**

The forced swim test was performed using male ICR mice weighing 30–40 g. KNT-127 (1 mg/kg, s.c.) or imipramine (6 mg/kg, s.c.), a tricyclic antidepressant, was administered 30 min before the test session. Naltrexone (1 mg/kg, s.c.), a selective DOP antagonist, was administered 30 min before KNT-127 administration. Convulsive effects on mice were measured for 20 min after the drug treatment.

**Results:**

In mice subjected to the forced swim test, KNT-127 significantly decreased the duration of immobility and increased the duration of swimming. These behavioral changes were similar to that observed for imipramine. The antidepressant-like effect of KNT-127 in mice was antagonized by pretreatment with naltrexone. On the other hand, KNT-127 produced no convulsions at doses of up to 100 mg/kg.

**Conclusion:**

The present study demonstrated that a novel DOP agonist, KNT-127, induces antidepressant-like effects without producing convulsions in mice. We propose that KNT-127 should be considered as a candidate compound for the development of DOP-based antidepressants that have fewer undesired side effects.
Neuronal correlates of antidepressant effect in the forced swim test in mice

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Objective: The forced swim test (FST) has been widely used as a behavior test to evaluate antidepressant effects of drugs, while the relevant neuronal pathways remain elusive.

Methods: BALB/c mice, pretreated with imipramine (IMP; 10 mg/kg, i.p.) or saline, were subjected to single session of the FST (10 min). Mice were perfused 2 hours after onset of the FST, and the expression of c-Fos, a marker of neuronal activation, was examined through immunohistochemical method.

Results: Pretreatment with IMP significantly decreased the duration of immobility in FST. IMP pretreatment increased expression of c-Fos in a few subdivisions of the bed nucleus of the stria terminals (BNST) and the preoptic area of the hypothalamus. The densities of the c-Fos immunoreactivity in some other regions showed positive or negative correlations with the duration of immobility in the FST.

Conclusion: The present result suggests that the BNST and hypothalamus are involved in antidepressant effect in the FST. Segregated networks of the neurons might regulate active and passive stress-coping behaviors.

Neuroprotective effect of novel low-molecular NGF mimetic GK-2 was completely blocked via PI3K/Akt pathways inhibition

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Objective: The neuroprotective action of nerve growth factor NGF are mediated by tyrosine kinase receptor and phosphatidylinositide 3 kinase (PI3K)/Akt pathways. The dimeric linear dipetide mimetic of NGF loop 4, hexamethylenediamide bis-(N-succinyl-glutamyl-lysinine), named GK-2 was synthesized in Zakusov’s Institute of Pharmacology RAMN. We have previously shown that GK-2 had neuroprotective properties on cell models of oxidative stress, glutamate toxicity and MPTP-induced injury of neurons. HT-22 cells were pretreated with 100 mkM LY294002 for 30 min prior to GK-2 stimulation. Cell viability was measured in medium without agents. HT-22 cells were pretreated with 100 mkM LY294002 in 0.5 mM hydrogen peroxide (H2O2) to evaluate the neuroprotective action of GK-2 on model of oxidative stress.;

Methods: Experiments were carried out on hippocampal cell culture line HT-22. Cells damages were provoked by 1.5 mM hydrogen peroxide for 30 min. After that, medium was changed to original medium without agents. HT-22 cells were pretreated with 100 mM LY294002 for 30 min prior to GK-2 stimulation. Cell viability was measured by MTT-test.

Results: It was shown that LY294002 blocked the neuroprotective effects of GK-2 (10-5 and 10-8 M) and NGF (100 ng/ml) against hydrogen peroxide-induced cell death in all experimental time points. A PI3K/Akt pathways were shown to be involved in the neuroprotective effect of GK-2 as well as that of NGF.

Critical care in psychiatry

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Objective: Psychiatric medications are frequently an essential component of care for critically ill patients. Their use may lead to medical complications, however, as a result of direct toxicity from psychotropic medications, drug-drug interactions, or intoxication or withdrawal states. These complications may be a nuisance (e.g., dry mouth and nausea) or serious and life-threatening (e.g., neuroleptic malignant syndrome [NMS] and cardiac arrhythmias). This symposium addresses the most important medical complications of psychiatric treatment, in critical care set up.

Methods: The use of psychiatric medications in critically ill patients is an important component of comprehensive care. Many times a psychiatrist is consulted by ICU Internists for alteration in behaviour, mood, thinking and perception of reality. Because the emergence of psychiatric symptoms may be precipitated and exacerbated by various medical conditions, proper evaluation and emergency management is of utmost importance. Many psychotropic drugs are notorious for causing sudden and life threatening physical complications needing ICU management, like Neuroleptic Malignant Syndrome, Serotonin Syndrome, Electrolyte imbalance, Cardiac Arrhythmias etc.

Conclusion: Psychotropic drugs can cause toxicity, intoxication and withdrawal states, severe drug reactions like rashes, S-S Syndrome, drug interaction with several drugs used in general medical conditions etc, which need to be evaluated and managed. In this regard, it is essential to consider the potential complications of psychotropics while balancing the important role they serve in treatment of the medically ill.
Objective: To date, few studies on the switch from Quetiapine Immediate Release (IR) to XR in patients with affective disorders 160

Methods: Twenty-nine patients with Affective Disorders (9 with Major Depression, 20 with Bipolar Depression) switched from Quetiapine IR to XR. We showed that FSL rats displayed hippocampal CA1 synaptic plasticity impairment and increased spontaneous excitatory post-synaptic currents (eEPSCs) in CA1 pyramidal cells compared to Sprague Dawley rats. Western blotting revealed hippocampal reduced levels of the glia glutamate transporter EAAT1 and the NMDA receptor subunit NR2A. Moreover, FSL exhibited recognition memory deficits in the novel object recognition test (NOR). We have used pharmacological treatments to target different mechanisms of glutamate regulation. D-serine bathing application restored in vitro CA1-LTP by acting on NMDA receptors, while acute systemic administration restored the recognition memory deficit. Bath application of the mGlur2/3 receptor agonist LY354740 reduced CA1 eEPSCs and LY354740 chronic treatment was able to partially restore in vitro CA1-LTP (Gómez-Galán et al., 2012). At present, we have assessed the behavioral and physiological effects of the H3-receptor antagonist clobenpropit in FSL rats. Clobenpropit acutely restored memory impairments (in NOR and passive avoidance test), and had an antidepressant-like effect in the forced swim test. Clobenpropit bath application did not affect eEPSCs although acute systemic administration increased NR2A protein expression levels in the hippocampus of FSL rats.

Conclusion: Glutamatergic alterations associated to depression might require selective targeted modulation to exert both anti-depressant and pro-cognitive effects. Understanding how to regulate the glutamatergic system directly or through the modulatory effect of monoamines would help in the development of new therapies in depression.

Methods: To carry out this aim we combine electrophysiological, biochemical and behavioral approaches.

Results: We showed that FSL rats displayed hippocampal CA1 synaptic plasticity impairment and increased spontaneous excitatory post-synaptic currents (eEPSCs) in CA1 pyramidal cells compared to Sprague Dawley rats. Western blotting revealed hippocampal reduced levels of the glia glutamate transporter EAAT1 and the NMDA receptor subunit NR2A. Moreover, FSL exhibited recognition memory deficits in the novel object recognition test (NOR). We have used pharmacological treatments to target different mechanisms of glutamate regulation. D-serine bathing application restored in vitro CA1-LTP by acting on NMDA receptors, while acute systemic administration restored the recognition memory deficit. Bath application of the mGlur2/3 receptor agonist LY354740 reduced CA1 eEPSCs and LY354740 chronic treatment was able to partially restore in vitro CA1-LTP (Gómez-Galán et al., 2012). At present, we have assessed the behavioral and physiological effects of the H3-receptor antagonist clobenpropit in FSL rats. Clobenpropit acutely restored memory impairments (in NOR and passive avoidance test), and had an antidepressant-like effect in the forced swim test. Clobenpropit bath application did not affect eEPSCs although acute systemic administration increased NR2A protein expression levels in the hippocampus of FSL rats.

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Conclusion: Glutamatergic alterations associated to depression might require selective targeted modulation to exert both anti-depressant and pro-cognitive effects. Understanding how to regulate the glutamatergic system directly or through the modulatory effect of monoamines would help in the development of new therapies in depression.
through the outflow of endoplasmic reticulum calcium and finally activated PKC.

**Conclusion:** These results suggested that fluvoxamine may have a selective effect and different mechanism based on the condition of animal.

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**P-10-008** The cytochrome P450-mediated synthesis of serotonin in the brain: An in vitro study

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**Objective:** Brain cytochrome P450 (CYP) may be involved in the local metabolism of drugs and endogenous substances such as neurotransmitters or monoaminergic neurotransmitters. The CYP2D-mediated synthesis of dopamine and serotonin has been shown in vitro and in vivo; however, the formation of serotonin by this enzyme in the brain has not been demonstrated as yet. Therefore the aim of the present study was to demonstrate that the CYP2D-mediated synthesis of serotonin from 5-methoxytryptamine took place in the brain.

**Methods:** The experiment was carried out on male Wistar rats. The ability of CYP2D isoforms to O-demethylate 5-methoxytryptamine to serotonin was tested using rat recombinant CYP2D isoforms (CYP2D1/2/4/18) and human CYP2D6. The obtained results were compared with those concerning other CYP isoforms from the subfamilies CYP2A, 2B, 2C and 3A. Then O-demethylation of 5-methoxytryptamine was studied in brain microsomes in the absence or presence of the CYP2D inhibitor quinidine or fluoxetine. Microsomes were prepared from the whole brain or from different brain structures including the brainstem (containing serotonergic raphe neurons) of control rats. The concentration of serotonin formed in vitro was measured using HPLC.

**Results:** Of the rat CYP isoforms studied, CYP2D isoforms (CYP2D2, CYP2D4 and CYP2D18) were the most effective in catalyzing the O-demethylation of 5-methoxytryptamine to serotonin; however, human CYP2D6 was more active than rat CYP2D isoforms in this respect. The formation of serotonin from 5-methoxytryptamine was demonstrated in microsomes derived from different brain structures. The reaction was inhibited by the two CYP2D inhibitors, quinidine and fluoxetine.

**Conclusion:** In conclusion, brain CYP2D isoforms are able to catalyze the formation of serotonin from 5-methoxytryptamine, which may be of pharmacological importance to the treatment of psychiatric diseases. (Grant 01DFG126/1, European Union and the Ministry of Science and Higher Education, Warsaw, Poland) and statutory funds from the Institute of Pharmacology, PAS).

**P-10-009** Dopaminergic signalling and associative learning in the nematode caenorhabditis elegans

I. Hellwig, W. Kaschka, S. Hodgkinson, 1 University of Ulm, Ravensburg, Germany; 2 University of Ulm, ZF Südwürttemberg, Ravensburg, Germany

**Objective:** Introduction: Defective dopaminergic signalling has been implicated in the aetiology of a number of neuropsychiatric disorders. However, although the molecular mechanisms involved in the stimulus-reward pathway are relatively well characterised, their role in behavioural plasticity remains unclear. We use the nematode Caenorhabditis elegans (C.elegans) as a model to study behavioural plasticity as it has a simple nervous system, comprising just 302 neurons, whilst at the same time exhibiting relatively complex behavioural strategies.

**Methods:** Using a chemotaxis assay, we tested the role dopamine signaling played in olfactory associative learning. We compared olfactory chemotaxis in C.elegans wildtype (N2), the dopamine negative mutant (cat-2), and the serotonin negative mutant (tph-1). The Chemotaxis Index (CI), a measure of the strength of association between food and a volatile odour (benzaldehyde) was determined for each of the strains.

**Results:** As reported in previous work, the serotonin-deficient mutant tph-1 exhibited no olfactory chemotaxis. The dopamine-deficient mutant cat-2 exhibited a similar profile to the wildtype except for a raised CI 60 minutes after the end of the conditioning phase. This increase in CI could be reduced by exposing cat-2 mutants to exogenous dopamine.

**Conclusion:** The loss of the conditioning in the cat-2 mutants after 60 minutes and its reinstatement by exogenously applied dopamine suggests a complex balance exists between dopamine and other pathways involved in the maintenance of conditioning. One possible mechanism would involve the repression of an ‘association signal’ by dopamine. In the cat-2 mutant the ‘association signal’ is expressed and, in the presence of food-odour stimuli, association gradually returns reaching a maximum after 60 minutes. The subsequent decrease in the CI after 60 minutes in the cat-2 mutant can be explained by a negative feedback mechanism. We are working to identify this signal and testing whether there is a dopamine dose effect on this mechanism.

**P-10-010** Temporal and spatial changes in tryptophan hydroxylase expression are associated with behaviour switching in caenorhabditis elegans

J. Hellwig, S. Hodgkinson, W. Kaschka, 1 University of Ulm, Ravensburg, Germany; 2 University of Ulm, ZF Südwürttemberg, Ravensburg, Germany

**Objective:** Background: Tryptophan hydroxylase (tph) is a key enzyme in the biosynthesis of the neurotransmitter serotonin (5-HT). During the adult stage of development and in response to particular external conditions (presence of food), the nematode Caenorhabditis elegans switches behavior from feeding to egg laying. This behavior switching is controlled by serotonin but the mechanism remains unclear.

**Methods:** Wildtype C.elegans carrying a tph-1 promotor: gfp construct were live mounted on 5% agarose and changes in tph-gfp was documented via fluorescence microscopy as worms entered the egg-laying phase of their life cycle.

**Results:** We show that wildtype worms entering the egg laying phase upregulate tph expression in specific tissues including muscle tissue adjacent to the vulva. This pattern of expression is not seen in worms during the other stages of larval and adult development.

**Conclusion:** 5-HT has both a stimulatory (via a G protein-coupled receptor) and inhibitory (via a 5-HT-gated CI-channel) effect on egg laying. Long term exposure to 5-HT attenuates this inhibitory response. The local actions of 5-HT include the stimulation of vulval contractions. Taken together, the changes in tph expression we observed support the hypothesis that tph expression plays a role in mediating the transition from feeding to egg laying behavior. We are now looking for potential candidates that might regulate tph transcription consistent with the expression patterns we observed.

**P-10-011** Stress regulates the gene expression of neuronal PAS domain 4 (Npas4), via glucocorticoid receptor

Y. Hibi, J. Yuni, T. Naga, K. Yamada, 1 Nagoya University, Japan

**Objective:** The expression levels of neuronal PAS domain 4 (Npas4) mRNA are decreased in the hippocampus of socially-isolated or chronically restricted mice, which is accompanied by impairments of memory and emotional behavior with a reduced hippocampal neurogenesis. The reduction of Npas4 expression induced by psychosocial stress may play a role in mental disorders, since Npas4 has recently been shown to regulate the development of GABAergic inhibitory neurons. In this study, we investigate the transcriptional regulation of Npas4 expression by stress, we focused on the effect of corticosterone (CS) on Npas4 transcription.

**Methods:** Npas4 expression level in the hippocampus of ICR mice were measured 2 hours after the CS (10 mg/kg) injection or 1 week after the adrenalectomy. Effect of CS on Npas4 expression in restraint stressed mice was evaluated by using a glucocorticoid receptor (GR) antagonist, RU486. The effect of GR on the Npas4 promoter activity in Neuro2a cells was determined by a luciferase assay. Interaction of GR and Npas4 promoter was confirmed by a chromatin immunoprecipitation assay.
Results: Acute CS treatment significantly decreased the expression level of Npas4 mRNA in the hippocampus of mice, while the expression level was increased by adrenalectomy. The GR antagonist RU486 inhibited the reduction of Npas4 expression induced by restraint stress. Reduced Npas4 mRNA expression was also observed in CS-treated Neuro2a cells. Putative GREs were found at −2.1 kb to −1 kb upstream of the transcription initiation site of Npas4 promoter. The Npas4 promoter activity was increased by deletion of GREs rich sequence or treatment with RU486. Moreover, chromatin immunoprecipitation assay revealed the binding of ligand-bound GR to Npas4 promoter region.

Conclusion: These results suggest that psychosocial stress reduces the Npas4 gene expression via the binding of CS/GR complex to GREs located on the promoter region of the gene.

P-10-012 Potentiation of nerve growth factor-induced neurite outgrowth in PC12 cells by aripiprazole
T. Ishima1, M. Ito1, K. Hashimoto3, 1Chiba University, Japan
Objective: Accumulating evidence suggests that neuronal plasticity plays a role in the mechanisms of action of atypical antipsychotic drugs. The atypical antipsychotic drug aripiprazole has been used as a treatment for psychiatric diseases such as schizophrenia, major depression, bipolar disorder, and autism. In this study, we examined whether aripiprazole could affect nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells.

Methods: Twenty-four hours after plating, the medium was replaced with DMEM containing 0.5% FBS, 1% penicillin and 1% streptomycin with NGF (2.5 ng/ml), with or without aripiprazole, WAY-100635 (5-HT1A receptor antagonist), xestospongin C, 2-APB (IP3 receptor antagonists) or several specific inhibitors of cellular signaling pathways (PLC-c, PI3K, Akt, p38 MAPK, and c-Jun N-terminal kinase (JNK)), and the Ras/Raf/ERK/MAPK. Four days after incubation with NGF and test drugs, morphometric analysis on neurite outgrowth in PC12 cells was performed.

Results: Aripiprazole significantly potentiated NGF-induced neurite outgrowth, in a concentration dependent manner. Potentiation of NGF-induced neurite outgrowth mediated by aripiprazole was significantly antagonized by co-administration of the selective 5-HT1A receptor antagonist WAY-100635, but not the dopamine D2 receptor antagonist sulpiride. Furthermore, the potentiation of NGF-induced neurite outgrowth by aripiprazole was significantly blocked by IP3 receptor antagonists (xestospongin C and 2-APB). Moreover, selective inhibitors of several cellular signaling pathways significantly blocked the potentiation of NGF-induced neurite outgrowth by aripiprazole.

Conclusion: These findings suggest that aripiprazole could potentiate NGF-induced neurite outgrowth in PC12 cells, and that the beneficial effects of aripiprazole on neuronal plasticity may be involved in the mechanisms of its action.

P-10-014 Modulation of the extracellular D-serine contents by the a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate type glutamate receptor in the rat medial frontal cortex as revealed by in vivo microdialysis
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Objective: It has been widely accepted that D-serine plays a pivotal role in the control of the N-methyl-D-aspartate (NMDA) type glutamate receptor as its endogenous co-agonist in the mammalian brain. Abnormalities in the extracellular D-serine signal, which lead to the NMDA receptor dysfunction, have been implicated in the pathology of psychiatric diseases such as schizophrenia. The exact mechanisms underlying regulation of extracellular release of D-serine, however, await further elucidation. To get an insight into this issue, we have characterized the effects of agents acting at the a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) type glutamate receptor on the extracellular contents of cortical D-serine in vivo, because in vitro experiments have suggested the involvement of the AMPA receptor in the control over the extracellular release of D-serine in the central nervous system although there is so far no in vivo evidence to for this interaction.

Methods: The present animal studies have been approved by the ethics committees of the Tokyo Medical and Dental University. We used an in vivo microdialysis technique in combination with high-performance liquid chromatography with fluorometric detection.

Results: We have shown that intra-medial frontal cortex infusion of the S-enantiomer of AMPA, an active enantiomer at the AMPA receptor causes a significant reduction in the extracellular contents of D-serine in the cortical area of the rat in a concentration-dependent, an AMPA/kainate receptor antagonist NBQX- and a calcium permeable AMPA receptor antagonist NAPQI-resistant manner. The reducing effects of S-AMPA are augmented by co-infusion of an allotropic modulator of the AMPA receptor, cyclothiazide, which prevents AMPA receptor desensitization.

Conclusion: Our data support the view that the calcium permeable subtype of the AMPA receptor might exert a phasic inhibitory influence on the extracellular release of D-serine in the mammalian frontal cortical area in vivo.

P-10-015 Potentiation of nerve growth factor-induced neurite outgrowth in PC12 cells by ifenprodil: The role of sigma-1 and IP3 receptors
T. Ishima1, K. Hashimoto3, 1Chiba University, Japan
Objective: Ifenprodil (Cerocal®) has been used as a cerebral vasodilator in a limited number of countries, including Japan and France. In addition to both the a-adrenergic receptor and N-methyl-D-aspartate (NMDA) receptor antagonists, ifenprodil binds to the two subtypes (1 and 2) of sigma receptor. In this study, we examined the effects of ifenprodil on nerve growth factor (NGF)-induced neurite outgrowth in PC12 cells. Furthermore, we examine the role of these receptors in the potentiation of NGF-induced neurite outgrowth by ifenprodil.

Methods: Twenty-four hours after plating, the medium was replaced with DMEM containing 0.5% FBS, 1% penicillin and 1% streptomycin with NGF (2.5 ng/ml), with or without ifenprodil, prazosin (a a-adrenergic receptor antagonist), Ro 25-6981 (NMDA receptor NR2B antagonist), NE-100 (sigma-1 receptor antagonist), SM-21 (sigma-2 receptor antagonist), xestospongin C (inositol 1,4,5-trisphosphate (IP3) receptor antagonist) or 2-aminoethoxydiphenyl borate (2-APB) (IP3 receptor antagonist). Four days after incubation with NGF and test drugs, morphometric analysis on neurite outgrowth in PC12 cells was performed.

Results: Ifenprodil significantly potentiated NGF-induced neurite outgrowth, in a concentration-dependent manner. In contrast, prazosin and Ro 25-6981 did not alter NGF-induced neurite outgrowth. Potentiates neurite outgrowth mediated by ifenprodil was significantly antagonized by co-administration of the selective sigma-1 receptor antagonist NE-100, but not the sigma-2 receptor antagonist SM-21. Furthermore, the potentiation of NGF-induced neurite outgrowth by ifenprodil was significantly blocked by treatment with the IP3 receptor antagonists, xestospongin C or 2-APB.

Conclusion: These findings suggest that activation at sigma-1 receptor and subsequent interaction with IP3 receptor may mediate the pharmacological effects of ifenprodil on neurite outgrowth.

P-10-016 Afobazole decrease menadione genotoxicity
I. Kadnikov1, M. Voronin1, S. Seredenin1, 1SF IPK RAMS, Moscow, Russia
Objective: NRH quinone reductase 2 (NQO2) is a structural analog of well known phase-II biotransformation enzyme NAD(P)H quinone reductase 1 (NQO1). NQO2 catalyze two-electron reduction of p- and q-quinones. However, because of specifics in the tertiary structure it is capable for one-electron reduction of quinones, menadione for one, and generation of reactive oxygen species. Oxidative stress caused by NQO2 is associated with Alzheimer’s disease and idiopathic Parkinson’s disease, which pathogenesis is related to ROS generation due to products of catecholamine self-oxidation, dopa-quinone first of all. Our previous studies had revealed ligand properties of selective anxiolytic with neuroprotective activity afobazole towards to MT3 receptor, also known as regulatory site of NQO2 enzyme. In the next set of experiments we established that afobazole is NQO2 inhibitor with Ki = 2.54 x 10-4 M (obtained for human recombinant NQO2).

Poster Sessions, Tuesday, 5 June 2012

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The purpose of present study was to determine the influence of afobazole on NQO2-dependant quinone mediated genotoxicity as a marker of oxidative stress in the model of menadione toxicity in vitro.

Methods: Materials and methods: We have used the single cell gel electrophoresis assay (comet assay) as a marker of oxidative stress to investigate the novel quinone compound menadione genotoxic effects in mice bone marrow cells.

Results: Our experiments on menadione genotoxicity have shown that incubation of mice bone marrow cells with dicoumarol in concentration of 10 μM, a potent selective NQO1 inhibitor, lead to 5,4-fold increase in the amount of DNA-strand breaks contrary to control group. Afobazole administration in concentration of 10 μM in same conditions lead to 1,7-fold decreased toxicity.

Conclusion: Afobazole decrease NQO2 mediated menadione genotoxicity. Obtained data assume one of the possible molecular mechanisms of neuroprotective activity of afobazole. Thus the further investigations are required.

P-10-017 Antidepressants enhance hippocampal dendritic outgrowth via mTOR signaling pathway

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Objective: A growing body of evidence has pointed to the rapid antidepressant effect of the subanesthetic dose of ketamine, N-methyl-D-aspartate (NMDA) receptor antagonist, via mammalian target of rapamycin (mTOR) signaling. mTOR signaling plays a fundamental role in axonal and dendritic growth. However, the mechanisms underlying this action of antidepressants have not been identified. We examined whether certain antidepressants (escitalopram, fluoxetine, paroxetine, sertraline, imipramine and tranylcypromine) promote neurite outgrowth via mTOR signaling in primary cultured hippocampal neurons.

Methods: Rat hippocampal cells were treated with ketamine or antidepressants for 5 days. Rapamycin, mTOR inhibitor, was added to the model quinone compound menadione genotype effects in mice bone marrow cells.

Results: Our experiments on menadione genotoxicity have shown that incubation of mice bone marrow cells with dicoumarol in concentration of 10 μM, a potent selective NQO1 inhibitor, lead to 5,4-fold increase in the amount of DNA-strand breaks contrary to control group. Afobazole administration in concentration of 10 μM in same conditions lead to 1,7-fold decreased toxicity.

Conclusion: Afobazole decrease NQO2 mediated menadione genotoxicity. Obtained data assume one of the possible molecular mechanisms of neuroprotective activity of afobazole. Thus the further investigations are required.

P-10-018 Comparative study of hemantane and amantadine in rats with experimental intracerebral posttraumatic hematoma

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Objective: Hemantane (H) (N-(2-adamantyl)hexaaminylimine hydrochloride) is novel antiparkinsonian drug with complex mechanism of action including NMDA receptor antagonism and antiradical activity which allows to suppose the neuroprotective effect of H. The aim of the study was to assess the effects of H in comparison with amantadine (AMA) in rats with intracerebral posttraumatic haematomata (IPH) which could be considered as a model of haemorragic stroke.

Methods: Sham-operated and rats with IPH were treated with saline (groups 1 and 2). H (5 mg/kg, i.v.) or AMA (20 mg/kg, i.v.) (groups 3 and 4). Saline and drugs were administered first at 3, 5 hours after surgery and then for 4 consecutive days. On days 1, 7 and 14 after surgery animals were placed in open field, elevated plus-maze, rotated and passive avoidance tests.

Results: It was shown that both drugs significantly decreased mortality and improved motor activity and exploratory behavior in open field. AMA was little more effective in improving motor activity and exploratory behavior. In passive avoidance test no impairment of hole reflex in all groups of rats was registered. Impaired acquisition in animals with IPH was revealed in all retention trials. H. and AMA prevented these alterations. H 5 mg/kg i.v. demonstrated more pronounced activity in restoring memory. There was no difference in retrieval testing between treated with H. and sham-operated animals in all days of testing sessions, while termination of AMA treatment caused decrease in retrieval of memory trace on day 7.

Conclusion: The results obtained testify for neuroprotective properties of the novel antiparkinsonian drug hemantane.

P-10-020 Serum pro-brain derived neurotrophic factor and remission in depressed patients after selective serotonin reuptake inhibitors treatment

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Objective: The role of brain-derived neurotrophic factor (BDNF) has been mainly known, implicating in the hippocampal neurogenesis after antidepressant administration. It have been reported that serum BDNF content is related to depression etiology and antidepressant treatment, but they are controversial. Recent studies found that proBDNF before processing is related to apoptosis by binding to p75 NTR (neurotrophin receptor) and may facilitate long-term depression. Our hypothesis is that the two forms of BDNF(pro- and total-) are related to depression susceptibility and remission after Selective Serotonin Reuptake Inhibitors(SSRI) treatment in elderly depressed patients.

Methods: Twenty-nine elderly patients, diagnosed as major depression according to criteria for depression of DSM-IV, entered a 6 week clinical trial with SSRIand documented the several clinical variables and plasma drug concentrations. Remission was defined as < 7 score of HAM-D. Patients and 29 normal volunteers were drawn venous blood between 9 ~ 12 a.m. Serum proBDNF immunoreactivity was determined by western blot and total BDNF(proBDNF) content by BDNF Enzym Immunoassay System. Comparison between two groups was analyzed using t-test or Mann-Whitney test in SPSS ver.10.1.

Results: No serum proBDNF immunoreactivity and total BDNF contents was differed between normal volunteer and depressed patients. After 6 week of SSRI administration, proBDNF immunoreactivity was increased in remitted patients compared than in remitted patients (p = 0.041, by t test).

Conclusion: Our results suggest that serum proBDNF is possible to be candidate marker for remission after SSRI treatment. Further studies should elucidate the mechanism of the two types of BDNF in serum related to SSRI action.

P-10-021 Comparative receptor binding profile of lurasidone and other first and second generation antipsychotics

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Objective: To characterize the receptor binding profile of lurasidone compared to other first and second generation antipsychotics.

Methods: Binding affinities for lurasidone and other antipsychotics were determined in side-by-side assays using membrane preparations from non-human CNS or cell lines expressing cloned human receptor.

Results: Lurasidone displayed potent binding and full antagonism at dopamine D2 (Ki, 1.68 nM) and 5-HT7 (Ki, 0.49 nM) receptors; lurasidone had the highest affinity for the dopamine D2 receptor among antipsychotics tested, followed by risperidone and haloperidol. Lurasidone also showed full antagonism and high affinity at
serotonin 5-HT2A receptors (Ki, 2.03 nM). Lurasidone had nanomolar affinity (Ki = 6.75 nM) for serotonin 5-HT1A receptors, behaving as a weak-moderate partial agonist. Relative to dopamine D2 receptor binding, lurasidone showed higher affinity for 5-HT7, 5-HT2A, and 5-HT1A than the other antipsychotic agents tested. Lurasidone’s binding to dopamine receptors was selective for dopamine D2 receptors: compared to its dopamine D2 receptor affinity, its Ki for D1 receptors was 156-fold higher, for D3/1-fold higher, and 30-fold higher for D4 receptors. Lurasidone had a favorable binding-profile at several receptors that are suspected of being associated with undesirable effects, with minimal affinity for 5-HT2C receptors (Ki, 415 nM), and no affinity for histamine H1 (IC50 > 1000 nM) and muscarinic [cholinergic] M1 (IC50 > 1000 nM) receptors. Lurasidone also displayed only moderate affinity for 5αX adrenergic receptors (Ki, 10.8 nM), and moderate-affinity weak affinity for β1 adrenoceptors (Ki, 48 nM).

Conclusion: Lurasidone has potent and selective antagonist activity at the D2 receptor, coupled with equally potent antagonist activity at both 5-HT7 and 5-HT2A receptors. This profile is consistent with the expected antipsychotic efficacy, a moderate likelihood of EPS, a low potential for weight gain and related metabolic consequences, and the potential for beneficial impact on mood and impaired cognitive function.

Policy of full disclosure: Drs. Loebel, Cucchiaro, Werner and Pikalov are full-time employees of Sunovion Pharmaceuticals Inc, Fort Lee, NJ. Dr. Ishiyama, Horisawa, Tokuda, Ogasa and Ishihashi are full-time employees of Dainippon Sumitomo Pharma, Osaka, Japan.

Objective: Brain-derived neurotrophic factor (BDNF) deficiency contributes a lot to the pathogenesis of most neurodegenerative diseases. The cellular actions of BDNF are mediated through the activation of the Trk receptors. The novel dipeptide analogue of BDNF, GSB-106, was synthesized in Zakusov Institute of Pharmacology RAMS. We have previously shown that GSB-106 had neuroprotective effects in different models of cell damages: oxidative stress, glutamate or 6-hydroxydopamine-induced toxicity. This study was undertaking in order to evaluate the possible mechanisms of this neuroprotective effect.

Methods: Experiments were performed on hippocampal neurons in culture HT-22. Oxidative stress was modeled by addition of H2O2 (1.5 mM) into the cell medium. GSB-106 (10-8 M) was added after damaging factor. BDNF (50 ng/ml) was added as a positive control. Western blot analysis was used for the detection of phosphorylated Trk-B level and synthesis of heme oxygenase-1 (HO-1).

Results: It is shown that GSB-106 caused a significant increase in phosphorylation of Trk-B; this effect appeared already in 30 sec interval. These data allow to suggest that GSB-106 similar to BDNF acts via the TrkB receptors. HO-1 is a stress-inducible enzyme involved in protection cell from oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study, we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study, we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study, we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress. However, limitation of HO-1 overexpression is an important component of neuroprotection. On the next stage of this study, we investigated the influence of GSB-106 on the synthesis of HO-1 by oxidative stress.
P-10-025 Synergistic or independent relationships of MAO B platelet activity, MAO B and COMT polymorphisms to impulsivity, aggression and novelty seeking?

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Objective: Low platelet MAO B activity and the COMT polymorphism genotype MetMet would result in higher DA levels and have been shown to be associated with Impulsivity, Novelty Seeking, Aggression and alcoholism. So far it is not clear, how the A/G intron 13 polymorphism of the MAO B gene relates to MAO B activity in platelets and personality traits, and if the three biomarkers act synergistically or independently on personality traits. This was investigated in the present study.

Methods: 60 male abstinent alcoholics participated in a reaction time task, filled in personality questionnaires and gave blood samples for genetic analyses and MAO B activity in platelets.

Results: Although platelet MAO B activity and MAO B genotype were not associated, interactions revealed that participants with low MAO B activity among G allele carriers scored highest on Aggression, A allele carriers in the MetMet group highest on Experience Seeking. Motor Impulsivity was only related to high MAO B activity, not to genetics, and faster reaction times were only observed in G allele carriers.

Conclusion: These results are compatible with the findings by Balciuniene et al. (2002) that the G allele indicates lower MAO B activity in brain than A, yielding higher DA levels and therefore perhaps higher speed and aggression which adds to the low MAO B activity in platelets. Data also suggest that low DA resulting from the Val/Val genotype acts synergically with the A allele in producing attention deficits. So the three biomarkers evidently differentially affect impulsivity, aggression, attention deficits and novelty seeking. The MAO B intron A/G polymorphism is only one of several genetic polymorphisms for MAO B activity, but does indicate relevance as a behavioral marker.

P-10-026 Antibody-capture scintillation proximity assayeny of [35S]GTPγS binding to Gα functionally coupled with M1 acetylcholine receptors and 5-HT2A receptors in rat brain membranes

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Objective: To investigate receptor-mediated functional activation of heterotrimeric G proteins other than Gα/β subtypes.

Methods: Immuno-capture of Gα subunits with anti-Gα antibodies following [35S]GTPγS binding to rat brain membranes was combined with scintillation proximity assay (SPA) technology.

Results: Preliminary experiments using a series of agonists and commercially available anti-Gα antibodies indicated the increase in specific [35S]GTPγS binding to Gαq determined with anti-Gα (E-17) (sc-393, Santa Cruz Biotechnology) evoked by carbachol or glutamate. CCh was pharmacologically relevant. Under the optimized conditions, CCh-stimulated specific [35S]GTPγS binding to Gαq in a concentration-dependent and saturable manner with an EC50 of around 10 nM in all of the membranes prepared from rat hippocampus, cerebral cortex, and striatum. The addition of MT-7, a snake toxin with high selectivity for M1 over the other muscarinic acetylcholine receptors (mACHRs) (M2-4), almost completely extinguished CCh-stimulated [35S]GTPγS binding to Gαq, even at a concentration as low as 1 nM, indicative of the exclusive involvement of M1 receptors in this response. The detailed pharmacological characterization was further investigated by means of a series of muscarinic agonists, antagonists, and allosteric modulators in hippocampal and cerebral cortical membranes. Under the same condition, 5-HT also stimulated specific [35S]GTPγS binding to Gαq in cortical membranes in a concentration-dependent manner. However, the stimulatory effects of 5-HT were not saturable and apparently biphasic. The inhibitory effects of ketanserin indicated that 5-HT2A receptor-mediated activation of Gαq might be detectable when lower concentrations (up to 10 μM) of 5-HT were used.

Conclusion: Both receptors are implicated in pathophysiology of several neuropsychiatric disorders as well as mechanisms of action of psychotropic drugs. The assay developed in the present study will be of help for the investigations in the field of biological psychiatry as well as drug discovery.

P-10-027 Changes in vascular endothelial growth factor (VEGF) induced by the morris water maze task


Objective: The present study was undertaken to evaluate the effects on hippocampal vascular endothelial growth factor (VEGF) levels in rats when they experience hippocampal-dependent spatial learning via the Morris water maze (MWM) task.

Methods: After one day of intensive training, a highly sensitive enzyme-linked immunosorbent assay (ELISA) was used to measure VEGF protein levels in the hippocampus, cortex, and serum.

Results: Higher levels of VEGF were found in the trained group compared to a naive control group. VEGF levels also increased in rats that swam only for durations equal to the intensive training periods. In contrast, rats trained under the weaker MWM paradigm for five days showed a decrease in hippocampal VEGF protein level. Mimicking increases in neuronal VEGF in the hippocampus by direct infusion of VEGF into CA1 resulted in up-regulation of the phosphorylation of the cAMP response element-binding (CREB) protein and the Ca2+/calmodulin-dependent protein kinases II (CaMKII).

Conclusion: These results suggest that VEGF may be a physiological parameter involved in learning procedures that include physical activity.

P-10-028 Comparison of neurite outgrowth induced by erythropoietin (EPO) and carbamylated erythropoietin (CEPO) in cultured hippocampal neural progenitor cells


Objective: A previous animal study has shown the effects of EPO and its non-erythropoietic carbamylated derivative (CEPO) on neurogenesis in the dentate gyrus. In the present study, we sought to investigate the effect of EPO on adult hippocampal neurogenesis, and to compare the ability of EPO and CEPO promoting dendrite elongation in cultured hippocampal neural progenitor cells.

Methods: Two-month-old male BALB/c mice were given daily injections of EPO (5 U/g) for seven days and were sacrificed 12 hours after the final injection. Proliferation assays demonstrated that EPO treatment increased the density of bromodeoxyuridine (BrdU)-labeled cells in the subgranular zone (SGZ) compared to that in vehicle-treated controls (p < 0.05).

Results: Functional differentiation studies using dissociated hippocampal cultures revealed that EPO treatment also increased the number of double-labeled BrdU/MAP2 (microtubule-associated protein 2) neurons compared to those in vehicle-treated controls (p < 0.05). Both EPO and CEPO treatment significantly increased the length of neurites extending from MAP2 (+) cell soma, with CEPO (p < 0.01) having a better effect than EPO (p < 0.05).

Conclusion: In summary, these results provide strong evidences that EPO and CEPO promote adult hippocampal neurogenesis. We speculate that EPO and CEPO could be a good candidate for treating neuropsychiatric disorders such as depression and anxiety associated with reduced hippocampal neurogenesis.
**P-10-029** Tianeptine treatment reverses increase on oxidative damage and decrease of antioxidant defense enzymes into the brain of rats submitted to the chronic mild stress model

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**Objective:** A growing body of evidence has suggested that reactive oxygen species may play an important role in the pathophysiology and treatment of depression. The present study was aimed to evaluate the effects of tianeptine (an antidepressant, which enhances the reuptake of serotonin) administration on the oxidative stress parameters in the brain of rats exposed to chronic mild stress (CMS) procedure.

**Methods:** To this aim, after 40 days of exposure to CMS Wistar rats were treated with tianeptine (15 mg/kg) or saline for 7 days. Then, the lipid and protein oxidation, and superoxide dismutase (SOD) and catalase (CAT) activities were evaluated in the rat brain.

**Results:** Our findings demonstrated that lipid oxidation was increased in stressed rats, and tianeptine reversed this effect in the prefrontal cortex and amygdala. In stressed rats there was an increase on the protein oxidation in the hippocampus and amygdala, but this effect was reversed only in the amygdala by tianeptine; in the nucleus accumbens there was a reduced on the protein oxidation in stressed rats treated with tianeptine, compared to stress group treated with saline. The SOD activity was reduced in all brain areas from stressed rats treated with saline, but treatment with tianeptine reversed these effects. The CAT activity decreased in stressed rats in the prefrontal cortex and amygdala, and treatment with tianeptine reversed these effects; in the hippocampus and nucleus accumbens there were an increase in the CAT activity in stressed rats treated with tianeptine, compared to control and stress group treated with saline.

**Conclusion:** Our data indicate that stress produces oxidants and impairment in the SOD and CAT activities, which could contribute to depression. In addition, tianeptine antidepressant exerted positive effects on the oxidative stress parameters, decreasing lipid and protein oxidation and increasing SOD and CAT activities in rats submitted to CMS.

**P-10-030** The dopamine stabilizers ACR16 and (−)-OSU6162 display nanomolar affinities at the α1 receptor

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**Objective:** Converging in vivo evidence has advanced the α1 receptor as a pharmacological target for the treatment of neurological and psychiatric disorders such as L-DOPA-induced dyskinesia, schizophrenia, drug addiction, and depression. Considering their close structural resemblance to known α1 receptor ligands we investigated the ability of dopaminergic stabilizers, a new class of phenylpiperidine compounds, to bind α1 receptors.

**Methods:** α1 receptor ligand binding characteristics were determined by both saturation and competition assays using the specific α1 receptor agonist [3H](+)-pentazocine. Radioligand binding experiments were performed in membranes prepared from HEK293 cells that were transiently transfected with the human α1 receptor and in rat striatal membranes.

**Results:** Our results reveal that the dopaminergic stabilizers, (−)-OSU6162 and ACR16, display nanomolar affinity for the human α1 receptor heterologously expressed in HEK293 cells, as well as in rat striatal membranes. The affinity of ACR16 appears to be indistinguishable from that of the structurally related compound (+)-5-PPP, a ligand which has been widely used to study α1 receptors.

**Conclusion:** Dopaminergic stabilizers are a novel class of drug candidates that have shown clinical promise in the treatment of several severe neurological and neuropsychiatric disorders. While their exact mechanism of action is still under investigation, our data point to a previously overlooked aspect of their pharmacology. The present findings warrant further exploration of the relevance of α1 receptor binding for the in vivo actions of dopaminergic stabilizers.

**P-10-031** Analysis of neuroadaptive changes following co-treatment of lurasidone and valproic acid in rats

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**Objective:** Combinatory therapy is widely used in psychiatry owing to the possibility that drugs with different mechanisms of action may synergize in order to improve specific functions, which are deteriorated in schizophrenia, bipolar disorders and major depression. While synaptic mechanisms may contribute to drug combination strategies, it should also be considered that, on the long-term, two drugs may ‘cooperate’ in modulating neuronal plasticity, which represents a downstream target crucial for functional recovery.

**Methods:** On this basis, in the present study we have investigated neuroadaptive changes set in motion upon chronic concomitant administration of the novel antipsychotic lurasidone (LUR) with the mood stabilizer valproate (VPA). The two agents were given to rats for 21 days and the animals were sacrificed 24 h after the last drug administration for the molecular analyses. We investigated the expression of the neurotrophin BDNF that represents a key marker of neuronal plasticity and cellular resiliency.

**Results:** The results emerging from these analyses suggest that co-administration of LUR and VPA produces a larger increase of BDNF expression in ventral hippocampus, through the regulation of specific neurotrophic transcripts, compared to each drug alone. We also found that the expression of HDAC-2 and DNMT1, two genes involved in the epigenetic machinery, were also significantly regulated by the combination LUR+VPA, suggesting that some of the transcriptional changes may be sustained by epigenetic mechanisms. Other genes important for neuronal adaptation, such Arc (Activity-regulated cytoskeletal associated protein), are significantly regulated by chronic treatment with LUR and VPA, although their combination does not provide any advantage over the drugs employed alone.

**Conclusion:** Our results suggest that the beneficial effects associated with combinatory treatment between a second-generation antipsychotic and a mood stabilizer could result from the ability to modulate neuroplastic molecules such as BDNF, whose expression and function is deteriorated in different psychiatric conditions.

**Policy of full disclosure:** This work was supported from funding by Sunovion Pharmaceuticals Inc.

**P-10-032** Chronic lurasidone treatment restores functional and neuroplastic deficits in serotonin transporter knockout rats, an animal model of depression

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**Objective:** Lurasidone is a novel antipsychotic drug characterized by a multi-receptor signature. Some of these receptor mechanisms have been associated with antidepressant activity, including blockade of 5HT2a, 5HT7 as well as activation of 5HT1a. Furthermore, we have recently shown that chronic administration of lurasidone can increase the expression of BDNF, a marker of neuronal plasticity that has been associated with clinical antidepressant properties.

**Methods:** In the present work we specifically addressed the potential antidepressant activity of lurasidone by employing a genetic model of the disease, namely serotonin transporter knockout (SERT KO) rats, which are characterized by an anxious and depressive phenotype. To this purpose we chronically administered lurasidone to wild type or SERT KO rats and investigated behavioral and molecular changes produce by the drug.

**Results:** At behavioral level, we found that, chronic lurasidone treatment significantly increased fear extinction in SERT KO rats (p < 0.01), without affecting wild-type animals. At molecular level, lurasidone was able to normalize the reduced expression of the neurotrophin BDNF in the prefrontal cortex SERT KO rats. Such effect occurred through the regulation of specific neurotrophic transcripts, primarily of exon VI, and it was sustained by epigenetic mechanisms as demonstrated by the significant up-regulation of the DNA demethylating gene Gadd45β. We also found that, when given to SERT KO rats, chronic lurasidone treatment was able to restore the reduced...
expression of different GABAergic markers, including GAD67, parvalbumin and somatostatin.

Conclusion: Our results show that larusidone can improve depression-related dysfunction of SERT KO rats, with a primary impact on prefrontal cortex, also through the modulation of the neurotrophin BDNF. The adaptive changes set in motion by repeated treatment with larusidone may contribute to the amelioration of functional capacities, closely associated with neuronal plasticity, which are deteriorated in patients with schizophrenia, bipolar disease and major depression.

Policy of full disclosure: This work was supported by funding from Sunovion Pharmaceuticals Inc.

P-10-033 Antagonist dissociation from dopamine D2 receptors – dopamine stabilizers unbind faster than clozapine and quetiapine

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Objective: Medication with dopamine D2 antagonists is often associated with extrapyramidal symptoms and increased serum prolactin. The side-effect liability of antipsychotics correlates inversely with their rates of receptor dissociation. Recent studies indicate that the novel D2 receptor ligands, ACR16 (pridopline) and (−)-OSU6162, initially described as ‘dopamine stabilizers,’ act as antagonists with similarly high dissociation rates as clozapine and quetiapine. Those studies measured ligand dissociation from membrane preparations or used modified G proteins in functional assays. We aimed to examine antagonist dissociation in living cells, using an assay based on activation of G protein-coupled potassium (GIRK) channels. This assay uses native G proteins and has higher temporal resolution than previous studies.

Methods: GIRK current responses to dopamine receptor activation were recorded using two-electrode voltage clamp in Xenopus oocytes expressing dopamine D2L or D2S receptors, Regulator of G protein Signaling-4, and GIRK1/4 channels. First, dopamine (100 nM) was applied, eliciting a ‘baseline’ response. Next, a maximally effective concentration of antagonist was washed in. After achieving steady-state inhibition the antagonist was washed out, still in the presence of dopamine. The time to half-maximal response recovery (T1/2) and the response recovery amplitude relative to baseline were taken as measures of antagonist dissociation.

Results: With clozapine and quetiapine, similar recovery time courses were observed (T1/2 = 48 ± 5.5 s, and 60 ± 2.2 s, respectively). About 50% response recovery was observed. The dopamine stabilizers, ACR16 and (−)-OSU6162, lacked detectable efficacy in our assay. These compounds washed out faster than clozapine and quetiapine (T1/2 = 8.2 ± 1.8 s, and 6.1 ± 0.4 s, respectively); and near-complete response recovery was observed.

Conclusion: The present data suggest that the ‘dopamine stabilizers’ ACR16 and (−)-OSU6162 dissociate faster than clozapine and quetiapine. Such very rapid dissociation might be relevant to the low incidence of side-effects reported from clinical trials with these compounds.

P-10-034 Matrixmetalloproteinase-9 in schizophrenia and depression – is this the link within the hierarchical disease model?

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Objective: Recently it has been reported that the protein expression of the matrixmetalloproteinase-9 (MMP9), an extracellular protease, is similarly increased in patients suffering from schizophrenia and depression. Given the long discussed hypothesis that schizophrenia and affective disorder follow a hierarchical disease model and might have overlapping pathophysiological dysfunction processes MMP9 might mirror a biological link between schizophrenia and affective disorder.

Methods: Therefore, within this pilot study the blood concentration of MMP9 and its inhibitor TIMP1 (Tissue Inhibitors of Metalloproteinases) was examined in 37 patients with a DSM-IV diagnosis of a schizophrenia spectrum disorder, 78 patients with a DSM-IV diagnosis of a major depression and 38 healthy controls. The Positive and Negative Syndrome Scale (PANSS) as well as the Hamilton Depression Rating Scale (HAM-D-17) were applied Blood draws and clinical interviews were performed at baseline and every two weeks within the six weeks study period. ANOVA and univariate tests were calculated using the statistical program 2.11.1.

Results: The MMP9 concentration differed significantly between the patients and healthy controls (schizophrenia 143 ± 101 ng/ml, depression 135 ± 141 ng/ml; healthy controls 54 ± 48 ng/ml; ANOVA F = 7.06, p = 0.001). A significant positive correlation was found between illness severity of the depressed patients via the HAMD and the MMP9 concentration both at study entry (Pearson 0.234; p = 0.040) and also at endpoint (Pearson 0.302; p = 0.001). Also, in the schizophrenia patients a significant positive association was found in terms of the severity of depressive symptoms measured via the depression item (Pearson 0.50; p = 0.011) and the PANSS depression subscore (Pearson 0.44; p = 0.028) at baseline.

Conclusion: These are the first preliminary results of MMP9 in the blood of patients with schizophrenia and depression. This suggests that both diseases might share more biological underpinnings than thought before. Future studies are warranted to replicate these first results.

P-10-035 High-throughput screening for allosteric modulators of the D2 dopamine receptor

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Objective: The D2 dopamine receptor (DAR) is central in the etiology and/or therapy of many neuropsychiatric disorders, however, truly specific drugs for this receptor have been difficult to obtain. A novel approach towards receptor-selective ligands is to identify allosteric modulators that bind to less conserved sites on the receptor and have the potential to be exquisitely selective. In order to identify allosteric modulators of the D2 DAR, we developed a high throughput-screening (HTS) platform to interrogate large chemical compound libraries.

Methods: The primary HTS assay utilizes a cell line expressing the D2 DAR coupled to a chimeric Ca2+ sensor, thereby linking receptor activation to robust Ca2+ mobilization. Counter-screens against other DAR subtypes and radioligand binding studies were also carried out.

Results: Through the NIH Molecular Libraries Program, a 370,000 small molecule library was screened to identify agonists (allosteric or orthosteric), positive allosteric modulators, or antagonists (allosteric or orthosteric). From this primary screen, 2,288 compounds with agonist activity, 1,408 compounds with potentiator activity, and 2,294 compounds with antagonist activity were cherry-picked. Upon further evaluation, none of the potentiators confirmed while 650 agonists and 858 antagonists did not confirm. The remaining confirmed agonist and antagonist ligands were subjected to orthogonal and counter-screening functional assays. On the basis of these analyses, 745 agonist and 499 antagonist compounds were evaluated using radioligand competition binding assays as a filter to separate orthosteric and allosteric ligands. These experiments resulted in the identification of 47 agonists and 48 antagonists that had insignificant effects on radioligand binding. These compounds would thus appear to be allosteric agonists and negative allosteric modulators of the D2 DAR.

Conclusion: We have conducted a high through-put screen of the NIH Molecular Libraries Program small molecule repository. Numerous lead compounds with agonist or antagonist activities were identified that appear to exert their functional effects via allosteric mechanisms. The most promising of these ligands are undergoing further characterization.
Compromising sigma-1 receptors at the ER renders cytotoxicity to physiologically relevant concentrations of dopamine in a NF-kB/Bcl-2 dependent mechanism: Potential relevance to Parkinson’s disease

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Objective: To examine if the endoplasmic reticulum (ER) chaperone the sigma-1 receptor (Sig-1R) may play a role in Parkinsonism.

Methods: Dopamine (DA)-induced apoptosis was examined in wild type CHO cells and in Sig-1R knockout CHO cells.

Results: DA in physiological concentrations (e.g., lower than 10 μM) does not cause apoptosis. However, the same concentrations of DA cause apoptosis in Sig-1R knockdown CHO cells. In search for a mechanism explanation, we found that unfolded protein response is not involved. Rather, the level of protective protein Bcl-2 is critically involved in this DA/Sig-1R knockdown-induced apoptosis. Specifically, the DA/Sig-1R knockdown causes a synergistic proteasomal conversion of NF-kB p105 to the active form of p50 which is known to downregulate the transcription of Bcl-2. Importantly, the DA/Sig-1R knockdown-induced apoptosis is blocked by the over-expression of Bcl-2.

Conclusion: Our results therefore indicate that DA is involved in the activation of NF-kB and suggest that endogenous Sig-1Rs are tonically inhibiting the proteasomal conversion/activation of NF-kB caused by physiologically relevant concentrations of DA which would otherwise cause apoptosis. Thus, Sig-1Rs and associated ligands may represent new therapeutic targets for the treatment of Parkinsonism.

Effect of N-acetylcysteine on L-buthionine-SR-sulfoximine-induced reduction of cell viability in a-synuclein-transfected SH-SYSY cells

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Objective: It is well known that α-synuclein (α-syn) plays an important role in the pathogenesis of Parkinson’s disease (PD). Moreover, oxidative stress is also thought to be an important factor in PD due to dopaminergic neuronal cell death by free radicals and enhancement of α-syn fibrillation by oxidized stress.

Methods: In the present study, we examined the effects of L-buthionine-SR-sulfoximine (BSO), a GSH synthase inhibitor, with or without N-acetylcysteine (NAC), a source of GSH, on α-syn-induced cell injury in human neuroblastoma SH-SYSY cells, to clarify the role of GSH, an intracellular antioxidant, on the molecular mechanism of α-syn-induced cell injury.

Results: Treatment with BSO significantly reduced cell viability of both empty-vector- and α-syn-transfected SH-SYSY cells in a dose-dependent manner, although the ratio of α-syn-induced reduction of cell viability in α-syn-transfected cells was much greater than that in empty-vector-transfected cells. Moreover, BSO significantly reduced the intracellular total GSH level in both types of transformant cells. However, NAC significantly prevented BSO-induced reduction of both cell viability and GSH level in the α-syn-transfected cells.

Conclusion: Thus, these findings suggest that GSH plays an important role in α-syn-induced cell injury by reducing cell viability, although further study is needed to clarify the molecular basis of α-syn-induced cell injury.

The Sigma-1 receptor chaperone plays an essential role in neural circuits

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Objective: The endoplasmic reticulum protein sigma-1 receptor (Sig-1R) is a novel chaperone and has been implicated in CNS diseases such as Alzheimer’s disease, depression, and drug abuse. It is known that Sig-1Rs are particularly enriched in the mitochondrial associate ER membrane, MAM; however, little is known about how Sig-1R regulate neuronal mitochondria. We previously showed that Sig-1R promote the process of neurotregenesis and dendirto-genesis in hippocampal neurons via the regulation of Rho GTP signaling pathways. In this study, we further examined the effects of Sig-1R siRNA on axon elongation and synaptic mitochondrial activities.

Methods: Neurons were transfected at DIV 1 and axon lengths were measured on both DIV 3 and DIV 7 by using tau immunostaining. We also examined synaptosomal mitochondrial mass and membrane potentials by using flow cytometry analysis. Rhodamine 123 and 10-N-nonyl acridine orange (NAO) were used as membrane potential- or mass-dependent fluorescent dyes, respectively.

Results: Knocking down of Sig-1R impaired axon elongation significantly. The lengths of axon of the Sig-1R knockdown neurons were as short as 40% of the controls at DIV 3. The difference in axon lengths became more noteworthy as neuron culture extended. Although Sig-1R siRNA-transfected neurons were able to extend axon gradually in time, they showed a slower extension rate. Knocking down of Sig-1R caused aberrant axon extension was also associated with hyperphosphorylation of tau as indicated by MC1 antibody that recognized an early conformational change in tau. Our data showed that Sig-1R siRNA transduced neurons possessed significantly less mitochondrial mass and lower membrane potentials in the synaptosome. Mitochondrial movement in the growth cone areas was less active in Sig-1R siRNA neurons as well.

Conclusion: The observed changes in axon extension and synaptic mitochondrial activities in Sig-1R knockdown neurons indicated the importance of Sig-1R in maintaining synaptic functions and their significance in averting CNS diseases.
P-11. Dementia

**P-10-040** GABAergic regulation of extracellular D-serine concentrations in the rat medial frontal cortex of the rat as revealed by in vivo microdialysis

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**Objective**: It has now been well accepted that D-serine may be an intrinsic cosynaptic for the N-methyl-D-aspartate (NMDA) type glutamate receptor in the mammalian brain. Thus, D-serine facilitates various functions of the NMDA receptor by stereospecifically stimulating the glycine site and is present in the tissue and extracellular fluid in high contents throughout life with a GRIN2B subunit-like distribution. Moreover, selective elimination of D-serine by D-amino acid oxidase or D-serine deaminase has been shown to reduce the NMDA receptor functioning such as cGMP production and long-term potentiation formation in the rat brain. Although these findings suggest that the synaptic and/or extra-synaptic D-serine may play an important role in the regulation of the NMDA receptors, the molecular and cellular mechanisms of the physiological control of the extracellular D-serine concentrations are still unclear.

**Methods**: Therefore, we have investigated by using an in vivo microdialysis technique and a HPLC with fluorometric detection method the effects of GABAergic agents on the extracellular contents of D-serine in the medial frontal cortex of the freely moving rats. The present animal experiments have been approved by the ethics committee of the Tokyo Medical and Dental University.

**Results**: We found that the local perfusion of a selective GABAA receptor antagonist, bicuculline or picrotoxinin into the medial frontal cortex lowered significantly the cortical extracellular contents of D-serine. The decreasing effects of bicuculline was completely reversed by the local co-infusion of a selective GABAA receptor agonist muscimol. Neither GABAB nor GABAC selective antagonist failed to change the extracellular D-serine levels.

**Conclusion**: The present study gives us the field of view that the extracellular D-serine release may be under a tonic facilitatory control by GABAergic transmission via the GABAA receptor at least in the rat medial frontal cortex.

**P-10-041** Intravenous hemantane improves levodopa-induced dyskinesias in 6-hydroxydopamine-lesioned rats

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**Objective**: Levodopa-induced dyskinesia (LID) becomes an extremely common and debilitating problem. An overactive glutamae receptor in the basal ganglia has been suggested to play a key role in the pathophysiology of Parkinson's disease (PD) and LID. NMDA receptor antagonist amantadine (AMA) is widely used to improve levodopa induced motor complications. Hemantane (H.) (N-(2-adamantyl)hexamethylenamine hydrochloride) is effective in animal models and in patients with early stages of PD. H. has complex mechanism of action, including properties of uncompetitive, low-affinity NMDA receptor open-channel blocker. The aim of the study was to assess the effects of H. in parkinsonian rats with LID.

**Methods**: To induce parkinsonian syndrome 6-OHDA (12 µg) was injected into the left medial forebrain bundle (MFB). Levodopa (10 mg/kg) with benzserazine (15 mg/kg) was administered starting 3 weeks after lesion daily during next 4 weeks. The dyskinetic effects of levodopa were evaluated using a validated rat AIMs scale, where axial, limb, orolingual and rotation AIMs represent the rodent equivalent of peak-dose dyskinesia in PD. Rats with LID were selected and divided in 2 groups. For 5 following days levodopa administration was preceded by injection of H. (5 mg/kg, i.v.) or AMA (20 mg/kg, i.v.). AIMs were registered 35 min after levodopa administration 4 times during 140 min.

**Results**: Co-administration of levodopa with H. or AMA resulted in significantly less dyskinesia than levodopa alone. Effects of acute injection of H. were less pronounced than of AMA. After 5 days treatment H. was more effective in reducing orolingual and rotation AIMs.

**Conclusion**: Hemantane could be used as adjunctive therapy for levodopa-induced dyskinesia.

**P-10-042** Pre-analysis storage conditions influence measured peripheral blood BDNF levels

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**Objective**: Brain-derived neurotrophic factor (BDNF) is a neurotrophin with a pivotal role in the regulation of neuronal function throughout life and is regarded as a potential biomarker of mental disorders. Previous studies suggest that plasma BDNF levels are more variable than serum BDNF levels.

**Methods**: We determined the influence of time and temperature on the measured peripheral blood BDNF levels. Blood samples were aliquoted into 4 types of tubes: heparin, EDTA and citrate tubes for plasma and anticoagulant-free tubes for serum. The samples were stored at 4 °C or 25 °C for 0, 1, 2, 4, 6, 24 or 48 hours.

**Results**: The plasma and serum BDNF levels were measured by ELISA. The measured plasma BDNF levels increased over time, whereas the serum BDNF levels were unchanged. The BDNF levels detected in heparin-plasma and EDTA-plasma samples stored at 4 °C were much higher than those in samples stored at 25 °C.

**Conclusion**: This study indicates that the measured plasma BDNF levels are dependent on the time and the temperature of storage after blood sampling.

P-11. Dementia

**P-11-001** Psychopathology in Alzheimer's disease

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**Objective**: In this review we analyze the psychopathological variants found in this stereotype of patient and diagnostic difficulties.

**Methods**: It carries out a review about the data currently available on this topic.

**Results**: Semiology psychic: depressive syndrome (20 to 40%), psychotic symptoms (30 to 50%) are not correlated with the severity of dementia, aggression and psychomotor agitation (20%) and sleep disturbance (40 to 70%). They also appear frequently delirium, progressive deterioration in recent memory, disinhibited or socially inappropriate behavior, personality changes and emotional liability. Somatic semiology: Table afas-aprasic-agnostic. It should also be noted that the prognosis may overshadow the association with extra-pyramidal signs, psychotic disorders and myoclonus.

**Conclusion**: We note that Alzheimer's disease and psychopathology are correlated. It hath in mind the existing diagnostic difficulties have to go deeper into these issues.

**P-11-002** Depressive disorders and medical conditions among patients with Alzheimer's disease: A case-control study of a national managed care database

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**Objective**: To compare the prevalence of depression and comorbid medical conditions between patients with a diagnosis of Alzheimer’s Disease (AD) (cases) in comparison with a matched control group of patients without AD, in the National Managed Care Benchmark Database (IHCIS).

**Methods**: The prevalence of depression and comorbid medical conditions was compared between patients with AD (defined by ICD-9 codes) and controls using data from the IHCIS, a fully de-identified, HIPAA compliant database made up of more than 35 Managed Care health plans within the US and covering seven census regions. Matched case-control method was used to compare depression and medical comorbidity. Controls were matched to cases by type of health plan and pharmacy benefit on a 3:1 ratio.

**Results**: Among the 488,091 patients with full year of eligibility during 2001, 2,947 were identified with a diagnosis of AD and 63.6% were women. The prevalence of depressive disorders was much higher in the AD group compared to the random selection of matched non AD patients 12,880 (32.48% vs. 3.45%, p < 0.001). AD patients had...
more comorbid medical conditions than patients without dementia. In general, AD patients had more convulsions [odds ratio (OR) = 6.16, 95% CI = 3.3–11.5]; hypotension (OR = 2.96, 95% CI = 2.0–4.2); anemia (OR = 2.31, 95% CI = 1.4–3.8); heart failure (OR = 2.21, 95% CI = 2.0–2.9); urinary system disorders (OR = 1.73, 95% CI = 1.4–2.7); COPD (OR = 1.53, 95% CI = 1.2–1.8); gastrointestinal hemorrhage (OR = 1.46, 95% CI = 1.2–1.9); and circulatory disease (OR = 1.39, 95% CI = 1.0–1.9); compared with the controls.

Conclusion: The present study confirms that depressive disorders and medical comorbidities are complications of AD and physicians should be alert to the presence of this clinically important diseases in patients with AD.

Policy of full disclosure: Dr. Castilla-Puentes is currently working as Global Medical Safety Physician with Johnson & Johnson, Pharmaceutical Research and Development.

P-11-003 Comparison of cognition measured by MMSE between Alzheimer’s disease and depression

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Objective: The Mini-Mental State Examination (MMSE) is the most widely used screening measure for cognitive impairment. The aims of this study are to compare the psychometric properties of the Mini-Mental State Examination – Korean Version (MMSE-KC) between Alzheimer’s disease and depression and to detect differential item function (DIF).

Methods: Data were analyzed from a nationwide sample of Korean elders, a total of 485 participants age 65 or older from cross-sectional community-based study. All participants were assessed using Mini-Mental State Examination by door-to-door home visit. Diagnostic assessments of depression and dementia were administered using the Korean version of the Consortium to Establish a Registry for Alzheimer’s Disease Assessment Packet (CERAD-K) Clinical Assessment Battery.

Results: All items of MMSE-KC fit the model and together spanned a range of threshold parameter (difficulty) from −3.86 (easier) to 1.15 (more difficult) logits, and slope parameter (discrimination) from 0.55 to 8.6 logits. Depression group were more likely to have errors like items about ‘recall of three words’ and ‘attention’ were the most difficult items. In contrast, dementia group had errors in most items. Detecting DIF using IRTLRDIF, people with dementia showed DIF such items as orientation to place, the last two items of ‘recall of three words’ (car and cap), and ‘The last two items of attention’, ‘three stage command’. People with depression showed DIF such items as ‘time orientation (week)’, ‘repetition’, ‘recall of three words’ (car).

Conclusion: The MMSE-KC can provide a reliable and valid quantitative estimate of cognitive ability. However, some items have DIF in case of people with depression or dementia. Therefore, more attention should be paid to items showing DIF.

P-11-004 The outcome of mild cognitive impairment after administering treatment

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Objective: Mild cognitive impairment(MCI) is a frequent clinical entity, considered today to be a prodromal stage of Alzheimer’s dementia. The aim of this study is to determine the outcome of the patients diagnosed with MCI treated with different therapies and the patients diagnosed with MCI and non-treated.

Methods: The study comprises a number of 157 patients (over 60 years) diagnosed with MCI. The patients were evaluated with MMSE (Mini Mental State Evaluation) at the inclusion into the study, after 6 months, after 1 year and after 2 years. The patients were divided in: group A – 43 patients with MCI treated with Galantamine (16 mg/day) group B – 44 patients with MCI treated with Rhodiola rosea, Scopolamines /day group C – 41 patients with MCI treated with Vitamin E, 800 UI/day group D – 29 patients with MCI, which did not received treatment.

Results: The average of MMSE scores at the inclusion into the study was 23.62 points for group A, 24.36 for group B, 24.82 for group C and 25.0 for group D. After 1 year, cognitive performance improves with 2.07 points for group A, with 2.04 for group B, 2.69 in group C; in group D we did not observed any improvement. After 2 years of treatment cognitive performance improves with 3.14 points for group A, 2.48 points for group B, 2.25 points for group C and in group D we have observed an impairment of cognitive performance with 2.49 points.

Conclusion: Comparing the outcome of patients long time treatment show a better improvement in group treated with cholinesterase inhibitor (galantamine). The study prove the importance of early treatment of MCI to improve the cognitive function and to delay the progression to dementia.

P-11-005 Clozapine as mono-therapy in the management of Huntington’s chorea

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Objective: Huntington’s Chorea, an autosomal dominant neurodegenerative disorder comprising movement disorder, cognitive deficits and distressing psychiatric symptoms, often poses a significant therapeutic and management challenge to clinicians and caregivers alike. While a number of medication strategies, including amantadine, tetrabenazine (the first drug to receive specific US FDA approval for the managing the choreic component of the disorder), clonazepam and antipsychotics like haloperidol and risper- idone, have been tried, none seems to produce sustained symptomatic relief or significantly reduced care-giving burden. Psychotic symp- toms, irritability, aggression, depression, apathy and suicidality are major contributors to the care-giver burden and, despite considerable research, often remain unaddressed or inadequately managed. Clozapine, with its demonstrated superior efficacy and extremely low risk of extra-pyramidal side-effects (EPS) and tardive dyskinesia (TD), would appear to be the ideal antipsychotic for the purpose and its usefulness in this regard is supported by findings from several studies. Unfortunately, however, it remains under-used in patients with Huntington’s Chorea.

Methods: This naturalistic observational study describes an illustrative case. The patient, a 57 year old (European) male with the diagnosis of Huntington’s Chorea and persisting paranoid delusions, aggressive/disruptive/violent behaviour, aggravated movement disorder despite multiple medications (including risperidone 6 mg/day) was referred for review as he had become unmanageable in the rest-home where he had been assigned to live. He was transitioned un-eventually to clozapine 100 mg/day, with amelioration of psychotic symptoms, as well as improvement in the movement disorder.

Results: Complete remission of psychotic symptoms, aggression, disruptive and violent behaviour, along with significant improvement in the movement component.

Conclusion: Clozapine monotherapy is an effective and safe therapeutic option in patients with Huntington’s Chorea. Further re- search is required to generate robust evidence in this area.

P-11-006 Effects of intestinal endotoxemia (IETM) on learning memory ability and brain levels of Aβ, Tau protein in rats with Alzheimer’s disease

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Objective: To investigate the relationship between intestinal endotoxemia (IETM) and learning memory ability, brain levels of β-amyloid protein (Aβ), Tau protein in rats with Alzheimer’s disease (AD).

Methods: The AD model of wistar rats were produced by injecting D-galacitce and AIC13 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and Tau protein were determined by ELISA; the apoptotic neuron was detected by Flow cytometry; the expression levels of Aβ was tested by Immunohistochemical.
**Objective:** To investigate the relationship between intestinal endotoxemia (IETM) and learning memory ability, cell apoptosis in rats with Alzheimer’s disease (AD).

**Methods:** The AD model of wistar rats were produced by injecting D-galactose and AlCl3 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze test; LPS, TNF-α (IL-1β) and PD in AD rats were increased (P<0.05). The AD rat model of wistar rats was produced by injecting D-galactose and AlCl3 intraperitoneally for 90 days. Subsequently, learning and memory ability of the rats were evaluated by Morris water maze; the level of lipopolysaccharide (LPS) and tumor necrosis factor-α (TNF-α) were determined by ELISA; the apoptotic neuron was detected by (TUNEL); hippocampal gene expression of amyloid precursor protein (APP) and presenilin1 (PS1) was tested by RT-PCR.

**Results:** Compared with the normal control group, the model group had longer latency (P<0.01) and more error times (P<0.05) in Morris water maze test; LPS, TNF-α and IL-1β in the sera of Alzheimer disease’s rats were markedly increased (P<0.05) in hippocampal gene expression of amyloid precursor protein (APP) and presenilin1 (PS1).

**Conclusion:** The rat model of Alzheimer’s disease is accompanied IETM and that may plays an important role in the development of AD.
Objective: To investigate the changes in cerebral blood flow in dementia patient with hyper sexuality after anti-androgen therapy.

Methods: We performed 99mTc-ECD SPECT studies before and after anti-androgen therapy in a same dementia patient with hyper sexuality using statistical parametric mapping analysis.

Results: Statistical parametric mapping analysis showed that increased cerebral blood flow occurred in bilateral frontal gyrus after anti-androgen therapy. Furthermore, temporal gyrus showed marked increased cerebral blood flow compared with baseline study. Patient improved the sexual problem after the therapy, but cognitive function did not change throughout the study.

Conclusion: Our findings indicate that the change of blood flow in frontal and temporal cortices may reflect the effect of anti-androgen therapy in patient with hyper sexuality. The patient with fronto-temporal dementia sometimes shows abnormal behavior like hyper sexuality. Our results might contribute to solving the problem.

Objective: To evaluate the behavioural and neurochemical evidence of Biochanin-A in cognitive deficit mice for the management of Alzheimer’s disease.

Methods: Elevated Plus Maze, Passive Avoidance Shock were used. Brain AchE, GSH and TBARS were analysed. Neurochemical evidence was obtained by assay of brain Dopamine and Noradrenaline assay, brain tissue damage was analysed.

Results: BCA decreased in the Transfer Latency, increased Step Through latency significantly in Scopolamine treated and natural aged mice in Elevated Plus Maze and Passive Shock Avoidance Paradigm. A dose dependent (BCA 40, 20 & 10 mg/kg) significant (P<0.01) antioxidant (TBARS & GSH) and inhibition of acetylcholinesterase activity was observed as compared to Standard Piracetam (400 mg/kg). BCA insignificantly (P>0.05) reduced Dopamine and Nor-adrenaline content of young mice, where as in scopolamine treated mice showed significant (P<0.01) increase in the content of Nor-adrenaline and insignificant (P>0.05) increase in Dopamine which is sign of dementia.

Conclusion: Further in histopathology of hippocampus of BCA treated mice protected the formation of pyknotic black neurons compared to Scopolamine. In the light of above, it may be worthwhile to explore the potential of this Biochanin-A in the management of Alzheimer’s disease.

Objective: We designed this study to diagnose Mixed dementia (MD) using brain imaging data as well as clinical criteria, and compare the clinical features and neuropsychological characteristics of AD (Alzheimer’s disease) and MD.

Methods: A total of 1757 AD patients and 987 MD patients were included from the Clinical Research Center for Dementia of South Korea (CREDOS). All patients underwent comprehensive neuropsychological tests as follows: the Korean version of the Mini-Mental State Examination (K-MMSE), the Clinical Dementia Rating (CDR) scale, the Barthel Index for Daily Living Activities (Barthel-ADL), the Seoul-Instrumental Activities of Daily Living (S-IADL), the Korean Neuropsychiatric Inventory (K-NPI), the 15-item Geriatric Depression Scale (GDS), and the Dementia version of Seoul Neuropsychological Screening Battery (SNSB-D).

Results: The results of a clinical features comparison revealed that depressed mood and vascular factors such as hypertension, heart disease, focal neurological symptoms and signs, and stroke were present in MD patients more than in those with AD. With respect to cognitive function, no significant difference was found between AD and MD patients in terms of SNSB-D scores except frontal/executive function. Also, AD patients showed better performance than MD patients with respect to activities of daily living.

Conclusion: This study reports that MD patients showed significantly different clinical and neuropsychological features than AD patients. These findings will be helpful in the development of prevention and treatment strategies for MD.

Objective: The purpose of this study was to compare the efficacy of galantamine treatment, especially attention ability between patients with pure Alzheimer’s disease (AD) and Mixed dementia (MD) during a 24-week trial.

Methods: A total of 40 patients were recruited for this 24-week study. The effect of galantamine on attention was measured using Seoul Computerized NeuroCognitive Function Test (SCNT) and frontal functions test of Seoul Neuropsychological Screening Battery (SNSB). Patients’ activities of daily living using the Seoul-Activities of Daily Living (S-ADL) and the Seoul- Instrumental Activities of Daily Living (S-IADL); behavioral symptoms using the Korean version Neuropsychiatric Inventory (K-NPI) were measured at baseline and 24-week.

Results: 17 pure AD patients and 23 MD patients were analyzed in this study. Attention as measured by SCNT was not significantly different from baseline after 24 weeks of treatment in both groups. There was no significant difference between two groups in mean change from baseline in the SCNT, S-ADL, S-IADL and K-NPI scores at 24-week.

Conclusion: Galantamine showed a therapeutic effect on cognition, activities of daily living, neuropsychiatric symptoms in pure AD and MD. Furthermore, Galantamine may specifically help to maintain attention and it may have positive effects on other cognitive and functional abilities.

Policy of full disclosure: This study was supported by Janssen Korea Ltd.

Objective: Alzheimer disease (AD) is the most common disease in the cognitive impairment diseases, and the AD patients have been increasing in recent years. AD shows memory impairment, disturbance of orientation and higher brain dysfunction such as visuospatial disorder and executive dysfunction with disease progression. In AD, the hippocampal atrophy is progressively seen in disease course. Meanwhile, it is suggested that donepezil has neuropsychotrophic effect and prevents the disease progression. However, there are patients of AD for whom donepezil is effective or not. In this study, we followed the AD patients who were medicated with donepezil and investigated hippocampal volume change with each of the donepezil responder and non-responder.

Policy of full disclosure: This study was supported by Samsung Biomedical Research Institute, #SBRI C-A9-205.
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Methods: Voxel-based morphometry analysis was performed in 13 AD patients who are prevented in cognitive decline with donepezil treatment and 14 who are not. All participants were medicated with donepezil. In the analysis, Voxel-based Specific Regional Analysis System for Alzheimer’s disease (VSRAD: developed by Eisai Co., Ltd. & Pfizer Japan) was used, and calculated hippocampal region atrophy index defined as Z score. The subjects were performed magnetic resonance imaging scan at the baseline and the follow point, and calculated the difference between the Z score at baseline and follow point. Group analysis was performed using Mann-whitney U test.

Results: There was a significant difference between donepezil effective and donepezil non-effective patients in AD regarding the severity of hippocampal region atrophy (p = 0.038).

Conclusion: In this study, we found that the progression of the hippocampal atrophy was more suppressed in AD patients who were effective with donepezil treatment than those who were non-effective. It is suggested that donepezil may play an important role in the suppression of the neurodegeneration and help the neuronal protection, and consequently delay the cognitive decline in AD patients.

P-11-016 Effects of high-frequency transcranial magnetic stimulation on cognition of elderly with cognitive impairment no-dementia (CIND)

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Objective: To verify the effects of high-frequency rTMS to the left dorsolateral prefrontal cortex (DLPFC) on global cognition of functionally independent elderly with subjective complaints of memory decline.

Methods: Clinical trial. Nineteen (8 male and 11 female) elderly, aged between 60 and 74 years old (mean age = 64.5 ± 3.8), independent for instrumental activities of daily living (IADL) with subjective memory complaints and evidence of some impairment in neuropsychological assessment, characterizing cognitive impairment no-dementia (CIND). The MoCA test was used for screening. For each patient, a brain magnetic resonance image excluded major causes of cerebrovascular disease and white matter lesions, evidence of focal atrophy or lacunes. Subjects were randomized into two groups: (I) active rTMS (n = 9) and (II) sham rTMS (n = 10). A rapid magnetic stimulator and a figure-of-eight cooled coil was used. We delivered 10 sessions of high-frequency rTMS (10 Hz) for 5 seconds to the left DLPFC, with the parameters: 50 stimuli/train, 40 trains, 25 seconds of intertrain interval, 2,000 pulses/session and intensity of 110% of motor threshold. The placebo group used a sham coil. Follow-up ('off-line' paradigm) was obtained by detailed neuropsychological assessment encompassing all cognitive domains including the Rivermead Memory Behavioural Test (RMBT) and Stroop. Testing was applied at baseline, after rTMS and one month later. All participants gave written informed consent.

Results: These preliminary results showed improvement higher than 10% in the performance of RMBT and Stroop tests (ANOVA, p = 0.028 and p = 0.038, respectively) after rTMS sessions. The improvement was sustained after one month on RMBT scores, but not on STROOP test. (Updated results will be showed on the poster presentation).

Conclusion: Although sample size is still statistically limiting, the results suggest cognitive response in memory and attention to high-frequency rTMS, and a sustained effect in memory after one month.

P-11-017 Vascular risk factors and cognition in persons with moderate cognitive impairment

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Objective: To investigate the impact of vascular diseases (assessed by the number of vascular risk factors) on the cognition of persons with amnestic moderate impairment. Persons with moderate cognitive impairment are characterized by marked memory deficits and show brain atrophy in the mediotemporal areas of the brain.

Methods: This study included a total of 110 participants, including 52 persons with CI (cognitive impairment) and 58 healthy elderly controls. Vascular risk factors (hypertension, hypotension, diabetes mellitus) and vascular diseases (transient cerebral ischemia, carotid stenosis, coronary artery disease) are clinically reported or recorded in the individual charts of patients by their treating physician. All participants were tested on a range of cognitive tests.

Results: A larger vascular burden among patients with cognitive impairment is associated with lower performance in the executive domain. There was no other significant correlation in patients with CI. There was no significant correlation in the control group.

Conclusion: Our results show that vascular load is related to executive dysfunctions in patients with CI similar to what has been repeatedly reported in healthy older adults. In this study vascular load was not associated with processing speed, episodic memory or overall cognitive functioning.

P-11-018 Comparing frontotemporal dementia and schizophrenia using EEG microstate analysis

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Objective: Recent study reveals electroencephalogram (EEG) microstate map D is correlated with functional association network linked to frontoparietal network or executive-control network, and map C is correlated with salience network: hub of attention and controls the other networks. To determine the relationship of resting stage networks from EEG and mental disorders, microstate analysis was performed in mild frontotemporal dementia (FTD) patients, which has typical frontal lobe degeneration and hypoactivity in the salience network, and compared with schizophrenia (SZ) patients whose microstate abnormalities are well established.

Methods: We performed EEG Microstate analysis in mild FTD, and in SZ. Moreover, we collected a sample of age-matched normal controls (NC) for each of the two study groups. Firstly, we compared the duration of each Microstate map (A, B, C, and D) of the FTD and the SZ group separately to the NC using a t-test. Next, we were interested in the comparison of the standardized values of the durations of map C and D between FTD and SZ.

Results: In FTD patients, the duration of the map C was significantly decreased compared to NC. However, in SZ patients, the duration of the maps A, B and D were significantly decreasing in comparison to NC. No group difference in the Map C was detected between FTD and SZ, while the duration of the map D showed a tendency towards a shorter duration in SZ than in FTD patients.

Conclusion: Previous results support the view that the duration of various microstates (map A, B, D) in SZ were affected, on the contrary, mild FTD demonstrates showed more limited pathological changes (only Map C). We speculate that the decreasing duration in the map C is specific for the FTD, while the difference in the duration in schizophrenia may represent the wide range dysfunction in total brain.
problems in 15 patients with probable AD according to the criteria for ARD proposed by Oslin and colleagues. All participants were selected from patients attended at the Alcoholism Program in our hospital ("12 de Octubre" University Hospital, Madrid, Spain). The CERAD-K (Consortium to Establish a Registry for Alzheimer’s Disease – Spanish version) and several clinical assessment scales were completed before and after the 12-week memantine treatment period.

**Results:** Significant improvements in the mean scores from baseline to final assessment were observed in the Global Deterioration Scale (p < 0.05), Brief Psychiatric Rating Scale (p < 0.01) and Alcohol consumption (p < 0.05).

**Conclusion:** In this open-label study, patients with AD treated with 20 mg/d memantine for 12 weeks showed improvement on global cognition, behavioural symptoms and alcohol consumption. The result of this study suggests the possible usefulness of memantine for the treatment of AD.

**P-11-020 Response to galantamine administration in patients with Alzheimer’s disease: Exploring subdomains of cognitive function**

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**Objective:** To investigate galantamine’s effect on cognitive subdomains, we examined the clinical response to galantamine in patients with Alzheimer’s disease (AD) during a 12-month trial.

**Methods:** Sixty-six patients with mild to moderate AD were recruited for this 52-week study. The effect of galantamine on cognitive function was measured using the Korean version of Alzheimer’s Disease Assessment Scale–cognitive subscale (K-ADAS-cog). To assess frontal/executive dysfunction, K-ADAS-cog included trail making test-part A and B, digit span, and category fluency. Patients’ activities of daily living using the Seoul-Functional Assessment of Daily Living (S-ADL) and Seoul-Activities of Daily Living (S-ADL); and behavioral symptoms using the Neuropsychiatric Inventory (NPI) were measured at a given point of time. We defined patients responsive to galantamine as either those who have shown a cognitive improvement or no change during the first six-month clinical trial.

**Results:** Overall, patients administered with galantamine showed less cognitive decline through a 52-week period than those with a placebo, as predicted by the Stern equation. Based on the operational criteria, 66.7% of patients were ascribed to treatment responders. The responders showed effects in the cognitive subdomains of memory and language through a 26-week period. The responder group had an average 2-point drop in the memory subdomain and a 1.18-point drop in the language subdomain, while the non-responder group had an average 2-point drop in the memory subdomain and a 1.18-point drop in the language subdomain.

**Conclusion:** Approximately two-thirds of the patients responded to galantamine, and they have shown maintenance or improvement of cognitive functions through 6 months of the clinical trial. The responders gained a cognitive improvement in memory and language functions.

**P-11-021 Comparative efficacy of cholinesterase inhibitors in dementia associated with Parkinson’s disease**

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**Objective:** All the cholinesterase inhibitors were investigated in PDD, but there is a lack of head-to-head drug comparisons in this field. There are important reasons, both pharmaco-economic and clinical, to investigate if cholinesterase inhibitors are equally efficient in the treatment of PDD.

**Methods:** In order to assess the comparative efficacy of these drugs we selected a group of 45 patients with PDD, who presented a documented history of PD for at least 3 years, and we randomized them on single-blinded flexible doses of galantamine (mean daily dose 16 mg, dose range 8–24 mg/day, n = 16), donepezil (mean daily dose 7.5 mg, dose range 5–10 mg/day, n = 15) or rivastigmine (mean daily dose 9 mg, dose range 6–12 mg/day, n = 14). Patients were evaluated every 4 weeks for 6 months using Mini-Mental State Examination (MMSE), Alzheimer Disease Assessment Scale–Cognitive subscale (ADAS-Cog), Global Assessment of Functioning (GAF) and Unified Parkinson Disease Rating Scale (UPDRS).

**Results:** Patients diagnosed with dementia had a better evolution under treatment with rivastigmine and galantamine, without significantly intergroup differences (+0.9±0.7 points on MMSE, +0.3±0.3 points on ADAS-Cog and +1.1±2.4 on GAF, p < 0.05). Donepezil had a positive impact over the mental clinical status, but lesser than the other two cholinesterase inhibitors (+0.8±1.0 MMSE and +2.1±1.9 ADAS-Cog), although the intergroup difference didn’t reach a level of significance of 0.05. There was recorded no drop out due to adverse events during the study. The UPDRS scores didn’t vary significantly, reported to baseline, in none of the three groups.

**Conclusion:** Patients with PDD associated dementia responded better to galantamine and rivastigmine, in the absence of significant impact over the basic neurologic disease symptoms. Donepezil was also efficient in PDD, with no clinical significant negative interference with Parkinson’s disease evolution.

**P-11-022 An internet based instrument for cognitive function assessment**

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**Objective:** Many large scale registry trials in normal and pathological aging are being planned or conducted. In Alzheimer’s disease, interest is turning to prevention studies which may be conducted in healthy populations identified to be at risk of developing Alzheimer’s disease.

**Methods:** Four tests from a computer based cognitive methodology, the CDR System, were internet enabled. Participants logged on to a website, entered their age and gender, and performed the tests online. Their data were compared to normative data from the standard administration of these CDR tests.

**Results:** A total of 52,237 individuals aged 18 or over performed at least one of the tests. There were highly significant declines with increasing age on the measures of speed on all tasks, as well as for the ability to correctly identify the pictures. Further, variability in reaction times increased with age, as did cognitive reaction time (the difference between choice and simple reaction time). The declines from 18 to 25 years to successive five year age bandings (eg 26 to 30, 31 to 36 etc) were generally comparable between the internet based testing and the standard administration. Also performance on a number of measures was directly comparable between the two forms of administration.

**Conclusion:** This study has shown that large cohorts can be assessed using internet based cognitive tests, and that the general performance on these tests is directly comparable to that from the same tasks administered in the standard fashion. Notably, rates of decline with aging were directly comparable, as were the patterns of declines on various measures. These findings suggest that internet based cognitive testing is a viable technique in large patient trials, and should prove a useful and convenient means of longitudinally assessing cognition in patient registry studies or large long-term clinical trials.
Policy of full disclosure: The CDR System is owned by Bracket Global and is offered as a service in clinical trials. Keith Wesnes is employed by Bracket and owns stock in the company.

Objective: The deficits to cognitive function which occur in normal ageing can potentially be treated with pharmaceutical and other products. Further, as criteria have now been proposed for pre-clinical dementia, trials are now being planned with compounds designed to prevent or reduce cognitive decline in groups of 'healthy volunteers' identified to be at risk of developing Alzheimer's disease. However, in order to conduct such trials, cognitive tests need to be employed which can reliably assess such change.

Methods: The CDR System is a computerised set of 9 tests of attention, working and episodic memory which has been widely used in trials of potential cognitive enhancements in healthy volunteers, age-related cognitive decline, MCI and the dementias. 256 normotensive subjects, aged 70 to 90 years, mean MMSE 28.8 (range 23 to 30), were trained on the CDR System before a baseline was established, and then retested yearly for up to 5 years.

Results: Composite factor scores were derived from the various test measures. Performance was found to decline significantly over the study period on four of the five scores: power of attention (p < 0.0001), quality of episodic recognition memory (p < 0.0002), quality of working memory (p < 0.015) and speed of retrieval of information held in memory (p < 0.0001). Power of attention showed significant deficits from year one onwards, two other measures showed deficits by year one, and all showed significant deficits from year three onwards.

Conclusion: This study has demonstrated that the use of validated and sensitive tests of cognitive function can detect decline over a 5-year period in healthy elderly volunteers. Such testing is therefore fit for purpose for the evaluation of treatments aimed at preventing or even reversing age-related declines in cognitive function, as well as treatments which may delay the onset of Alzheimer's disease in high risk but otherwise healthy populations.

Policy of full disclosure: The CDR System is owned by Bracket Global which offer the use of this in clinical trials as a scientific service. Keith Wesnes is an employee of Bracket Global and owns stock in the company.

Objective: BDNF levels were analyzed by the enzyme-linked immunosorbent assay (ELISA) method.

Results: Decreased serum BDNF levels were observed for AD, LBD, VSD and FTD patients when compared with the control group (p = 0.005, p = 0.006, p = 0.017 and p = 0.003 respectively). No significant differences were observed for PD patients. Moreover, lower BDNF levels were evidenced in patients taking benzodiazepines (p = 0.024) while increased concentrations were detected in PD patients treated with L-DOPA (p = 0.008).

Methods: BDNF levels were evidenced in patients taking benzodiazepines (p = 0.024) while increased concentrations were detected in PD patients treated with L-DOPA (p = 0.008).

Policy of full disclosure: The CDR System is owned by Bracket Global and is offered as a service in clinical trials. Keith Wesnes is employed by Bracket and owns stock in the company.
Conclusion: In conclusion, our results support the hypothesis that BDNF alterations are involved in the neurodegenerative mechanisms and suggest the potential usefulness of the serum dosage as a marker for differential diagnosis in dementias and movement disorders.

P-12. Childhood & Adolescent Disorders

P-12-001 Neuroeducation: Neurocognitive enhancement of the developing brain
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Objective: I report clinical evidence in children from 4 to 9 years old that have been treated through neurocognitive enhancement techniques. The objective of these studies has been to improve specific cognitive functions targeted through diagnoses of cognitive and emotional disturbances and assessed through neurocognitive analyses and testing.

Methods: In response to specific disorders, for instance dyslexia, dysgraphia or dyscalculia, specific neurocognitive training tasks have been proposed and used on an individual basis to specifically remEDIATE the assessed condition-disorder. More specifically, the treatment of a purely dysgraphic child, a severely disabled learning condition resulting from difficulty in expressing thoughts in writing, including literacy and deduction impairments, requested selective use of auditory tone discrimination tests, auditory noise-background discrimination, vowel or consonant word completion, visual scanning ability and kinesthetic working memory tasks.

Results: Sessions of intensive and frequent neurocognitive training resulted in massive reduction of the disability manifestations in clinical assessment and school performance. In experimental post-treatment measures, highly improved general processing speed abilities and word visual and auditory recognition scores have been obtained.

Conclusion: Our clinical results of neurocognitive enhancement in children highly support straightforward improvement of specific cognitive disturbances through selective training of their cognitive sub-components. The effects of this type of improvement seem exhibiting a structural or long-lasting character, conserving however the specificity of the cognitive abilities that have been endorsed.

P-12-002 Teen depression prevention – an issue of great social impact
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Objective: The number of depressive episodes in teenagers has increased dramatically for the past two decades. Depression is a common condition among teenagers, with prevalence between 3% and 8%, becoming acknowledged as a public health problem. More than 25% of teenagers of about 18 have had at least one depressive episode.

Methods: This is a retrospective study, assessing suicide attempts of adolescents registered for a period of three years (2006-2008) and was carried out at the Iasi Children Hospital. The study group consisted of 19 teenagers aged between 14 and 18 years. Only one of these cases was diagnosed as depression and medication associated with psychotherapy was prescribed. The other 18 cases are under the observation of family and family physicians.

Results: The conclusions state that males resorted more easily to suicide methods, even compared to the girls-boys’ ratio of 1.5:1 for the entire population. The teenagers living in rural areas represented only 13% of the attempted suicide cases, because they are less frequently subjected to the risk factors of depression and suicidal idea-

Conclusion: The study is the first published research comparing the risks of suicide attempts before and after treatment. It shows that suicide attempts are twice as common in teenagers than in adults patients. Still, a time model is contained in both age groups: an attempted suicide most likely occurs before treatment, the chances decrease by 50% after starting the treatment, to almost disappear after treatment.

P-12-003 Asperger syndrome with recurrent psychosis in adulthood
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Objective: Asperger syndrome (AS) is a pervasive developmental disorder characterized by autistic social dysfunction and idiosyncratic interests in the presence of normal intelligence. We try to analyze the aspects of psychosis in two cases of Asperger syndrome and the response at treatment.

Methods: Two male patients (18-20 years) diagnosis with AS were hospitalized for psychotic symptoms. One of them was born prematurely and the other has family history of psychotic syndrome. Both patients finished with difficulty the high school and presented aggressivity and hostility; the psychotic syndrome included ideas of revenge about the colleagues. Behavioral and emotional disturbance was characteristics. After hospitalization one patient was included in cognitive-behavioral therapy (CBT). For measurement the psychotic symptoms we used Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions-Severity (CGI-S). Functioning was evidenced on Quality of Life Scale (QLS). Period of study 4 month with visits.

Results: The patients presented resistance at many antipsychotics and the remission of symptoms was difficult with long period of hospitalization. In first case the psychotic syndrome was resolved with Quetiapine 600 mg/day and in the second case we use Venlafaxine 225 mg/day and Risperidone 4 mg/day. Venlafaxine was necessary because one of the patients had a depressive symptoms with suicidal ideation.

Conclusion: AS has comorbid psychiatric conditions with resistance at therapy. CBT is important in a second period of recovery. The family involvement has a positive role in remission psychotic episode.

P-12-004 Clinical experience in Chile with clozapine in child and adolescents under 18 years
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Objective: Increase in severe psychopathology in adolescents who are resistant to common treatment creates a need to search new alternatives in pharmacological treatment. Background: to describe a sample 47 child and adolescent patients treated with clozapine between 1985 and 2010, including: age, gender, diagnoses, hospitalization, electroconvulsive therapy, dosing, adverse effects specially hematological ones.

Methods: 47 patients between the ages of 10 and 18 were treated with clozapine. Review of clinical charts, protocol investigation and Excel statistical analysis.

Results: the sample consisted in: male: 40%, female: 60%, the youngest was 10 and the oldest 17 years and 11 month old; the most frequent age was 15 years. The mean number of hospitalization was 1.5. Diagnosis axis-I, DSM-IV: affective disorders 64 %, schizophrenia-form disorder 23 %. Electroconvulsive therapy: 57 %. Treatment indications: irreducible psychosis 23 %. Suicidability: 35 %. Average dosing 200 mg. Adverse effects: sedation: 76 %, hypotension: 68 %, increase in weight: 66 %. Neutropenia: not severe (more than 2000/mm3): 17 %; severe I: 15 %, severe II: 2 %, severe III: 2 %.

Conclusion: Clozapine appears as an effective drug, with moderate but frequent adverse effects. Hematologic adverse effects where transient; only one in 47 patients presented a severe neutropenia and require cancellation of treatment, which was reinstalled after three month without major side effects. There is a need for control studies with larger population and a longer period of time.

P-12-005 The factors associated with metabolic syndrome in Japanese patients with mental retardation
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Objective: Mental retardation sometimes co-occur with psychiatric and/or behavioral disorders, and those patients are usually treated by psychotropic agents. Adverse effects of antipsychotics are believed to cause Metabolic Syndrome (MetS), significantly contributing to the
risk of death due to coronary artery diseases. As is the case in patients with psychiatric disorders, patients with mental retardation may have an increased risk of MetS. We conducted a study of the MetS in patients with mental retardation to clarify the factors associated with its prevalence and incidence.

Methods: A total of 199 patients with mental retardation were eligible to participate in this study. All patients were engaged in ongoing outpatient visits or were inpatients admitted to support facilities for people with intellectual disabilities in Japan. We reviewed the patients’ medications and prevalence of MetS at the two periods: from October 2006 to March 2007 (term A), and from July 2011 to August 2011 (term B). The MetS diagnostic criteria were based on the consensus guidelines created by Japanese Society of Internal Medicine.

Results: We divided the patients into two groups with a diagnosis of MetS at term A into two groups: those diagnosed with MetS at term B ("A-B+ group") and those without a diagnosis of MetS at term B ("A-B-group"). And we examined the clinical characteristics of both groups. At term A, the "A-B+ group" showed a significantly larger diameter of waist circumference and a higher triglyceride compared to the "A-B-group." These significant differences were also observed in logistic regression analyses. On the other hand, a significant difference between the two groups was not found in terms of the use of psychotropic medications.

Conclusion: In the items of MetS diagnostic criteria, diameters of waist circumference and triglyceride may be important predictive factors for the future onset of MetS in patients with mental retardation.

P-12-006 Agreement and disagreement between parent and teacher regarding child psychopathology: Comparing SDQ with CBCL

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Objective: The assessment of childhood psychopathology requires data from multiple informants. Because children have a limited ability to describe themselves and are often affected by situations. And confusion in the diagnosis in outpatient department are often caused by the difference between parent’s and teacher’s perspectives about a child’s behavior. In Korea, no systematic review of the inter-rater disagreement has yet taken place. Considering SDQ is a brief screening questionnaire, this study was designed to evaluate the usefulness of SDQ in clinical setting using information regarding the level of parent-teacher agreement and symptoms with discordance.

Methods: K-CBCL and SDQ-Kr were completed by parents and teachers in charge of 105 children (28 girls, 77 boys) aged 6–12 years and the clinical diagnosis were made by a child and adolescent psychiatrist. Spearman’s correlations were computed to assess associations between parent’s and teacher’s ratings in subscale level. And we used Mann-Whitney U test to test the influence of child’s age and sex on parent-teacher report. Finally, AUC values were calculated to measure the diagnostic capacity of parent-teacher ratings, and the difference between two AUCs was tested with the z test.

Results: Correlations between parent- and teacher-reported SDQ were high (range 0.362–0.545, p < 0.01) in every scale except emotional problems. Parents were more sensitive to emotional symptoms of girls (p < 0.01), while teachers seemed to be more sensitive to conduct problems and inattention-hyperactivity of boys (p < 0.05). Parents were more sensitive to conduct problems of seniors, whereas teachers seemed to be more sensitive to inattention-hyperactivity of young children (p < 0.05). Teacher’s CBCL was shown to be most discriminating of conduct disorder/oppositional disorder and teacher’s SDQ demonstrated the highest prediction of ADHD and Emotional disorder (p < 0.05).

Conclusion: In situations where parents are unavailable or when their reliability is low, teacher’s SDQ can be used instead of parent’s report in identifying child psychopathology early.

P-12-007 Prevalence of mental disorders in Thailand: Results from the epidemiology of mental disorders national survey

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Objective: To estimate the prevalence rates of mood, anxiety, alcohol and psychotic disorders in Thailand.

Methods: Nationally representative face-to-face household survey based on a multistage area probability sample of non-institutionalized people aged 15 to 59 years (n = 17,100) and selected each stage by means of random sampling. The data were conducted between June and August 2008 using Mini International Neuropsychiatric Interview (M.I.N.I.) by trained psychiatric professional. The data analyses were calculated by means of adjusted weight with prevalence rate for generalized to Thai population.

Results: The participants of this survey were 17,140 people in 4 regions and the Bangkok accounted for 93% of response rate. The results of weighted analysis for estimate the prevalence rate in Thais population have shown any mental disorders about 7,348,902 people (15.2%) which indicated approximately 14.3% of any current mental disorders and 8.9% of any lifetime mental disorders. An alcohol dependence current was the highest prevalence of mental disorders accounted for 6.6% (SE = 0.30) and the prevalence rate of an alcohol abuse current was about 4.2% (SE = 0.24). Furthermore, the prevalence rates of a major depressive episode current accounted for 2.2% (SE = 0.2) and recurrent represented about 0.7% (SE = 0.1), while a dysthymic disorder episode found 0.7% (SE = 0.1).

Conclusion: The alcohol use disorders have shown the commonest of mental disorders in Thais especially in male and the major depressive episode has frequently found in female of Thailand. These findings have significantly been evidences for the establishment of mental health care and prevention programs.
Comorbidity in children and adolescents with behavioral disorders

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Objective: Behavioral disorders are frequent in children and adolescents. This is a common symptom, often associated with other psychiatric disorders. This comorbidity is a predictor of early onset of other disruptive behavior, with a more rapid evolution and a bad prognosis and many social problems. The interest of this study is to assess psychiatric comorbidity between the behavioral disorders and the other psychiatric disorders.

Methods: We conducted a retrospective study over a period of two years with 120 children and teenagers showed in consultation for behavioral disorder. The diagnosis of behavioral disorders and associated diseases was made according to the diagnostic criteria for DSM IV-TR. Analysis of the results was made by epinf10.

Results: The average age of patients is 7.34 years. 90% of our patients are boys. The diagnosis of ADHD was found in 68% of cases, conduct disorder in 77% of cases, the oppositional defiant disorder in 25% of cases. The comorbidity of behavioral disorders is noted in 70%. 68, 7% of patients have at least 2 concomitants disorders. The comorbidity with learning disorders is noted in 28.3%, with anxiety disorders in 23% of cases, with mood disorders in 13.3% of cases, with substance abuse in 15% of cases and with other medical disorders in 0.8% of cases.

Conclusion: behavioral disorders are frequent in child psychiatry. The comorbidity is multiple, the management is multidisciplinary and depends on the type of behavioral disorder and associated disorders.

Suicidality in autism: A review

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Objective: This review focuses on suicide in patients with pervasive developmental disorders as well as risk factors and comorbidities seen in patients who have attempted suicide.

Methods: Research in PubMed for articles dating from 1999 to 2011 on this subject. 25 articles were found.

Results: Suicide in autism is largely understudied. A higher mortality in autistic patients is related to medical disorders like epilepsy and accidents. Suicide occurs more frequently in high functioning autism. Patients with PDD present with most of the risk factors leading to suicide. Furthermore, a history of mood disorders is frequently associated with suicide attempts as well as personal vulnerabilities and other psychiatric comorbidities.

Conclusion: Patients with PDD present risk factors inherent to their diagnosis, along with risk factors pertaining to the general population. The inactivity of persons with PDD to express emotions and thoughts makes the diagnosis of suicidal ideation difficult. Therefore, more studies are needed on the issue.

Functional restoration as an adjunct to pharmacotherapy in treatment of postural orthostatic tachycardia syndrome (POTS)

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Objective: Introduction: POTS is a clinical syndrome that has been estimated to affect up to 500,000 adults in the US and is being increasingly recognized and identified in adolescents. POTS is defined by the presence of excessive tachycardia, (>30 beats per minute) on the assumption of an upright posture. Associated symptoms can include lightheadedness, dizziness, palpitations, and sweating. The functional disability observed in these patients can be severe and can include incapacitation such as being bed or wheelchair bound. The treatment of POTS to date has focused upon pharmacological treatment and has included the use of beta blockers, midodrine, and fludrocortisone. No studies have examined the effectiveness of a functional restoration program in adolescents with POTS. The current study examines the efficacy of such a program as an adjunct to pharmacotherapy for adolescents with POTS.

Methods: Patients, who were severely impaired despite adequate pharmacotherapy, were referred to participate in a program designed to restore their function. In a group setting, patients and their parents learn how to adaptively self-manage their chronic physical symptoms through a structured, multidisciplinary intervention that utilized medical, psychological, PT, and OT services. Functional status was assessed with the Functional Disability Index.

Results: Thirty-three patients, all internationally registered (NHI), were participants in this study. Seventy-four percent of patients with a diagnosis of POTS were on one or more POTS medications upon admission including beta blockers, Midodrine and fludrocortisone. Pharmacotherapy initiated for the treatment of POTS was continued during the program. After participation in the program, adolescents with POTS demonstrated a significant increase in overall functional abilities (t=6.166, p<0.001).

Conclusion: A functional restoration program appears to be successful as an adjunct to the pharmacotherapy currently used for the treatment of POTS in adolescents.

Development of new diagnostic measure based on integrated correlation analysis of behavior and physiological parameters for socio-emotional difficulties in Asperger’s disorders (AD)

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Objective: Early diagnosis and intervention is crucial to improve the quality of child life suffering developmental disorder like AD. Brain imaging and genetics/epigenetic analyses which are two major diagnostic tools are not fully applicable for developing child. Here we developed another diagnostic measure based on non-contact or least contact way of behavioral and physiological measurement, which can be applicable at every-day clinic and non-clinical situations. This algorithm that freely bridges over objective and subjective information was named as BOUQUET (Senoo et al., Koshiba et al., 2011).

Methods: The study population comprised two groups, one diagnosed as asperger’s disorders (AD) (male 5, female 2, 6–13 years old) according to DSM-IV and ADI-R and another, their healthy siblings (Typically developed, TD) (male 1, female 4, 7–15 years old). They were interviewed alternatively by unfamiliar lady, unfamiliar gentle- man, their doctor in charge, and finally their mother for 2–5 min each. As the default condition, they played TV game. We recorded them by video-camera and infrared camera during the interview. We also recorded EEG (Fp1, Fp2, T3, T4, Cz, O1, 2) and ECG (Intercross 410). Serum cortisol and prolactin were measured a month before the interview and just after the interview. All the protocol was approved by Sawa hospital, Osaka and internationally registered (NHI). The correlation of behavioral and physiological parameters was analyzed by BOUQUET based on principal component analysis.

Results: The difference between two groups was visualized in the feature space reconstituted by two major principal components. The parameters which contributed to the discrimination was high variations of EEG and head surface temperature in AD, head movement velocity and gaze-frequency toward interviewer during self or family episode consolidation in AD.

Conclusion: These results suggest the usefulness of the integrated correlation analysis of behavior and physiological parameters by BOUQUET to extract the feature of socio-emotional adaptability in AD compared with TD child.

Violence in adolescents: Gender differences

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Objective: Violence phenomenon in urban centres is understood as a social process including wide spectrum of forms of aggression having an expansive and multiplying effect not only on the victims but also on the whole society; for this reason its increase is a source of concern. Objective: To determine some feature of violent adolescents and their association with some personal, familial and environmental characteristics in youngsters taken care by the National Council for the Youngsters and the Family.
Methods: Material and Methods: Violent adolescent was defined when having participating in fights (physical aggression) during the preceding year. Population: 522 adolescents, both sexes, ages 10 to 21 years, assisted in the National Council for the Youngsters and the Family. Survey Instrument: Two epidemiologic questionnaires (including the Present State Examination) to register current psychic state as well as personal, familial and environmental history.

Results: With violent behaviour 21.3%. Males showed significant association with diagnosis of disocial behaviour and consume of tobacco, marijuana, cocaine and sedatives. In women significant association was found with diagnoses of mild depression, delinquent behaviour, history of sexual harassment, and consume of alcohol.

Conclusion: The psychopharmacological treatment covers the etiologic diagnosis insofar as it has been studied that the selective serotonin reuptake inhibitors (SSRIs) not only have a therapeutic effect but also exert equilibrium on the serotoninergic function. At adequate doses, both neuroleptics as well as antirecurrence agents decrease the violent behavior.

P-13. Psychoneuroimmunology

P-13-001 Antidepressant effects of macrophage migration inhibitory factor gene deletion

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Objective: Depression is a global health problem with high mortality. Current treatment strategies only give sufficient symptom relief to approximately half of the patients. It has been established that depressed patients display immune alterations. Recently it was reported that the cytokine macrophage migration inhibitory factor (MIF) correlates positively with depression scores. It has also been shown that depressed individuals show exaggerated MIF levels following antigen challenges. In the current study we wished to examine the causality between MIF and depression. We therefore examined whether MIF knockout (KO) mice would show altered depressive-like behaviour compared to wildtype (WT) animals.

Methods: Male and female MIF KO mice and WT littermates were tested for locomotor behaviour in the open field, anhedonia in the sucrose preference test (SPT), and despair in the forced swim test (FST) and tail suspension test (TST). Brain mRNA expression of the cytokines IL-1B and IL-6 was subsequently examined using RT-qPCR.

Results: Results showed that MIF KO mice had a slight decrease in locomotor activity compared to WTs. In SPT a genotype/gender interaction was found, with male KO animals showing increased sucrose preference compared to control males. A similar interaction was found for FST, where male KO mice showed decreased immobility. In TST both male and female KO mice showed decreased immobility. No genotype/gender effects were found on IL-1B or IL-6 expression, but a significant positive correlation was found between IL-6 and stillness in the TST.

Conclusion: Our results suggest that MIF gene deletion has clear antidepressant effects, possibly most pronounced in male animals. Furthermore, a positive relationship between depressive-like behaviour in the TST and IL-6 was found, suggesting that IL-6 is involved in this behaviour. These data supports the growing line of evidence for a potential antidepressant effect of MIF and its receptors.

P-13-003 IL-1β induces TDO and provokes the release of kynurenic acid from human astrocytes in vitro

M.E. Kegel, C.I. Svensson, S. Erhardt, M. Mårtensson, L. Brundin

Objective: Kynurenic acid (KYN) and interleukin-1β (IL-1β) are elevated in the cerebrospinal fluid (CSF) of patients with schizophrenia. KYN is an antagonist of the nicotinic α7 acetylcholine receptor and the glycine site of the N-methyl D-aspartate (NMDA) receptor and has been shown to modulate dopaminergic neurotransmission, implicating a role for KYN in schizophrenia pathology. Indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) are the rate limiting enzymes of the kynurenine pathway. Intraperitoneal injection of IL-1β in mice induces TDO expression and CSF KYN levels observed in patients with schizophrenia.

Methods: Human astrocytes were cultured in AM medium supplemented with 10% fetal bovine serum and a mix of growth factors. Following 24 hours serum starvation cells were stimulated with IL-1β (10 ng/ml) or vehicle. Cell culture supernatants were collected and RNA and protein was extracted. RNA was reverse transcribed to cDNA and real time quantitative PCR was performed. Protein levels of IDO and TDO were analyzed using Western Blots. Levels of KYN in supernatants were analyzed using a high performance liquid chromatography system.

Results: IL-1β increased levels of KYN in the cell culture medium. Stimulation with IL-1β also induced the expression of TDO mRNA and protein. IDO was however only induced on the transcriptional level.

Conclusion: This study shows that KYN production increases following IL-1β-induced upregulation of TDO. Interestingly, increased TDO expression and activity have previously been reported in patients with schizophrenia. Present results thus highlight the notion that increased TDO expression and CSF KYN levels observed in patients with schizophrenia may result from activation of brain IL-1β signaling pathways.
Objective: The objective of the present study was to identify biological patterns (factors) among 20 cerebrospinal fluid (CSF) biomarkers in suicide attempters and subsequently analyse their association with suicidal behaviour.

Methods: We measured kynurenic acid, orexin, homovanillic acid (HVA), 5-hydroxyindoleacetic acid (5-HIAA), 3-methoxy-4-hydroxyphenylglycol, chemokines, matrix metalloproteases and cytokines in the CSF of 124 drug-free suicide attempters. Patients were evaluated for suicidality and psychiatric symptoms using well-defined psychiatric rating scales and followed-up regarding future suicide. We used principal component analysis to identify factors among the biological substances.

Results: Four factors were extracted from the 20 biomarkers, explaining 52.4% of the total variance. Factor 1 and 2 were characterized by high loadings of chemokines and cytokines respectively. They were both associated with severe depressive symptoms. Factor 2 was also associated with a high suicidal intent. Factor 4 was characterized by strong loadings of the monoamine metabolites 5-HIAA and HVA, as well as orexin and interleukin-6. High scores on this factor were found in patients who performed a violent suicide attempt and in patients who subsequently completed suicide.

Conclusion: Our results suggest that specific combinations of CSF biomarkers may discriminate between types of suicidal behaviour and indicate increased risk for future suicide.

Objective: To study dynamic of parameters of the immunity in group of schizophrenic patients with different efficacy of treatment.

Methods: Dynamic of psychopathological symptoms in 388 schizophrenics was registered with “Clinical Global Impression” (CGI) in two points – at baseline and after 6 weeks of appropriate for mental state treatment. According to results of clinical dynamic patients were divided into 3 groups: group 1 (n=54) – with significant improvement of mental state; group 2 (n=143) – with essential improvement; group 3 (n=191) – with insignificant improvement and without changes of mental state. Immunological examination included identification of phenotypes of surface receptors of immunocompetent cells, immunoglobulins IgM, IgG, IgA, level of circulating immune complexes (CIC); spontaneous and mitogen-induced production of IFN-γ, IL-4, TNFα by mononuclear leukocytes of patients, serum concentration of cortisol and aminotransferases.

Results: It has been shown that in the first two groups as compared with group 3 reliably higher values of T-helpers-inducers CD4+ (p=0.0001), cytotoxic T-lymphocytes CD8+ (p=0.0001), mitogen-induced production of IFN-γ (p=0.0001) and reliably low values of production of TNF-α (p=0.0001), CD95+ lymphocytes, levels of CIC, C3 and C4, cases were high in all groups (p=0.0001 regarding to control in all groups). Study of psychoneuroimmunodulation under influence of psychotropic therapy has shown that in the first two groups high clinical efficacy was accompanied by normalization of most parameters of homeostasis: T-lymphocytes CD4+, CD8+, CD89+ lymphocytes, levels of CIC, cortisol and aminotransferases, mitogeninduced production of IFN-γ and TNF-α. In group of absence of the effect to the therapy positive dynamic of immunobiological indices has not been revealed.

Conclusion: Thus, it has been shown that favorable clinical dynamic in process of 6 weeks therapy of schizophrenic patients was accompanied by positive dynamic of some indices of the immunity what probably reflects optimization of mechanisms of psychoneuroimmune interaction.

Objective: The objective of the present study was to identify the address of the relevance of S100B+ lymphocytes in mediating such responses. S100B expression was determined in human peripheral blood leukocytes isolated from healthy volunteers using flow cytometry. S100B+ lymphocytes were characterized for phenotype, cytokine production and S100B secretion. In addition, we investigated whether S100B activates monocytes and neutrophils.

Methods: We used principal component analysis to identify factors among the biological substances.

Results: S100B+ cells comprised 2-4% of all lymphocytes and the majority displayed a CD3+ CD8+ phenotype; fewer cells were CD3+ CD56+ NK lymphocytes. Comparison of S100B+ and S100B+ cell cytokine profiles revealed no differences in production of interferon gamma (IFN-gamma) and interleukin-2 (IL-2). Stimulation of S100B+ CD3+ CD8+ lymphocytes with anti-CD3 and phytohaemagglutinin resulted in release of S100B. High concentrations of recombinant human S100B triggered upregulation of CD11b and membrane shedding of CD62L in granulocytes and monocytes.

Conclusion: These findings set the stage for a new field of research addressing a S100B-mediated crosstalk between the innate and adaptive immune systems if close proximity of effector and responder cells accomplishes sufficient local S100B levels. In various physiological and pathological conditions S100B might function as an interface to immunological processes, distinct from known cytokine- and chemokine-mediated pathways.
**P-13-008** Mind-Body Interface: Polysaturated fatty acids and somatic symptoms in major depressive disorder

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**Objective:** Lower n-3 polysaturated fatty acids (n-3 or omega-3 PUFAs) levels and genetic variations on their metabolic enzymes of PUFA metabolic enzymes, phospholipase A2 (PLA2) and cyclo-oxygenase-2 (COX2), have been found to be associated with the risk of depression (1-4). In this study, we aimed to examine specific roles of n-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and the polymorphisms on PLA2 and COX2 in different clusters of depressive symptoms.

**Methods:** Patients with major depressive disorders (n = 122) and their healthy controlled subjects (n = 122) were assessed to examine the effects of PUFA levels and single nucleotide polymorphisms (SNPs) of PLA2 Band and COX2 n4648308 genes on the development of major depression and on specific clusters of depressive symptoms.

**Results:** Patients with major depressive disorders had a significant lower level of EPA (p = 0.03) and a trend of lower level of DHA (p = 0.08). The COX2 n4648308 AG genotype was associated with a higher risk of major depression (p = 0.006; odds ratio = 2.36, 95% CI = 1.27-4.40), while the PLAA Band GG genotype had a borderline effect (p = 0.06; odds ratio = 1.81, 95% CI = 0.87-3.79). The “at risk” COX2 polymorphism was associated with more somatic symptoms (p = 0.003) and lower DHA (p = 0.002), and the “at risk” PLA2 polymorphism was associated with more somatic symptoms (p = 0.025). In addition, lower EPA and DHA levels were both significantly correlated with more somatic symptoms in patients with depression.

**Conclusion:** Genetic variations in the COX2 and PLA2 genes have effects on depression and somatic features, possibly by affecting the levels of EPA and DHA. N-3 PUFAs may be a potential biomarker to understand clinical subtypes of depression (1).

**References**


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**P-14. Depression**

**P-14-001** Relation between unintended pregnancy among teenagers and post-partum blues

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**Objective:** Unintended pregnancy continue to many countries in the world especially among teenagers. The aim of this study was to assess the prevalence of post-partum blues in teenage mothers with unintended pregnancy, compared with teenage mothers with planned pregnancy.

**Methods:** 100 normal primiparous women with age less than 19 were studied and divided two groups who had unintended pregnancy and planned pregnancy. Maternity blues assessed in two groups.

**Results:** There was postpartum blues in women with unwanted pregnancies more than women with planned pregnancies in 3 and 10 days after delivery and this differences are statistically significant.

**Conclusion:** Unintended pregnancy may be a potential causal factor for maternity postpartum blues in teenagers.

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**P-14-002** Persistent effect of lead chronic toxicity on depression and anxiety in male Wistar rat

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**Objective:** The objective of this study was to investigate the persistent effect of lead on depression and anxiety of adult male Wistar rats.

**Methods:** Male adult Wistar rats are submitted to chronic intoxication by lead nitrate (50 mg/L) diluted in tap water during six months. After that, the intoxication was stopped for 4 months, and the neurobehavioral tests were assessed. Depression was evaluated using the Forced Swim Test (FST) by calculating the immobility time (IT). Anxiety was measured by calculating the number of Entries in Open Arm (EOA) and the time spent in the Open Arm (TOA), in the Elevated Plus Maze Test (EPM).

**Results:** The results have shown that the IT was significantly low in intoxicated rats even the administration of toxic was stopped (p < 0.05), compared to control ones. However, no significant difference was registered in the intoxicated rats compared to the control in the EOA and TOA.

**Conclusion:** Chronic lead toxicity had an antidepressant-like effect but had no effect on anxiety in rats even after stopping the intoxication.

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**P-14-003** The galanin system in the human brain with focus on locus coeruleus and the dorsal raphe nucleus

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**Objective:** Major depressive disorder is a serious disease that affects about 10% of all men and 20% of women in their lifetime. The noradrenaline (NA) neurons in the locus coeruleus (LC) and the 5-hydroxytryptamine (5-HT) neurons in the dorsal raphe nucleus (DRN) are a central focus in research on depression. The neuropeptide galanin, for which three receptors (GaIR1-3) have been cloned is of interest in relation to major depression (Branchek et al., 2000). Galanin coexists with 5-HT in the DRN as well as with NA in LC and has inhibitory actions on both NA and 5-HT neurons (Xu et al., 2005).

**Methods:** In this study, we have used in situ hybridization to visualize galanin and its receptors in LC and DRN of postmortem human brains, and in addition, tryptophan hydroxylase (TH), nitric oxide synthase (NOS) and vesicular glutamate transporters.

**Results:** Our results, when compared to rodent brains, show that galanin is found in LC of all three species, but only in rat DRN. GaIR1 was detected in rat LC, but in sharp contrast, GaIR3 seems to be the major galanin receptor in human LC and DRN. Thus in human, GaIR3 is expressed in two nuclei of key importance for depression, that is LC and DRN. In addition, VGLUT1 and −2 were strongly expressed in the pontine nuclei, but could not be detected either in LC neurons or 5-HT neurons. Neither was NOS found in these regions. Thus, considerable species differences occur with regard to brain messenger molecules, especially neuropeptides.

**Conclusion:** The present results, taken together with electrophysiological experiments in rats, suggest that a small, blood-brain barrier-penetrating GaIR3 antagonist could have anxiolytic and/or antidepressive activity. Such an antagonist has been developed and shown to have anxiolytic/antidepressive-like effects in animal models of depression (Swanson et al., 2005).

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**P-14-004** Levomilnacipran in the treatment of major depressive disorder: Functional health and well-being efficacy results from a phase III clinical trial

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**Objective:** Levomilnacipran is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with greater potency for norepinephrine than serotonin reuptake inhibition. Data from a positive Phase III trial (NCT00996970) were used to evaluate the functional health and well being of patients with major
P-14-005 The efficacy and safety of levomilnacipran in the treatment of major depressive disorder: Results from a phase III clinical trial

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Objective: Levomilnacipran (18, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with greater potency for norepinephrine than serotonin reuptake inhibition. Efficacy and safety were evaluated in a fixed-dose Phase III trial (NCT09069709).

Methods: A double-blind, multicenter, parallel-group, placebo-controlled, fixed-dose study with 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind taper. Patients (18-65 years) who met DSM-IV-TR criteria for MDD were randomized to placebo or once-daily levomilnacipran sustained release 40 mg, 80 mg, or 120 mg (titrated-up from an initial dose of 20 mg). Functional health and well being were measured using change from baseline to Week 8 on the SF-36 acute health survey. Individual health dimensions, and physical (PCS) and mental (MCS) component summary scores were compared for levomilnacipran and placebo (ITT population) using an ANCOVA model.

Results: Patients in both groups had deficits in mental-health at baseline (MCS scores: placebo, 17.2 ± 9.2; levomilnacipran, 18.2 ± 8.5); in contrast, baseline PCS scores (PBO: 52.6 ± 11.1; LVM: 51.1 ± 11.1) were slightly higher than the population norm. Following 8 weeks of treatment, levomilnacipran patients versus placebo demonstrated significantly greater MCS improvement (LVM: 4.4 ± 1.36; P = .0015) and on several individual dimensions (General Health [2.3 ± 0.69; P = .0007], Vitality [2.4 ± 1.05; P = .0228], Social Functioning [3.1 ± 1.17; P = .0086], Role Emotional [3.1 ± 1.20; P = .0097], and Mental Health [4.3 ± 1.16; P = .0003]). Nonsignificant PCS (−0.2 ± 0.74; P = .8386) and other dimension score changes were noted.

Conclusion: Levomilnacipran patients experienced statistically significant and clinically meaningful improvements in functional health and well being as measured by SF-36 MCS and associated individual dimensions. Changes in PCS and associated individual dimensions were nonsignificant potentially due to limited physical impairment at baseline.

Policy of full disclosure: Supported by funding from Forest Laboratories, Inc.

References

P-14-007 Desvenlafaxine naturalistic trial in outpatients

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Objective: This trial evaluated the efficacy and tolerability of desvenlafaxine in the treatment of major depressive disorder.

Methods: We worked during 6 months, in an open, naturalistic trial with adult outpatients (24-70 years) with a primary diagnosis of major depressive disorder (DSM IV criteria) rating outcome with Clinical Global Impression, Hamilton Scale for Depression, and Sheehan Disability Scale. Outpatients were followed from 30, 90 and 180 days.

Results: All patients included could complete the trial, with side effects that did not require removal. The results were statistically significant for all variables studied, with a special point that at first month they were observed.

Conclusion: Desvenlafaxine seems to be a useful therapeutic tool and well tolerated in outpatients with major depression, considering of course the limited study population and its characteristics.
Suicidal thoughts and reasons for living in hospitalized patients with severe depression: Post hoc analyses of a double-blind randomized trial of duloxetine

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Objective: To evaluate suicidal thoughts in relationship to depressive symptom severity and to Reasons For Living (RFL) in patients hospitalized for severe major depressive disorder (MDD).

Methods: Post-hoc analyses of a duloxetine trial in adult inpatients with MDD who met criteria of DSM-IV, showing a Montgomery-Asberg Depression Rating Scale [MADRS] score ≥30 and a Clinical Global Impression of Severity [CGI-S] ≥4. Suicidal thoughts were assessed with MADRS item-10 (suicidal thoughts), depression severity with the MADRS 6-item subscale and protective factors with the patient-rated RFL questionnaire assessing ‘survival and coping beliefs’, ‘responsibility to family’, ‘child-related concerns’, ‘fear of suicide’, ‘fear of social disapproval’ and ‘moral objectives’. Descriptive statistics and correlation analyses were performed.

Results: At baseline, patients (N = 336) had varying severity of suicidal thoughts on MADRS item-10: 18% had a score of ≥4 (4: “Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention”). The proportion of patients with a score ≥4 decreased to 7% at Week-1 and 1% at Week-8 of treatment. RFL scores at baseline were lower in patients with higher baseline suicidal thoughts; all RFL domain scores improved significantly during treatment (all P < 0.01). Correlations between RFL domains and single depressive symptoms were low and only negatively significant for suicidal thoughts (all P < 0.05) and pessimistic thoughts (5 of 7 P < 0.05). Suicidal thoughts were significantly, although poorly, positively correlated with depression severity (per MADRS 6-item core symptoms). RFL scores were not significantly correlated with the MADRS 6-item core symptoms.

Conclusion: 18% of inpatients with severe depression had explicit baseline suicidal thoughts scores, which decreased rapidly with treatment. Protective RFL scores increased with decreasing depression severity, suggesting that their protective power depends on the affective status. Depression severity, suicidal thoughts and RFL are mainly independent dimensions since most correlations were low.

Cerebrospinal fluid biomarkers for major depression confirm relevance of associated pathophysiology

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Objective: Individual characteristics of pathophysiology and course of depressive episodes are at present not considered in diagnostics. There are no biological markers available that can assist in categorizing subtypes of depression and detecting molecular variances related to disease causing mechanisms between depressed patients. Identification of such differences is important in order to create patient subgroups which will benefit from medications that specifically target the pathophysiology underlying their clinical condition.

Methods: In order to find characteristic biological markers for major depression we analyzed the cerebrospinal fluid proteome of twelve depressed versus twelve control persons using twodimensional polyacrylamide gel electrophoresis and time-of-flight mass spectrometry peptide profiling. Proteins of interest were identified by matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDI TOF/TOF). Validation of a subset of protein markers was performed by immuno-blotting.

Results: The cerebrospinal fluid proteome contained 31 cerebrospinal fluid proteins and 144 peptide features that differed significantly between depressed patients and controls. In addition, we detected differences in the phosphorylation pattern of several CSF proteins. A subset of the differentially expressed proteins implicated in brain metabolism or central nervous system disease was validated by immunoblotting. The identified proteins are involved in neuroprotection and neuronal development, sleep regulation and amyloid plaque deposition in the aging brain.

Conclusion: This is one of the first hypothesis-free studies that identifies characteristic protein expression differences in CSF of depressed patients. Proteomic approaches represent a powerful tool for the identification of disease markers for subgroups of patients with major depression.

Electrophysiological effects of long-term administration of paroxetine and bupropion on serotonin transmission in olfactory bulbectomized rats

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Objective: Olfactory bulbectomized (OB) rats generally manifest many of the neurochemical, physiological, and behavioral features of a depressive disorder in humans. Another interesting feature of this model is that it responds to chronic but not acute antidepressant treatments, including SSRIs. The purpose of the present study was first to characterize the firing activity of dorsal raphe serotonin (5-HT) neurons in OB rats and then examine the effects of two anti-depressants namely bupropion and paroxetine.

Methods: Olfactory bulbectomy was performed by aspirating olfactory bulbs in anesthetized rats. Vehicle and drugs were delivered for 2 and 14 days via subcutaneously implanted minipumps. In vivo electrophysiological recordings were carried out in male anesthetized Sprague-Dawley rats.

Results: Following ablation of olfactory bulbs, the firing rate of 5-HT neurons was decreased by 33%. In OB rats, bupropion (30 mg/kg/day) reversed firing rate of 5-HT neurons to control level following 2- and 14-day administration and also induced a disinhibition of CA3 pyramidal neurons following i.v. injection of WAY100605; paroxetine administration (10 mg/kg/day) did not result in normalizing the decrease observed in OB rats. In the hippocampus, although to a lesser extent than bupropion, paroxetine administration also resulted in disinhibition of pyramidal neurons.

Conclusion: The decrease in firing of 5-HT neurons in OB rats is consistent with the hypothesis of a decreased 5-HT neurotransmission in depression. This supports the use of this model to test the action of antidepressants on firing activity of monoaminergic systems. The present results also indicate that unlike paroxetine, bupropion administration promptly normalized 5-HT neuronal activity and increased tonic activation of the 5-HT1A receptors in hippocampus.

Policy of full disclosure: M. El Mansari, S. Manta and S. Shiom have no disclosures. P. Blier has received grants and/or honoraria from Astra Zeneca, Biovail, Bristol Myers Squibb, Eli Lilly, Valeant, Janssen, Labopharm, Lundbeck/Takeda, Schering-Plough/Merck, Sepracor, Servier, and Wyeth.

Electrophysiological effects of the multimodal antidepressant LU AA21004 on serotonin transmission in the rat hippocampus

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Objective: Newer classes of antidepressants with more than one mode of action have the potential to increase remission rates. LuAA21004 is a novel multimodal antidepressant that is a 5-HT3 and 5-HT7 receptor antagonist, a 5-HT1B receptor partial agonist, a 5-HT1A receptor agonist, and an inhibitor of the 5-HT transporter in vitro.

Methods: In vivo electrophysiological recordings and stimulations of the ascending 5-HT bundle originating from the raphe nuclei were used to determine the effects of LuAA21004 on CA3 hippocampal pyramidal neurons in anesthetized male rats. LuAA21004 was injected intraventricularly (2-6 mg/kg) or administered subcutaneously for 14 days, at a dose of 5 mg/kg/day via an osmotic minipump.

Results: The recovery time from complete inhibition of pyramidal neurons after micro-iontophoretically applied 5-HT, an index of 5-HT transporter activity, was increased after 14-day administration of LuAA21004. In contrast, the inhibition of CA3 pyramidal neurons...
after micro-iontophoretically applied 5-HT was unchanged. Injection of the 5-HT1A receptor antagonist WAY106663 increased CA3 pyramidal neuron firing, indicating an enhanced tonic activation of post-synaptic 5-HT1A receptors. Stimulation of the 5-HT bundle produced a decreased inhibition of the firing of CA3 pyramidal neurons at 5 Hz compared to 1 Hz.

**Conclusion:** LuAA21004 blocks 5-HT transporters, but does not dampen the sensitivity of postsynaptic 5-HT1A receptors. In addition, LuAA21004 decreased the function of the terminal 5-HT1B auto-receptor, thus showing that its partial agonism led to increased 5-HT release. Long-term LuAA21004 administration increased the tonic activation of the postsynaptic 5-HT1A receptor in the hippocampus, an effect common to all antidepressants.

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**P-14-012** Chronic low-grade inflammation induces depression-like behavior in rats

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**Objective:** Depression has been associated with a low-grade inflammation, as revealed by clinical studies showing elevated levels of pro-inflammatory cytokines in depressed patients. These patients are often treatment-resistant, and some studies have shown that elevated markers of inflammation predict a poor response to treatment. Furthermore, increasing evidences show that metabolic abnormalities such as obesity and diabetes mellitus type 2 are associated with a low-grade inflammation. The aim of this study is to investigate the effects of a systemic low-grade inflammation induced by lipopolysaccharide (LPS) on Sprague-Dawley rats on depression-like and metabolic parameters.

**Methods:** Chronic infusion of LPS (at a high, medium and low dose) for 28 days was performed by using subcutaneously implanted osmotic minipumps, administering LPS through a catheter into the abdomen. Depression-like behavior was assessed in the forced swim test (FST). Peripheral and central levels of pro-inflammatory cytokines (TNF-alpha, IL-1, IL-6) together with the expression of enzymes involved in the tryptophan-tyrrosine pathway, will be analyzed in specific brain regions using real-time qPCR. Body weight and food intake was measured once a week, while fasting glucose and insulin values. However, a high dose of LPS caused an increase in liver weight. Analysis of cytokine and mRNA expression levels is currently being carried out and these results are pending.

**Conclusion:** Our results indicate that a low dose of LPS can produce depression-like behavior, without inducing metabolic disturbances or sickness behavior. Thus, this model might help elucidating some of the mechanisms underlying inflammation-associated depression, in order to assist in developing more effective treatment strategies for this group of patients.

**P-14-013** Lower frequency of early discontinuation of mirtazapine in elderly Japanese patients with depression

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**Objective:** Mirtazapine is a noradrenergic and specific serotonergic antidepressant (NaSSA), and has been approved in many counties for the treatment of major depression. In Japan, it has been available since 2009 and has been safely used for elderly patients. Treatment continuation is an important measure of effectiveness in patients with depression, reflecting the efficacy, safety, and tolerability. This retrospective study examined whether there was association between age of patients and the rate of early discontinuation of mirtazapine.

**Methods:** A total of 89 patients with major depression, who were on mirtazapine monotherapy, were surveyed. The rate of the patients who discontinued mirtazapine within eight weeks from the initiation was compared between elderly patients (65 years or older, n = 33) and non-elderly patients (n = 56). In the patients who continued mirtazapine, the final dose, and its efficacy assessed by Clinical Global Impression – Improvement (CGI-I), were compared between the two groups.

**Results:** The discontinuation rate of elderly patients within eight weeks was significantly lower than that of non-elderly patients (18% vs. 63%, respectively, p < 0.001). In the patients continuing mirtazapine, there was no significant difference in the final dose between two groups (26 ± 11 mg/day vs. 26 ± 11 mg/day). In addition, there was no significant difference in the efficacy between two groups; the ratio of very much improved and much improved was 62% and 56%, respectively. The most common reasons of discontinuation in non-elderly patients were sedation (n = 16) and increased appetite (n = 4), while there were only two patients who developed sedation in elderly patients.

**Conclusion:** This study shows that the rate of early discontinuation of mirtazapine is lower in elderly patients than non-elderly patients, possibly due to lower incidence of side effects. Therefore, mirtazapine might be effective, safe and tolerable agent especially for elderly patients with depression.

**P-14-014** Levomilnacipran in the treatment of major depressive disorder: An analysis of efficacy and safety data from two phase III studies

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**Objective:** Levomilnacipran (1S, 2R-milnacipran) is a potent and selective serotonin and norepinephrine reuptake inhibitor (SNRI) with greater potency for norepinephrine than serotonin reuptake inhibition. Data from Phase III trials (Study 1: NCT00969709; Study 2: NCT00969150) were used to evaluate the efficacy and safety of levomilnacipran sustained release in major depressive disorder (MDD).

**Methods:** Studies were double-blind, multicenter, randomized, placebo-controlled with a 1-week single-blind, placebo lead-in, 8-week double-blind treatment, and 2-week double-blind down-taper. Patients with Montgomery-Asberg Depression Rating Scale-Clinician Rated (MADRS-CR) scores ≥30 with current major depressive episode ≥8 weeks (Study 1) or ≥4 weeks (Study 2) were randomized to once-daily levomilnacipran 40, 80, or 120 mg (Study 1; fixed-dose) or levomilnacipran 40–120 mg/day (Study 2; flex-dose) or placebo. Primary and secondary efficacy: MADRS-CR and SDS total score change from baseline to end of Week 8, respectively; safety: adverse events (AEs), laboratory measures/vital signs. Data were pooled and analyzed using a mixed-effects model for repeated measures (MMRM); statistical difference in primary efficacy was seen in Study 1 only.

**Results:** Pooled baseline characteristics were similar for placebo (n = 358) and levomilnacipran (n = 712); 80.2% of placebo and 70.6% of levomilnacipran patients completed the studies. Significant improvement was seen for levomilnacipran versus placebo on MADRS-CR (LSMD = −2.73; P = .0009) and SDS (LSMD = −1.44; P = .0190).

Discontinuation due to AEs occurred in 20.3% of placebo and 9.1% of levomilnacipran patients; 63.1% of placebo and 78.8% of levomilnacipran patients reported treatment-emergent AEs (TEAEs); the majority were transient and mild/moderate in intensity. The most common (≥10%) TEAEs (placebo vs. levomilnacipran) were headache (12% vs. 17%), nausea (5% vs. 16%), and dry mouth (8% vs. 10%).

**Conclusion:** Pooled analyses showed that levomilnacipran-treated patients achieved statistically significant and clinically meaningful improvement in depressive symptoms and functional impairment. Higher placebo response in Study 2 may explain different individual study outcomes. Levomilnacipran was generally well tolerated.

**Policy of full disclosure:** Supported by funding from Forest Laboratories, Inc.
P-14-015 Tolerability of polypharmacotherapy in psychiatry
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Objective: In this study we analyzed data from psychiatric inpatients treated under naturalistic conditions and supervised by therapeutic drug monitoring (TDM) to compare the occurrence of side effects under monotherapy and polypharmacy. Combination therapies were screened for potential risks to reveal if combinations considered as critical are associated with an increased risk of side effects.

Methods: Data were collected from the request and reporting forms of psychiatric inpatients for whom TDM of antipsychotic or antidepressant drugs was requested during a period of 6 months. All drug combinations were checked by a drug-drug interaction program (www.psiac.de) for potential risks.

Results: The study included data from 488 inpatients, most of them with the diagnosis of either schizophrenia (46%) or major depression (40%). The preferred antipsychotic drugs were olanzapine (n=139), quetiapine (n=101), clozapine (n=90) and risperidone (n=85). Antidepressant drugs included venlafaxine (n=145), mirtazapine (n=96), sertraline (n=72), escitalopram (n=37) and citalopram (n=32). Only 21% of the patients receiving antipsychotic drugs were under monotherapy and under antidepressant medication, we identified 23% of monotherapies. Side effects were reported for 16% of the patients under monotherapy and for 59% under polypharmacy with antipsychotic drugs. Most frequent were sleepiness and extrapyramidal symptoms. Treatment with antidepressant drugs was associated in 12% with side effects under monotherapy and in 29% under polypharmacy. Under combinations with antipsychotic drugs for which a potential risk was identified by the computer program side effects were reported for 51% of the cases. For antidepressant drugs, side effects were reported in only 20% of the combinations considered as critical.

Conclusion: Combination therapies with antipsychotic or antidepressant drugs is associated with reduced drug-tolerance. Polypharmacy must therefore be considered as a risk for more side effects. Computerized analysis of drug combinations could be useful to detect potential risks due to drug-drug interactions and thus improve tolerability.

P-14-016 Adjunctive acetaminophen therapy for major depression: A preliminary report
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Objective: To investigate the efficacy of adjunctive acetaminophen in the treatment of major depressive disorder.

Methods: In this preliminary open-label study, patients with major depressive disorder (DSM-IV), who were aged between 20 and 80 and failed to show a 20% reduction in the total score of Montgomery-Asberg Depression Rating Scale (MADRS) from screening to baseline were included. Exclusion criteria included presence of any psychotic feature and/or suicidal thought and any past history of, or current gastrointestinal ulceration, liver dysfunction, or allergic reactions to acetaminophen. Acetaminophen was given at a fixed dose of 1500 mg/day for 4 weeks while other psychotropic medications, including antidepressants, were kept constant during the study. Assessment scales included the MADRS; the Quick Inventory of Depressive Symptomatology self-report (QIDS-SR), and Visual Analogue Scale (VAS) for pain at baseline and 1, 2, and 4 weeks. Adverse effects were monitored at every visit. Data were reported, using a last-observation-carried-forward method.

Results: Seven patients entered this study. These patients had been treated with their antidepressants for 3–15 years at the time of baseline assessments. One patient showed an improvement during the screening phase and was therefore excluded. Thus, six patients proceeded to the augmentation stage and provided the data for analyses. One patient prematurely withdrew from this study due to abdominal discomfort and another due to deviation from the protocol. As a result of 4-week acetaminophen augmentation, mean total MADRS score was reduced from 21.7 to 12.2. Likewise, the mean total QIDS-SR score improved from 15.2 to 9.8, and the VAS score from 4.7 to 3.2.

Conclusion: Although the data are still preliminary, the results point to some possibility of acetaminophen as an augmentation strategy for patients with treatment-refractory major depressive disorder.

P-14-017 Personality dimensions in major depressive disorder predict cortisol reactivity to the combined dexamethasone/CRH test
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Objective: It is generally acknowledged that depression is associated with altered hypothalamic-pituitary-adrenal (HPA) axis function, most notably hypercortisolism. However, findings on HPA axis function in depression are not entirely unequivocal, such that hypercortisolism has not been observed in some studies. Another line of research has demonstrated that various psychiatric conditions, including atypical depression, are associated with hypocortisolism. Moreover, personality is shown to be associated with HPA axis alteration. Taken together, different personality patterns in depression may play a role in the distinct HPA axis alteration.

Methods: Eighty outpatients with DSM-IV major depressive disorder were recruited. Personality was assessed by the Temperament and Character Inventory (TCI). Depressive symptoms were assessed by the Hamilton Rating Scale for Depression, HPA axis reactivity was measured by the combined dexamethasone/corticotropin-releasing hormone (CRH) test. According to previous studies, two subgroups were considered based on their cortisol responses to the dexamethasone/CRH test: complete-suppressors whose cortisol response was exaggerated and enhanced-suppressors whose cortisol response was blunted.

Results: Of the seven TCI dimensions, cooperativeness was significantly positively correlated with cortisol levels after combined dexamethasone/CRH challenge (p = 0.001). Complete-suppressors scored significantly higher in cooperativeness than enhanced-suppressors (p = 0.003). A logistic regression analysis, controlling for age, gender and symptom severity, was performed to predict the cortisol suppression pattern (i.e., incomplete- vs. enhanced-suppression) from TCI scores, which revealed that reward dependence (p = 0.04) and cooperativeness (p = 0.003) were significant predictors for enhanced- and incomplete-suppression, respectively.

Conclusion: These findings can be viewed in light of the known association of atypical depression with personality pathology and hypercortisolism. Given the evidence that atypical depression and melancholic depression could benefit from different treatment approaches, our findings would be of clinical importance as they suggest the possibility of distinguishing these different types of depression based on the distinct directions of HPA axis alteration.

P-14-018 Dopamine transporter gene (DAT1) possible affects personality traits in early-onset patients with major depressive disorder
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Objective: Comorbid personality pathologies may affect the outcomes of patients with major depression (MD). The dopamine transporter gene DAT1 (SLC6A3) has been suggested to play a role in both depression and specific personality traits. The aim of this study selected five polymorphisms of DAT1 to explore whether this gene influences personality traits in patients with MD or its subgroups.

Methods: The DAT1 polymorphisms were analyzed in 463 unrelated Han Chinese MD patients. All patients were screened using the same assessment tool and the diagnosis of MD was made based on a consensus opinion. The personality traits novelty seeking (NS) and harm avoidance (HA) were examined using the Tridimensional Personality Questionnaire. The patients were also divided into four clinical subgroups based on differences in their sex (male or female) and age at disease onset (early or late).
Results: There was no association between DAT1 and either NS or HA in the total MD patient sample. However, in a subgroup analysis, male MD patients with the T/T genotype of rs2975226 had lower HA scores than patients with the other genotypes (Pcorrected = 0.015). Furthermore, early-onset MD patients with the G/G genotype of rs29750948 and the T/T genotype of rs2975226 had lower NS scores than patients with other genotypes (Pcorrected = 0.005 for rs29750948 and Pcorrected = 0.0005 for rs29750948).

Conclusion: Our study suggests that DAT1 promoter variants influence specific personality traits in male and early-onset subgroup of depressed patients among Han Chinese population. Further prospective cohort studies are required to verify our preliminary finding and to confirm the effects of personality susceptibility on long-term disease outcomes.

P-14-019 Depressed patients with a mild inflammatory phenotype display robust tryptophan depletion in the absence of kynurenine pathway activation

M. Hughes1, A. Carballedo2, D. McLaughlin3, A. Harkin3, F. Frolid2, T. Connor2

Objective: The kynurenine pathway (KP) and its rate-limiting tryptophan degrading enzyme indoleamine 2,3 dioxygenase (IDO), have been implicated in the pathogenesis of major depression. IDO expression is driven by the inflammatory cytokines IFN-γ and TNF-α, and it has been suggested that IDO induction and resultant KP activation may be the link between inflammation and a decrease in tryptophan availability, which could lead to a serotonergic deficit in depression.

Methods: Here we examined circulating concentrations of the acute phase protein CRP, the inflammatory cytokines IFN-γ, TNF-α and IL-6, alongside plasma tryptophan and kynurenine concentrations and whole blood IDO mRNA expression in a group of depressed patients (average HAM-D score 25) (n = 39) compared with healthy age and sex-matched control subjects (n = 39).

Results: Whilst no significant change was observed in plasma TNF-α, plasma concentrations of IFN-γ, IL-6 and CRP were increased in the depressed cohort relative to controls. Despite this inflammatory phenotype, IDO mRNA expression or plasma kynurenine concentrations were not significantly different between depressed and controls, indicating that the KP was not activated. Nonetheless, a robust depletion in tryptophan was evident in the depressed cohort relative to controls.

Conclusion: These data support the idea that a mild inflammatory signature is evident in depressed patients, and that this is accompanied by a depletion of tryptophan. However, we found no indication of KP activation in the depressed cohort suggesting that an alternative mechanism/pathway mediates the depletion of tryptophan observed in depressed patients.

P-14-020 Quality of living, depression and psychosomatic diseases in medical doctors

N. Bić1, V. Bić2

Objective: Material achieved from my four research works is used for composing of this paper. This paper is related to one target group – the medical doctors.

Methods: Thinking about doctor’s quality of living, from the aspect of free-time, without free-of-charge professional engagement, we have asked our colleagues specific questions (trought the anonymous questionnaire). The questionnaire analysis of 50 polled doctors aged 30–55 y gave the following results. Thirty polled doctors (60 %) used its own free-time for extra professional engagement. Seventeen polled doctors (34 %), partially managed to evade those activities, but only one third of them (6 %) did not practice extra professional activities.

Results: As a research instrument, the scale for self-estimation of depression (ZUNG) is used. Fifty two doctors of both sexes filled the questionnaire. The questionnaire analysis of 50 polled doctors aged 30–55 y gave the following results. Thirty polled doctors (60 %) used its own free-time for extra professional engagement. Seventeen polled doctors (34 %), partially managed to evade those activities, but only one third of them (6 %) did not practice extra professional activities.

Conclusion: Thinking about doctor’s quality of living, from the aspect of free-time, without free-of-charge professional engagement, we have asked our colleagues specific questions (trought the anonymous questionnaire). The questionnaire analysis of 50 polled doctors aged 30–55 y gave the following results. Thirty polled doctors (60 %) used its own free-time for extra professional engagement. Seventeen polled doctors (34 %), partially managed to evade those activities, but only one third of them (6 %) did not practice extra professional activities.

P-14-021 Recurrence of winter amenorrhea in affective illness

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Objective: Affective illness and endocrine dysfunction can worsen perimenopausal status. We described the phenomenon of winter amenorrhea in affective illness (Jacobsen and Comas-Diaz, 2004). Our longitudinal study now reveals that women suffering depressive illness may experience recurrent amenorrhea during successive winters, sometimes years before perimenopause.

Methods: Subjects were mood-stabilized female bipolar spectrum or unipolar outpatients without previous amenorrhea (skipping three consecutive periods) or recent steroid use. Naturalistic monitoring included bimonthly evaluation of menstrual cycling, sleep, appetite/weight, energy/activity, sexual function, cognition, and mood. Other data analysed included menarche, parity, laterality, diurnality, headache, neuroendocrinology, family genetic and treatment history.

Results: 26 women (17 bipolar, 9 unipolar) treated for 15.7±5.9 years experienced 4.6±1.9 months of fall/winter amenorrhea beginning age 48.8±3.3 years. 17 (65%) had past fall/winter depressions. 7 of 26 (19 %) had amenorrhea in 2+ successive winters – depression ratings remained unchanged during amenorrheic episodes. ~85% of winter amennorheics (N=22) suffered migraine (usually perimenstrual), which lessened in only 3 while amenorrheic. ~18% (69 %) reported feeling menstrual cycle manifestations while amenorrheic – two long-stabilized amenorrheic bipolar abruptly menstruated and switched into mixed-mania following 7+ days mid-winter exposure to greatly increased environmental sunlight+temperature – two unipolars experienced 7+ days of insomnia+racing thoughts coincident with abrupt resumption of menstruation in spring.

Conclusion: Winter amenorrhea can be a recurrent phenomenon in affective illness. During winter amenorrhea mood appears stable while physical feelings of menstrual cycling may recur, suggesting a complex relationship between seasonally decreased serotonergic function and perimenopausal estrogen decline. Sudden intense light+heat exposure during winter may dramatically alter endocrine and affective symptomatology in perimenopausal women.

P-14-022 Efficacy and clinical relevance of vilazodone in the treatment of major depressive disorder: A pooled analysis of phase III clinical trials

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Objective: Vilazodone, a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, is FDA approved for treatment of major depressive disorder (MDD) in adults. Data from Phase III trials, both of which were positive, were analyzed to evaluate efficacy across depression symptoms (MADRS total) and single items) and clinical relevance of results (number needed to treat [NNT] and harm [NNH].

Methods: Data from 2 double-blind, 8-week, randomized, placebo-controlled trials (NCT00285376, NCT00803592) were pooled. Patients...
Hormones, cytokines, and adipokines in the course of depression – potential biomarkers for treatment response?

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Objective: A plethora of alterations in different biological systems such as hormonal axes, immune system, and metabolic pathways have been described in major depression and gave rise to several theories regarding pathophysiological mechanisms of depressive disorders. This led us to investigate whether serum parameters indicating status and changes of these biological systems are altered among patients with major depression or could serve as potential biomarkers for treatment response in depressed patients.

Methods: We analyzed hormones, cytokines, and adipokines (cortisol, leptin, ghrelin, insulin, insulin like growth factor 1 (IGF-1), sexual hormone binding globulin (SHBG), testosterone, C-reactive protein (CRP), and interleukin 6 (IL6)) in healthy subjects and patients with major depression from the Munich Antidepressant Response Signature Project (MARS) at admission and after 6 weeks of antidepressant treatment.

Results: We observed significantly elevated IGF-1 in depressed patients compared to healthy controls. Additionally, IGF-1 was significantly decreased in patients responding to antidepressant treatment at baseline and after 6 weeks in comparison with non-responders. Furthermore, non-responders showed elevated inflammation parameters (IL6 at baseline and CRP after 6 weeks) and testosterone increased during antidepressant treatment in responders compared to non-responders.

Conclusion: We conclude that easily accessible serum parameters like IGF-1, CRP, IL6 or testosterone, could possibly serve as biomarkers in antidepressant treatment. In particular, differences in IGF-1 and IL6 levels between responders and non-responders were already present at baseline. Further validations in prospective studies as well as investigations particularly with regard to biological mechanisms in major depression are necessary to substantiate these findings.

The prevalence of major depressive disorders in Thailand: National survey

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Objective: This qualitative study aims to describe an explanatory model of illness in Thai women with Major Depressive episode.

Methods: The study was conducted in a semi-rural area with 25 Thai women who were diagnosed with major depressive disorder. These women were under a two-year project of the Thai Depression Surveillance System. Semi-structure interviews based on Kleinman’s explanatory framework were used. Data were collected by in-depth interviews and focus groups. Content analysis was used to disclose the relevant themes.

Results: Most participants called their illness as ‘stress’. Only seven participants perceived it as depressive disorder. All expressed that ‘thinking a lot’, especially around family related issues was the cause of their illness. The other common cause of their depression was the inability to let go (Thum-jai) of the unwanted situation. Almost all participants benefited from the use of antidepressants. However, they were not taken as prescribed. Some participants reported that listening to community broadcasting radio’s Dhrama was helpful. The other method was self-agency. All women felt stigmatized from getting treatment from a psychiatric hospital. They preferred to get treatment from a community hospital instead. Almost all revealed that they were more comfortable to receive treatment from a female therapist.

Conclusion: The findings suggest that effective psycho-education program on depressive disorder is needed. Therapists have to listen to and take patients’ perspectives into account. Mental illness treatment should be integrated in a primary care setting and Buddhist teaching should be employed.

Thai women with depressive disorder: Explanatory model

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Objective: This qualitative study aims to describe an explanatory model of illness in Thai women with Major Depressive episode.

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Results: Most participants called their illness as ‘stress’. Only seven participants perceived it as depressive disorder. All expressed that ‘thinking a lot’, especially around family related issues was the cause of their illness. The other common cause of their depression was the inability to let go (Thum-jai) of the unwanted situation. Almost all participants benefited from the use of antidepressants. However, they were not taken as prescribed. Some participants reported that listening to community broadcasting radio’s Dhrama was helpful. The other method was self-agency. All women felt stigmatized from getting treatment from a psychiatric hospital. They preferred to get treatment from a community hospital instead. Almost all revealed that they were more comfortable to receive treatment from a female therapist.

Conclusion: The findings suggest that effective psycho-education program on depressive disorder is needed. Therapists have to listen to and take patients’ perspectives into account. Mental illness treatment should be integrated in a primary care setting and Buddhist teaching should be employed.
P-14-027 Psychopharmacological studies on atorvastatin and its solvatomorphs in experimental paradigm of depression

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Objective: A complex relationship exists among stressful situations, body’s reaction to stress, and the onset of clinical depression. Chronic unpredictable stressors can produce a situation similar to clinical depression and such animal models can be used for the pre-clinical evaluation of antidepressants. There is a complex relationship between lipid-lowering drug therapy and psychological well-being and it remains an issue of debate for long. Atorvastatin’s poor bioavailability and brain penetration limits its neuroprotective efficacy. Polymorphism could enhance the stability, solubility and bioavailability of existing drugs. The present study was designed to investigate possible antidepressant potential of atorvastatin and its solvatomorph in unpredictable chronic stress-induced depressive like behavior.

Methods: Animals were subjected to different stress paradigms daily for a period of 21 days to induce depressive-like behavior. The sucrose preference, immobility period, locomotor activity, memory acquisition and retention were evaluated.

Results: Chronic treatment with atorvastatin and its solvatomorph significantly reversed the unpredictable chronic stress-induced behavioral (increased immobility period, reduced sucrose preference), biochemical (increased lipid peroxidation & nitrite levels; decreased glutathione levels, superoxide dismutase, catalase & MAO activities) and inflammation surge (serum TNF-α) in stressed mice.

Conclusion: The study revealed that atorvastatin and its solvatomorph exerted antidepressant-like effects in behavioral despair paradigm in chronically stressed mice, specifically by modulating central oxidative-nitrosative stress, MAO activity and inflammation independent of its lipid lowering effect. However, solvatomorph showed better antidepressant efficacy as compared to atorvastatin.

P-14-028 The concentration of brain glucagon-like peptides (GLP-1 and GLP-2) in an animal model of depression

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Objective: Recent findings have shown that insulin resistance and, in consequence, disturbed glucose metabolism in the brain might play a role in the pathogenesis of depressive disorder. Insulin action and metabolic processes are regulated by various hormones and proteins, interactions of which have been thoroughly examined in peripheral tissue, however, their role in brain tissues, especially in depression, is weakly recognized, yet. Among compounds crucially involved in insulin action, incretin hormones – glucagon-like peptides (GLP) play an important role. The aim of the present study was to find out whether there are any changes in the concentration of GLP-1 and GLP-2 in the frontal cortex. However, these changes were not accompanied by a significant difference in the concentration of incretin hormones.

Policy of full disclosure: This work was supported by the Operating Program of Innovative Economy 2007–2013, grant No. POIG.01.01.02-12-004/09.

P-14-029 Contribution of socioeconomic conditions to association studies of serotonin transporter gene-linked promoter polymorphism and depressionness

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Objective: Environmental varieties affect association between serotonin transporter gene-linked promoter polymorphism (5-HTTLPR) and depression [Karg et al., 2011, Arch Gen Psychiatry 68: 444–454]. In addition to the nature of stressful life events (SLE), other factors such as ethnicity should be considered as modifiers because ethnic minorities often experience socioeconomic disadvantages [Black et al., 2006, Rev Econ Stud 88: 300–313] and are therefore possibly more exposed to stress compared to ethnic majorities.

Methods: The data of the first and second follow-up of the older cohort of the Estonian Children Personality, Behaviour and Health Study [Harro et al. 2009, Biol Psychol 81: 9–13] were used. Data were collected in 2001 and 2008 when participants were 18 (n = 454, 194 male and 260 female; 356 Estonians, 98 Russians) and 25 years old (n = 540; 229 male and 311 female; 423 Estonians, 117 Russians), respectively. Symptoms of depression were measured with the self-report version of the Montgomery-Asberg Depression Rating Scale [Montgomery and Asberg 1979, Brit J Psychiat 134: 382–389]. The history of noninterpersonal SLE in the preceding year was self-reported at age 25.

Results: The score of depressiveness, education level and income were similar in Estonians and Russians. By age 25, Russians had experienced more stressful life events. Eighteen years old Estonians reported higher monthly income of both parents and better economic conditions compared to Russians. Estonian males with the I/’I genotype of the 5-HTTLPR and more SLE had higher depressiveness. On the contrary, in Russians, the ‘s-allele carriers who had experienced higher level of SLE reported higher depressiveness. In females, the 5-HTTLPR x environment interaction effect on depressiveness did not differ between Estonians and Russians.

Conclusion: In conclusion, association between the 5-HTTLPR genotype and depressiveness qualitatively depends on demographic variables and the impact of the latter can be gender-dependent.

P-14-030 Neonatal tryptophan depletion and corticosterone supplementation result in depressive-like abnormalities in adult male mice

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Objective: Current rodent models of human depression suffer from limited construct and external validity whereby they disregard the nature-nurture interactive origin of the disease and are normally suited to inflexible conditions (e.g. single background strain). We developed a novel animal model reproducing several depressive-like features (symptoms) through the combination of reduced serotonin and environmental stress during the early stages of postnatal life (aetiology). We tested whether the adult mice thereon obtained exhibited behavioural and neurochemical abnormalities isomorphic to symptoms of human depression.

Methods: We administered, to outbred CD1 mouse dams, during their first week of lactation, a L-tryptophan deficient diet (T) and corticosterone (C) via drinking water (80 mg/ml). Four groups of dams (animal facility rearing, AFR; T treated, T; C treated, C; T and C treated, TC) and their offspring were used in the study. Maternal care was scored throughout treatment and adult male offspring were tested for: anhedonia (progressive ratio schedule); anxiety-related behavior (approach-avoidance conflict paradigm); BDNF, dopamine and serotonin concentrations in selected brain areas.

Results: Compared to AFR, T, C and TC treatments reduced maternal care. Adult TC offspring showed significantly increased anxiety- and anhedonia-related behaviors, reduced striatal and
increased hypothalamic BDNF and reduced dopamine and serotonin in the prefrontal cortex and their turnover in the hippocampus.

**Conclusion:** The present mouse model recapitulates both the independent (aetiology) and the dependent (symptoms) variables involved in human depression. Furthermore, the independent variables studied in this study are plausible to be translated to different mammalian species and ultimately allow externally valid test strategies.

**P-14-031 Inflammation, cytokines and brain in psychiatric disorders**

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**Objective:** There is evidence that in many psychiatric disorders, like stress, depression, schizophrenia, and Alzheimer disease there are involved inflammatory and immune processes. The objective is to modulate them and reduce the symptoms. Psychoneuro-immuno-endocrinology PNIE is concerned with the interaction between the nervous, immune and endocrine system. The immune system influences the brain and endocrine system by releasing cytokines which also activate the central nervous and endocrine system, the hypothalamus and the hypothalamic-pituitary-adrenal (HPA axis). Cytokines can be synthesized and liberated in the brain by astrocytes and microglia. In depression proinflammatory cytokines are increased, IL1, IL6, TNF soluble receptors IL2 and IL6, there is a shift to Th1 cytokines. Antiinflammatory cytokines IL2, IL10, IL13, inhibit synthesis of cytokines. In schizophrenia there is a shift to the Th2 antiinflammatory cytokines and a reduction of IL2 and increment of IL6. In Alzheimer disease there is an elevation of IL1, IL6, cytokines and a reduction of IL2. They favor synthesis of amyloid precursors that produce senile plaques. Some cytokines like Interleteron, TNF, IL2 can alter neurotransmission, produce fatigue, depression, anxiety, suicidal ideation cognitive, psychotic and somatic symptoms.

**Methods:** Omega 3 fatty acids are the precursors of antiinflammatory prostaglandins, eicosanoids. In patients with moderate depression, we administered polysaturated fatty acids omega 3, of Chia capsules, 600 mg, 4 times a day, during 6 months. We evaluated the ratio of TGL/HDL, that are an indirect marker for inflammation, and with Beck depression scale.

**Results:** We obtained a lowering of the ratio TGL/HDL and an improvement in Beck scale with stabilization of mood.

**Conclusion:** We suggest omega 3 fatty acids as an adjuvant to modulate inflammatory and antiinflammatory eicosanoids and cytokines. A disbalance could affect the brain and modify the endocrine, immunological, neurological, behavioural responses and the functioning of the PNIE systems.

**P-14-032 Efficacy and safety of lisdexamfetamine dimesylate in adults with executive dysfunction and partial or full remission of major depressive disorder**

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**Objective:** Evaluate lisdexamfetamine dimesylate (LDEX) augmentation of antidepressant monotherapy for executive dysfunction in participants with major depressive disorder (MDD).

**Methods:** This randomized, placebo-controlled study enrolled participants (18–55 y) with mild MDD (Montgomery-Asberg Depression Rating Scale [MADRS] total score <18) and executive dysfunction (Behavior Rating Inventory of Executive Function–Adult Version [BRIEF-A] Global Executive Composite [GEC] T-score ≥60) on stable antidepressant monotherapy for ≥8 weeks. After 2 weeks of screening, participants were randomized to 9 weeks of double-blind LDX or placebo augmentation, followed by 2 weeks of single-blind placebo. Double-blind treatment was initiated at 20 mg/day and optimized over 6 weeks in 10-mg weekly increments (maximum dose, 70 mg/day); the optimized dose was maintained through week 9. Efficacy (change from baseline to endpoint in BRIEF-A GEC T-score [primary outcome] and MADRS total score [secondary outcome]) was analyzed using analysis of covariance with last observation carried forward. Treatment-emergent adverse events (TEAEs) were recorded.

**Results:** Of 143 randomized participants (placebo, n=72; LDX, n=71), 119 completed double-blind treatment (placebo, n=59; LDX, n=60). Mean ± SD BRIEF-A GEC T-scores decreased from baseline (placebo, 74.2 ± 8.88; LDX, 76.8 ± 9.66) to endpoint (placebo, 61.4 ± 16.61; LDX, 55.2 ± 16.15); the least squares (LS) mean (95% CI) treatment difference significantly favored LDX (−8.0 [−12.7, −3.3]; P<0.0009). Mean ± SD MADRS total scores decreased from baseline (placebo, 11.8 ± 3.77; LDX, 12.7 ± 3.23) to endpoint (placebo, 8.9 ± 5.67; LDX, 7.6 ± 6.28); the LS mean (95% CI) treatment difference significantly favored LDX (−1.9 [−3.7, 0.0]; P=0.0465). Double-blind TEAE rates were 73.6% with placebo and 78.9% with LDX and included 5 serious TEAEs (placebo, 3; LDX, 2).

**Conclusion:** LDX augmentation significantly improved executive dysfunction and depressive symptoms in participants with fully or partially remitted MDD. The safety profile was generally consistent with published data.

**Policy of full disclosure:** Dr. Madhoo is an employee of Shire Development, LLC and holds stock and/or stock options in Shire. This study was funded by Shire Development, LLC.

**P-14-033 Agomelatine vs. venlafaxine in major depression: Focus on anhedonia and tolerability**

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**Objective:** In this study we compared the effects of agomelatine and venlafaxine XR on anhedonia in patients with Major Depressive Disorder. Secondary endpoints were to test the overall clinical condition as to the evaluator (CGI) and the safety profile.

**Methods:** Sixty patients were enrolled and randomly assigned to two different treatments: agomelatine (25–50 mg/day; N=30 subjects) or venlafaxine XR (75–150 mg/day, N=30 subjects). Psychopathological assessment was performed at baseline and after eight weeks of treatment with the Sheehan Hamilton Rating Scale (SHAPS), the Hamilton Depression Rating Scale (HAM-D), and the Clinical Global Impression (CGI). Safety parameters were monitored with ECG, urinalysis, haematological and clinical chemical analyses of blood samples at the start and end of the study. Self-reported adverse events provided a measure of safety and tolerability.

**Results:** Both groups showed a significant reduction in time for SHAPS and HAM-D scores, with higher reduction in the agomelatine group for anhedonia scores. Only patients treated with agomelatine showed a statistically significant improvement in CGI scores. Common adverse events were reported in 1 (3.2%) patient of the ACO group and in 11 (39.2%) patients of the VLX group. Nausea and vomiting (n=6), dizziness (n=2) and hypotension (n=3) were the most common effects across the VLX group. Conclusion (n=1) was the adverse event that led to patient withdrawal from the study in the ACO group.

**Conclusion:** In this study, agomelatine showed significantly greater efficacy on anhedonia and similar antidepressant efficacy to the SNRI venlafaxine XR in patients with Major Depressive Disorder. The subjective evaluation of the treatment efficacy was in favor of agomelatine as to CGI. Agomelatine’s safety profile compared favourably with that of venlafaxine XR. Fewer patients withdrew and there were fewer withdrawals due to adverse events in the agomelatine group. In particular, agomelatine treatment was associated with lower incidence of nausea, vomiting and dizziness.

**P-14-034 Painful syndromes as signs of masked depression**

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**Objective:** Purpose of this paper is to show how primary painful syndromes, among them mostly cervical and lumbar, are often being unrecognized as depression symptoms.

**Methods:** 50 patients, diagnosed with cervical and lumbar syndromes have been followed. Age of these patients was between 25–55 years. Appropriate RTG diagnostics have been performed on these patients, in order to find the source to their pain. These
diagnostics excluded existence of serious diseases, which could explain intensity of pain at these patients. Patients have been treated for several months with analgesics and have undergone rehab treatment. After that, patients have been appointed to psychiatric examination. After appropriate psychiatric tests have been conducted (MADRS, HAM-D scales), scores confirmed diagnosis of depression at 34 patients.

Results: All 34 patients received drug therapy (antidepressants) and psychotherapy. 23 patients showed after three months significant improvement that was visible through decreasing of depressive symptoms and minimized score on MADRS and HAM-D scales.

Conclusion: Patients with symptoms of lumbar and cervical syndrome achieved significant improvement after receiving antidepressive treatment. When patient complains of pain in the cervical and lumbar area, it should be taken into consideration that this can be a symptom of depression.

P-14-035 A possible involvement of pro-BDNF processing enzymes in antidepressive effects of electroconvulsive seizure

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Objective: Electroconvulsive therapy (ECT) is the most effective treatment for antidepressant-resistant depression, though the molecular mechanisms remain to be fully elucidated. It was previously shown that electroconvulsive seizure (ECS) strongly increased mRNA levels of brain-derived neurotrophic factor (BDNF) in the rat hippocampus (Nibuuya et al., 1995). Although mature BDNF (mBDNF), that is produced through intracellular processing of biosynthetic precursor BDNF (pro-BDNF) in central nervous system neurons (Matsumoto et al., 2008), is antidepressive, recent studies demonstrate that pro-BDNF has negative effects on neurons if secreted. Here, we hypothesized that 1) robust transcription of BDNF induced by ECS led to excess production of pro-BDNF, 2) certain levels of pro-BDNF might be secreted without undergoing intracellular processing, and therefore 3) expression of prohormone convertase 1 (PC1) and tissue-plasminogen activator (t-PA), those are involved in intra- or extracellular processing of pro-BDNF respectively, might be regulated by ECS.

Methods: Male Sprague-Dawley rats (250–300 g) received ECS treatment as reported (Nibuya et al., 1995). Hippocampal levels of pro-BDNF and mBDNF were determined by immunoprecipitation/Western Blotting. PC1 and t-PA levels were determined by Western Blotting or zymography respectively.

Results: Hippocampal pro-BDNF increased within 2 hours after single administration of ECS. More rapidly, single ECS increased the levels of not only PC1 but also t-PA. Interestingly, both pro-BDNF and t-PA were transported to synaptic terminals within 4 hours after ECS, suggesting that t-PA is secreted together with pro-BDNF. Repeated ECS for 10 days increased mBDNF strongly. Finally, chronic treatment with tricyclic antidepressant imipramine slightly increased mBDNF, however, without changes in the levels of pro-BDNF, PC1 and t-PA.

Conclusion: These results suggest that ECS-induced increase in hippocampal mBDNF levels is supported by the robust induction of BDNF transcription and efficient pro-BDNF processing. Such strong increase in mBDNF levels may be important for antidepressive effects of ECT.

P-14-036 Dysregulated HPA-axis in major depression due to FKBP5 polymorphism

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Objective: The FK 506 binding protein 51 or FKBP5 has been implicated in the regulation of the glucocorticoid receptor (GR) sensitivity, especially in major depression and posttraumatic stress disorder. Since the dysregulation of the hypothalamic-pituitary-adrenal (HPA-) axis is one of the most robust biological findings in major depression, we wanted to characterize GR sensitivity in healthy volunteers and depressed patients in dependence of previously identified functional FKBP5 SNPs.

Methods: FKBP5 mRNA expression (baseline and following in vivo GR-stimulation with 1.5 mg dexamethasone p.o.) was analyzed together with plasma cortisol, ACTH, dexamethasone levels and FKBP5 polymorphism rs1360780 in 72 depressed patients and 88 healthy controls. To further evaluate the function of the HPA-axis, we employed the combined dexamethasone/corticotropin-releasing hormone (dex/CRH) test in a subgroup (n = 64/45).

Results: While there were no baseline differences in FKBP5 mRNA expression, patients showed less induction of FKBP5 mRNA expression following dexamethasone stimulation (p = 0.04). We also observe a significant interaction between disease status and FKBP5 risk allele carriers status (minor allele T), p = 0.007. Patients carrying the risk T allele, but not patients carrying the CC genotype showed a reduced induction of FKBP5 mRNA. Cortisol and ACTH suppression following dexamethasone was also differentially regulated between T allele and the CC carriers with a reduced suppression only in depressed patients carrying the T allele. These results remained significant when correction for differences in blood dexamethasone concentrations.

Conclusion: Only depressed patients carrying the FKBP5 rs1360780 risk allele show significant GR resistance compared to healthy controls, as measured by dexamethasone-induced FKBP5 mRNA induction and suppression of cortisol and ACTH. This finding might explain why endocrine alterations are not observed in all depressed patients.

P-14-037 Delivery of electroconvulsive therapy in Canada

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Objective: Electroconvulsive Therapy (ECT) continues to be used widely in Canada, but no account of current practices exists. The need for nationwide data about current practices was one of the motivating factors for the Canadian ECT Survey.

Methods: An association of clinicians for Canadian ECT Survey (CANECTS/ECANEC) was created. After first identifying all sites in Canada where ECT was delivered, we subsequently developed a detailed questionnaire (13 pages; 76 questions in 11 sections), translated it into French, piloted it at fourteen sites and then sent a final version to all 175 ECT centres.

Results: Thus we were able to gather wide ranging information pertaining to the practice of ECT in Canada, including the ECT apparatus used, the parameters of the electrical stimuli used to induce seizures, and stimulating electrode placements.

Conclusion: Our findings confirm that the practice of ECT in Canada is generally consistent with contemporary guidelines. Sine wave stimulation is rarely employed, and three placements of the stimulating electrodes are commonly used: bitemporal, bifrontal and right unilateral. Some practical suggestions are recommended to address a few specific concerns.

P-14-038 Vascular endothelial growth factor (VEGF) serum: Putative predictive biomarkers for the electroconvulsive therapy (ECT) in depressed patients

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Objective: Despite controversial issues, electroconvulsive therapy (ECT) remains one of the most effective therapies among patients with treatment resistant depression (TRD). The Vascular endothelial growth factor (VEGF) is an angiogenic cytokine able to induce vasopermeability in many types of tissues, including the Blood Brain Barrier. Our group have demonstrated that serum VEGF levels in major depressive disorder (MDD) patients were unaffected by escitalopram and that TRD patients have higher serum levels of VEGF following ECT. In addition, a correlation between the increase in VEGF expression and the amelioration of symptoms after ECT was observed. On these bases, the aim of the study was to investigate if VEGF serum levels before treatment might be predictive of ECT response in TRD patients.

Methods: The objective of this study was to assess the possible use of VEGF as a putative predictive biomarker for ECT in MDD patients and TRD patients. VEGF serum levels were measured in MDD patients (n = 20) and TRD patients (n = 10) before and after the first ECT session. VEGF serum levels were compared using the Student’s t-test. A correlation analysis between VEGF serum levels and depression severity before and after the first ECT session was performed using the Pearson correlation coefficient.
Methods: Sixty-four DSM-IV TRD patients were enrolled in the study. Patients were maintained on the same pharmacological treatment for at least 3 weeks before ECT and during the entire study period. Illness severity and the outcome of ECT treatment were assessed using the Montgomery and Asberg Depression Rating Scale (MADRS), before the treatment (T0), and one month later the end of ECT (T1). The Pearson coefficient was used to evaluate bivariate correlations. T-test was used to evaluate differences of means.

Results: The ECT treatment reduced symptomatology as measured with MADRS (p < 0.0001), and 73.4% of the patients were considered responders (non responder if percentage MADRS reduction at T1 was < 50%). VEGF serum levels at baseline correlate significantly with the percentage reduction of symptomatology after ECT (p = 0.004) and were significantly lower in patients non responder at follow-up (p = 0.02).

Conclusion: Our results suggested that VEGF serum levels might play a role in the mechanism of response to ECT in TRD patients. The dosage of serum VEGF may be helpful to identify patients who might have a significant benefit from ECT supporting physicians in choosing the better approach to treat TRD.

P-14-039 Investigation to effectiveness of neurofeedback on treatment major depressive disorder in patients' client of Qods hospital

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Objective: 20 patients that have received MDD diagnosis by psychiatrists of Qods hospital contributed in research, patients were divided to experimental and control group. 10 patients in experimental group and 10 patients in control group. Hamilton rating scale for depression scale (HDRS) was filled as pre test (before neurofeedback sessions) and post test (after neurofeedback sessions). In follow up session after 3 month HDRS was filled for both experimental and control group.

Methods: Technician of neurofeedback done neurofeedback sessions. Per patient in experimental group had received 12 sessions of neurofeedback therapy. Both groups have received psychiatric drugs. Cut off point for depression diagnosis was 13. Because of ethical aspects of research control group after research process have received 1 session neurofeedback.

Results: Results show that experimental group has more significant improvement than control group (p > 0/01). Results show 93% of differences relate to group membership.

Conclusion: Neurofeedback treatments for depression appear very promising not only in bringing relief from depression, but in modifying the underlying biological predisposition for becoming depressed. Neurofeedback focuses on retraining the brain, for example, reversing the frontal brainwave asymmetry, with the goal of producing an enduring change that does not require people to remain on medication indefinitely.

Policy of full disclosure: This article is a section of admitted research proposal that have received financial support of young researchers islamic azad university sanandaj, sanandaj branch.

P-14-040 Prognostic implications of somatic symptoms in patients with depression. Results from a three-month, prospective, observational study from Asia

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Objective: Patients with major depressive disorder (MDD) frequently suffer from concomitant somatic symptoms. This study aims to investigate the existence of a group of patients depending on the presence of somatic symptoms and to understand the impact of these symptoms on the course of depression.

Methods: Nine hundred and nine patients from Asia presenting with a new or first episode of MDD (DSM-IV/ICD-10) were enrolled in this 3-month prospective observational study. Depressive symptoms (Hamilton Depression Scale-HAMD-17 and Clinical Global Severity score – CGI-S) and somatic symptoms (Somatic Symptom Inventory) were assessed. A cluster analysis was used to define patient groups based on the presence of somatic symptoms. Confirmatory factor analysis was used to classify somatic symptoms in different groups. Regression models were employed to assess the relevance of somatic symptoms on outcomes.

Results: A three cluster solution was chosen based on the variance explained. Cluster 1 patients (39%) had a low level of somatic symptoms. Cluster 2 patients (53%) had a significant level of somatic symptoms. Cluster 3 patients (8%) had severe somatic symptoms. Patients with more somatic symptoms at baseline had more severe depression (HAMD17 and CGI-S) and lower response and remission rates. Response rates were 82% in cluster 1, 72% in cluster 2 and 55% in cluster 3. Remission rates were 68%, 55% and 29% respectively. Four groups of symptoms were validated with the confirmatory factor analysis: as Pain, Autonomic Symptoms, Energy and CNS symptoms. A regression model showed patients with pain symptoms had a lower response (OR = 0.65; 95% CI 0.53–0.80) and remission rates (OR = 0.61; 95% CI 0.49–0.74).

Conclusion: Somatic symptoms are frequent in Asian patients with MDD. Patients with more somatic symptoms have higher depression severity and lower response and remission rates. Pain symptoms are most associated with poorer outcomes.

Policy of full disclosure: Diego Novick, William Montgomery, Alan Brabich, Zbigniew Kadziola and Xiaomei Peng are full time Eli Lilly & Co. employees. Jordan Bertsch was a statistical consultant for the SOHO and EMBLEM studies. He was working with the Fundacio Sant Joan de Deu under a contract with Eli Lilly & Co. Josep Maria Haro has acted as a consultant, received grants, or acted as a speaker in activities sponsored by the following companies: Astra-Zeneca, Eli Lilly, Glaxo-Smith-Kline, and Lundbeck. Roberto Brugnoli has acted as a consultant, received grants, or acted as a speaker in activities sponsored by the following companies: BMS, Eli Lilly, Indovapharma and Sigma-Tau.

P-14-041 DNA methylation profiles of the brain-derived neurotrophic factor (BDNF) gene as a potential diagnostic biomarker in psychiatric disorders

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Objective: Psychiatric disorders, for example major depression or schizophrenia, are diagnosed on the basis of clinical symptoms in patients. The search for specific biological markers is of great importance to advance the method of diagnosis for psychiatric disorders. We examined the methylation profiles of the CpG islands at the promoter of exon I of the brain-derived neurotrophic factor (BDNF) gene, which is well known to be involved in the pathophysiology of depression.

Methods: We analyzed genomic DNA from peripheral blood of 38 Japanese patients with major depression and 40 patients with schizophrenia and 18 healthy subjects to identify an appropriate epigenetic biomarker to aid in the establishment of an objective system for the diagnosis of psychiatric disorders. Methylation rates at each CpG unit was measured using a MassArray® system (SEQUENOM), and 2-dimensional hierarchical clustering analyses were undertaken to determine the validity of these methylation profiles as a diagnostic biomarker.

Results: Analyses of the dendrogram from methylation profiles of the CpG islands at the promoter of exon I of the brain-derived neurotrophic factor (BDNF) gene, which is well known to be involved in the pathophysiology of depression.
Conclusion: Despite the small number of subjects, our results indicate that the classification based on the DNA methylation profiles of the CpG islands of the BDNF gene may be a valuable diagnostic biomarker for psychiatric disorders.

P-14-042 Prediction of antidepressant drug response of patients with major depression by citalopram serum concentrations on day 7 and clinical improvement on day 14

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Objective: Clinical trials have shown that early improvement on the Hamilton depression rating (HAM-D) scale and citalopram serum concentrations on day 7 are required to attain appropriate clinical response. The aim of this study was to calculate cut off levels for serum concentrations of citalopram and clinical improvement during the early phase of treatment to predict later response and to analyse the predictive power of the combined marker.

Methods: Data of 55 inpatients with a major depressive disorder (MDD) according to ICD-10 who received citalopram were submitted to the analyses. Psychopathology was assessed by the 17-item HAMD rating scale and in parallel serum concentrations of citalopram were measured in weekly intervals for five weeks.

Results: Receiver Operating Characteristic (ROC) analysis revealed for citalopram a serum concentration of 53 ng/ml on day 7 and clinical improvement on the HAMD scale by at least 24% on day 14 to predict response on day 35. The serum concentration of citalopram on day 7 and early improvement on day 14 taken together, predicted response on week 5 with 73% sensitivity and 85% specificity.

Conclusion: Our results show that treatment with citalopram should be guided by symptom rating on day 14 and serum concentration measurement on day 7 to guide antidepressant drug treatment and minimize the risk of treatment failure in patients suffering from major depression.

P-14-043 Dopamine and adenosine antagonism have opposite effects on the activational and the directional components of sucrose-motivated behavior: Studies in rats and mice

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Objective: Functional interactions between adenosine and dopamine (DA) receptors play an integral part in the regulation of striatal areas, including nucleus accumbens (Nac). Mesolimbic DA is a key component of the brain circuitry regulating motivated behaviors, and Nac DA regulates behavioral activation and effort-related processes. Caffeine and theophylline are minor psychostimulants that act as nonselective adenosine receptor antagonists. While adenosine antagonists increase motor activities, DA antagonists reduce them. However, because studies in the literature argued for a reduction in the hedonic value of sucrose after DA antagonism, the present experiments were undertaken to study the impact of adenosine and DA antagonism on the activational and directional components of motivated behaviors using sucrose as the reinforcer.

Results: Male CD-1 mice with one-hour access per day to a solution containing 10% sucrose in the home cage consumed significant amounts of sucrose. A low dose of the DA D2 antagonist haloperidol did not block sucrose consumption. A2A KO mice however, consumed less sucrose than WT animals. A stimulus associated with sucrose presentation in the home cage stimulated exploratory activity in a novel environment. A low dose of haloperidol blocked this conditioned behavioral activation. On a FR/free access choice procedure, Sprague-Dawley rats press the lever to obtain 5% sucrose and drink low quantities of free 0.3% sucrose. Haloperidol decreased lever pressing for 5% sucrose but increased free 0.3% sucrose intake, thus inducing a shift in the choice towards a less effortful behavior. Caffeine reduced lever pressing but also free access sucrose consumption. These pharmacological manipulations in rats drinking in the home cage under free access conditions do not change preference for the high concentration and do not reduce total sucrose intake.

Conclusion: These results may have implications for understanding phenomena related to motivation and energy-related disorders such as psychomotor slowing or anergia in depression.

P-14-044 Meta-analysis on cognitive function of depressive patients compared with healthy controls

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Objective: Depression is a neurodegenerative disorder related with chronic elevated corticosteroid level and decreased hippocampal size. Functional decline in the cognitive functions including memory, attention, and concentration often related with easy forgetfulness, mild cognitive impairment, and dementia. However, the results about the relationship of cognitive function and depression are often controversial. Authors performed meta-analysis about the difference of cognitive function between depressive patients and control.

Methods: Reports of Randomized controlled trials (RCTs) of antidepressants from 2000, in which they measure cognitive domains were searched from PubMed and Cochrane library. Search terms were; (‘depression’ OR ‘major depression’, ‘OR ‘depressive illness’, ‘OR ‘major depressive disorder’, ‘OR ‘depressed’) AND (‘cognitive function’ OR ‘cognition’ OR ‘cognitive’ OR ‘neuropsychological’ OR ‘neuropsychology’). Values of cognitive functions (mean, standard deviation, and number of subjects) were recorded and the effect sizes, 95% confidence intervals of each study were calculated using Comprehensive Meta-Analysis Version 2.0 (Biostat Inc., Englewood, NJ, USA).

Results: Among 4,140 papers, 27 RCT papers were finally analyzed.

Conclusion: Depressive patients showed significant lowered performance in the subsets of Digit Span, CPT, TMT A, Digit Symbol, Stroop test, WCST, verbal fluency, verbal memory immediate. We might use these subsets to compare the cognitive change of depressive patients during their course of illness.

P-14-045 Efficacy and safety of lisdexamfetamine dimesylate as augmentation therapy in adults with major depressive disorder treated with an antidepressant

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Objective: Evaluate the efficacy and safety of lisdexamfetamine dimesylate (LDX) augmentation of antidepressant monotherapy in participants with major depressive disorder (MDD).

Methods: This randomized, double-blind, placebo-controlled trial enrolled participants (18–55 y) with nonpsychotic MDD. After 8 weeks of open-label escitalopram (week 1: 10 mg/d; 20 mg/d thereafter), participants with residual symptoms (Hamilton Rating Scale for Depression 17-item score ≥ 4) were randomized to 6 weeks of double-blind LDX (20, 30, or 50 mg/d) or placebo augmentation. The primary endpoint, mean change in Montgomery-Asberg Depression Rating Scale (MADRS) total score from augmentation baseline to study endpoint, was analyzed by analysis of covariance (prespecified α = 0.10) in nonremitters (i.e., participants with augmentation baseline MADRS total score > 10) who had ≥ 1 randomized study drug dose and ≥ 1 postrandomization MADRS assessments. Safety assessments included treatment-emergent adverse events (TEAEs).

Results: Of 246 enrolled participants, 173 (placebo, 85; LDX, 88) received double-blind treatment and 157 (placebo, 79; LDX, 78) completed the study. For the 129 nonremitters (placebo, 64; LDX, 65) receiving randomized treatment, mean ± SD MADRS total scores decreased from augmentation baseline (placebo, 20.8 ± 6.42; LDX, 20.3 ± 7.16) to study endpoint (placebo, 15.9 ± 9.17; LDX, 13.3 ± 8.77) the LS mean (90% CI) treatment difference significantly favored LDX (−2.3 [−4.5, −0.1]; P = 0.0092). During double-blind treatment,
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49.4% of patients receiving placebo and 60.2% receiving LDX had a TEAE; 1 serious TEAE occurred in a participant receiving placebo. TEAEs occurring in ≥5% of participants with placebo and LDX were dry mouth (0%, 11.4%, respectively), headache (4.7%, 11.4%), decreased appetite (2.4%, 6.8%), nasopharyngitis (3.5%, 5.7%), and insomnia (7.1%, 4.5%).

Conclusion: LDX augmentation of escitalopram monotherapy in participants with residual MDD symptoms met prespecified signal detection parameters. Further studies are needed. The safety profile of LDX was consistent with prior literature.

Policy of full disclosure: Dr. Patkar is a consultant for Avanir Pharma, Gilead, and Dey Pharma; is on the speakers bureau and received honoraria from Alkermes, Bristol-Myers Squibb, Dey Pharma, Merck, Sunovion, and Pfizer; has received grant support from National Institutes of Health (NIDA, NIAAA), SAMHSA, AstraZeneca, Bristol-Myers Squibb, Cephalon, Forest, J & J, Jazz Pharmaceuticals, Lundbeck, Merck, Organon, Pfizer, Sunovion, Shire and Titan. He is not a major stockholder in or employed by pharmaceutical companies, nor has he received other material support from pharmaceutical companies. This study was funded by Shire Development LLC.

P-14-046 Memory deficits produced by serotonin depletion in rats are reversed by the multimodal antidepressant Lu AA21004, but not escitalopram

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Objective: To compare the ability of escitalopram and the multimodal antidepressant Lu AA21004 to reverse serotonin (5HT) depletion-induced memory deficits in rats.

Methods: General design: SHF was depleted in female rats by administering the irreversible tryptophan hydroxylase inhibitor 4-chloro-DL-phenylalanine methyl ester HCl (PCPA; 100 mg/kg/day, sc, 4 days). Memory performance was assessed in novel object recognition (NOR) and spontaneous alternation (SA) tasks after acute vehicle or drug administration. Experiment 1: PCPA-treated females were administered vehicle or 1 mg/kg carbipeda + 50 mg/kg of the 5-HT precursor 5-hydroxytryptophan (5HTP). Experiment 2: PCPA-treated females were administered vehicle, 10 mg/kg Lu AA21004 or 0.5 mg/kg escitalopram (s.c.) and compared to PCPA-naive rats. Experiment 3: A dose-response curve was generated by administering vehicle, 0.1, 3, or 10 mg/kg Lu AA21004 to PCPA-treated animals.

Results: Experiment 1: PCPA impaired memory performance in NOR (F(2,22) = 9.6, p < 0.01) and SA tasks (F(2,19) = 10.8, p < 0.001). Restoring central 5HT levels with acute 5HTP normalized memory performance. Experiment 2: PCPA-treated females were impaired in NOR (F(3,28) = 13.7, p < 0.0001) and SA performance (F(3,27) = 19.2, p < 0.0001). Treatment with Lu AA21004 improved PCPA-induced memory deficits, while escitalopram had no effect despite similar 5HT transport occupancy. Experiment 3: Lu AA21004 dose-dependently improved memory compared to vehicle in PCPA-treated rats in NOR (F(4,45) = 6.5, p < 0.001) and SA (F(4,47) = 4.8, p < 0.01).

Conclusion: The current study demonstrates that PCPA-induced 5HT depletion leads to robust memory deficits as assessed by NOR and SA. Treatment with the 5HT precursor 5HTP or Lu AA21004, but not escitalopram, normalized memory deficits. These data imply that targets other than the 5HT transporter mediate the effects of Lu AA21004. The clinical implications of these findings remain to be investigated.

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P-14-047 Platelet serotonin re-uptake velocity predicts anterior cingulate activity

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Objective: Anterior cingulate cortex (ACC) activity has been related to emotion and social stress processing and alterations of ACC function have been implicated in depression. Although the serotonin transporter (5-HTT) rich subgenual portion of the ACC (sACC) has been demonstrated to be under significant genetic control of the serotonin transporter gene (SLC6A4), it remains unknown today whether transmembrane 5-HTT function mediates sACC activity under physiological conditions in adult humans.

Methods: Eight healthy male subjects were included in our [11C]DASB PET study, 48 healthy subjects were enrolled in our MRI study. During a block design fMRI task subjects underwent an emotion-inducing paradigm. Platelet solution (30 μl) was incubated using a dilution technique with unlabeled 5-HT to reveal Vmax and Km values.

Results: Here we show a linkage between maximal serotonin uptake velocity (Vmax) using a in vitro model system of neural 5-HTT function in blood platelets and neural activity of the sACC assessed by functional magnetic resonance imaging, a region also showing maximal 5-HTT availability within the cingulate cortex with positron emission tomography. We further report that genetic variation within SLC6A4 cannot sufficiently explain this linkage, which contributes to the understanding of the complex gene-protein-function relationship of 5-HTT.

Conclusion: Our findings expand the knowledge of neuronal consequences of altered 5-HTT protein function by relating in vitro measures of 5-HTT function to in vivo human brain activity for the first time. While genetic studies investigating the 5-HTT gene have provided insights about developmental effects on brain wiring and consecutive functional changes, this study among others underscores the importance to investigate protein function in order to untangle the complex gene-protein-function relationship in the context of mental illness.

P-14-048 Metabolic syndrom and C-reactive protein in patients with depression disorder on antidepressive medication

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Objective: The aim of this study was to investigate is there any difference in CRP levels in patients with Recurrent depressive disorder, treated with antidepressants medication, compared to health control group of subjects and if there is an association between increased CRP levels and the presence of MetS in these two groups.

Methods: Sixty subjects entered the study, the experimental group of patients (diagnosis of recurrent depressive disorder) included 35 subjects (18 male, 17 female), average age 47.85 ± 7.35 years. Healthy control group of subjects (n = 25), age 42.08 ± 4.93 years. The Metabolic syndrom central was defined according to NCEP ATP III criteria. The cut-off point for elevated CRP was set at 5 mg/L.

Results: There was no statistically significant difference in the prevalence of MetS and CRP values between the studied groups. As an independent variables, Age, Waist circumference and Total cholesterol levels were significantly different in favor of the experimental group. In addition, patients that fulfilled the NCEP ATP III criteria for MetS showed significant difference for its constituting variables Central obesity and Arterial hypertension, in a favor of experimental group, too. Elevated CRP levels were associated with increased risk for the development of MetS in depressed patients, while both CRP values and BMI were significant predictors of MetS for the control group. Smoking habit was a considerable predictor for high CRP values (< 5 mg/L) for depressed patients. Depression symptom severity (measured by HAMD score), length of illness, such as length of the antidepressant drug treatment didn’t show significant impact on both the MetS and CRP values.

Conclusion: Both the CRP levels and Metabolic risk profile screening may be beneficial in order to obtain better assessment for depressive long term medicated patients, preventing the risk for future cardiovascular events.
White matter integrity in major depressive disorder: A comparison between distinct stages of the illness
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Objective: To study the white matter (WM) integrity in patients with major depressive disorder (MDD) recruited in different illness stages as compared to healthy subjects, by means of diffusion tensor imaging (DTI). We hypothesized that WM disruptions of the neuronal circuits underlying the pathophysiology of MDD can be even worsened in those patients with higher past illness burden.

Methods: Magnetic resonance imaging protocol (3T scanner) and diffusion tensor images were acquired from a sample of forty-seven right-handed adult patients with MDD (DSM-IV criteria): 14 patients suffering a first episode (score >14 on the Hamilton Rating Scale for Depression; HRSD); 15 patients with more than two previous episodes and currently remitted in the last six months (HRSD <8); and 18 patients with a chronic depressive episode (HRS >17); and from 17 healthy subjects, comparable for age and years of schooling. DTI analyses were performed with the FMRIB Software Library, FSL v4.1.4 to obtain maps of fractional anisotropy (FA, WM integrity measure) by means of Tract-based Spatial Statistics Package (TBSS) using a general linear model (family wise error correction).

Results: Voxel-wise whole brain results revealed a generalized significant reduction of FA in chronic patients compared to healthy controls (FWE p<0.05) affecting bilateral inferior fronto-occipital fasciculus, bilateral inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus, forceps major and forceps minor, body of corpus callosum and bilateral cingulum (Fig. 1). Differences (FWE p<0.05) also appeared between treatment-resistant chronic and first episode patients, affecting body of corpus callosum, right inferior fronto-occipital fasciculus, bilateral superior longitudinal fasciculus, forceps minor, forceps major, bilateral cingulum, and bilateral inferior longitudinal fasciculus.

Conclusion: The results revealed that decrements of FA are observable in the most severe illness stages of MDD as compared to healthy controls, but also as compared to the earlier stages of the illness. Therefore, higher past illness burden entails greater white matter disruptions in patients suffering MDD.

Prevalence of depression among type II diabetes mellitus in primary family health care centers
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Objective: Diabetes is one of the major world health problems. Recent estimates from the World Health Organization (WHO) predict that if current trends continue, the number of people with diabetes will be more than double from 176 to 370 million people by 2030. In Egypt, the total number of persons with diagnosed and undiagnosed diabetes is estimated to be 17 million people. In this study, we aimed to determine the prevalence of depression among patients with type II diabetes mellitus in a primary family health care center.

Methods: A cross-sectional study was conducted in a primary family health care center in Alexandria, Egypt. A total of 300 patients with type II diabetes mellitus were recruited. The prevalence of depression was assessed using the Hospital Anxiety and Depression Scale (HADS). The study was approved by the ethics committee of the Faculty of Medicine, Tanta University, Alexandria, Egypt.

Results: The prevalence of depression among patients with type II diabetes mellitus was found to be 25.3% (76/300). The prevalence was higher in females (31.2%) compared to males (15.2%). The prevalence was also higher in patients with duration of diabetes >5 years (32.5%) compared to patients with duration of diabetes ≤5 years (17.3%). The prevalence was higher in patients receiving insulin (29.4%) compared to patients not receiving insulin (19.9%). The prevalence was also higher in patients with HbA1c >7% (34.3%) compared to patients with HbA1c ≤7% (19.9%).

Conclusion: Depression is a common comorbidity among patients with type II diabetes mellitus. Early detection and management of depression in these patients is crucial to improve the quality of life and outcomes of diabetes.
P-14. Depression

Diabetes is expected to increase more than double from 3.80 million to 8.80 million by the year 2025, compared with the prevalence of depression among normal subjects. These reports indicate that >25% of patients with diabetes reach clinical criteria for depression, a rate far higher than in the general population. The comorbidity of diabetes and depression is associated with adverse diabetic outcomes, compared with nondepressed diabetic patients. This work aims at determining the prevalence of depression among type II diabetic patients attending family health centers in Alexandria.

Methods: A sample size of approximately 303 adult diabetic cases of type II in the age category of (20–60) years old based on a prevalence of 27% of depression in diabetics, degree of precision of 5% and confidence level of 95%, will be randomly selected from the attendees of the studied family health centers. Two days of the week will be selected randomly to visit the studied primary health care facilities till the allocated sample size is reached. An interview questionnaire will be designed for depression assessment by using the Hamilton Depression Rating Scale (HAMD-D) among type II diabetic patients.

Results: 40.18% (n = 135) of diabetic patients in our study showed moderate to severe depression. 12.2% (n=41) showed mild depression while 47.62% (n = 160) showed normal values on HAMD-D scale. Moderate to severe depression was present in 39.1% and 40.7% in males and females respectively.

Conclusion: Awareness campaigns against depression for primary health physician is a major public health issue.

 Keyword: Differentiation schizophrenia and depression.

P-14-051 WCST Performance in schizophrenia and psychotic depression

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Objective: Differentiating between schizophrenia and major depression with psychotic features often reveals diagnostic dilemma. Both share psychotic features and severe impairment in occupational functions. Severe psychomotor retardation, not uncommon in psychotic depression, may simulate negative symptoms of schizophrenia. Our work aims at utilizing Wisconsin Card Sorting Test (WCST) performance as a potential differentiating neurocognitive tool.

Methods: 60 patients were recruited randomly from the outpatient service at Alexandria University Hospital: 30 patients with schizophrenia and 30 patients with chronic psychotic depression. They were subjected to Clinical Global Impression for Severity (CGI-S) scale and Wisconsin Card Sorting Test (WCST) 128 card computerized version.

Results: Both groups were balanced in terms of gender distribution, severity and duration of illness. The study compared all parameters of WCST. Only perseverative errors showed mild significant difference (P < 0.05) that disappeared when applying Bonferroni adaptation, setting significance level at 0.01 instead of 0.05.

Conclusion: Performance on WCST is similar in schizophrenia and severe depression with psychotic features in most of the measured parameters, hence WCST could not serve as a supplementary tool differentiating between both diagnoses in our study.

P-14-052 Efficacy and tolerability of vilazodone in patients with moderate, moderately severe, and severe depression–pool analyses from 2 phase III trials

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Objective: Vilazodone, a serotonin reuptake inhibitor and 5-HT1A receptor partial agonist, is approved for treatment of major depressive disorder (MDD) in adults. Post hoc analyses of the Phase III trials (NCT00283576, NCT00683992), both of which were positive, evaluated efficacy and tolerability across baseline depression severity.

Methods: Data from 2, double-blind, 8-week, randomized, placebo-controlled trials were pooled. Patients (18–70 years) with DSM-IV-TR-defined MDD and HAMD17 ≥ 22 were included; trials comprised a 1-week screening and 8-week double-blind treatment. Vilazodone was titrated to 40-mg (taken once daily with food) over a 2-week fixed-dose titration period. Primary efficacy outcome: MADRS total score change from baseline to Week 8 using an analysis of covariance model based on the Intent-to-Treat (ITT) Population and last observation carried forward approach. Severity of baseline depression for subgroup analyses was defined by MADRS threshold scores: moderate (MADR ≤ 30), moderately severe (30 ≤ MADR < 35), and severe (MADR ≥ 35).

Results: Baseline depression severity was moderate in 31% (placebo = 143; vilazodone = 130), moderately severe in 49% (placebo = 205; vilazodone = 220), and severe in 20% (placebo = 85; vilazodone = 86) of patients (Safety Population). Least squares mean difference (LSMD) in MADRS total score change from baseline to week 8 was significantly greater for vilazodone versus placebo in each depression subgroup: moderate (LSMD = −2.9; P = 0.0056), moderately severe (LSMD = −2.3; P = 0.0314), and severe (LSMD = −4.1; P = 0.017) (ITT Population). Response rates (>50% MADRS improvement) for vilazodone and placebo were 41% versus 31% in the moderate (P = 0.0810), 41% versus 29% in the moderately severe (P = 0.0130) and 44% versus 26% in the severe depression (P = 0.0124) subgroups. Adverse event profiles were similar across severity subgroups.

Conclusion: Vilazodone treatment versus placebo significantly improved MADRS scores in patients with moderate, moderately severe, and severe depression with no obvious trend across severity of illness; treatment effects (>2 point MADRS change from baseline) were clinically significant, with efficacy and tolerability similar among depression severity subgroups.

P-14-053 Electroconvulsive stimulation alters levels of BDNF-related microRNAs

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Objective: Electroconvulsive therapy (ECT) is one of the most effective treatments for severe depression but its mechanism of action is not yet fully understood. Electroconvulsive stimulation (ECS), an animal model of ECT, is known to increase levels of the neurotrophin brain derived neurotrophic factor (BDNF) within the brain, though the precise means by which this occurs and how it contributes to the antidepressant effects of ECS are unknown. One possibility is that such effects involve a recently identified class of endogenous, small RNA species termed microRNAs (miRNAs) since evidence suggests that BDNF can both regulate and be regulated by miRNAs. We therefore investigated the effects the expression of BDNF-related miRNA species in rat brain and blood following treatment with ECS.

Methods: Male Sprague-Dawley rats were randomised into groups to receive either “sham” or “real” ECS. ECS was administered either acutely (× 1) or chronically (× 10) following a protocol which mimics that of clinical ECT (100 pulses/s; 0.5 ms; 0.7 s; 75 mA; thrice weekly). Total RNA was extracted from dentate gyrus, hippocampus, frontal cortex, cerebellum and whole blood samples and TaqMan® RT-PCR was performed using stem-loop primers for BDNF-related miRNAs.

Results: Of the miRNAs examined, miR-212 levels were found to be significantly increased in dentate gyrus following both acute (p < 0.001) and chronic (p < 0.05) ECS. miR-212 levels were also increased in blood following chronic ECS. Notably, a positive correlation was observed between miR-212 levels in dentate gyrus and in blood (Pearson’s r = 0.61, p < 0.001).

Conclusion: Alterations in miRNA expression may be informative about the mechanism of action of ECS/ECT and in turn may give insight into the neurobiology of depression. Furthermore, examination of miRNAs in blood from severely depressed patients undergoing treatment with ECT will ascertain their potential to act as clinical biomarkers for the treatment of depression.

P-14-054 Impact of family history on drug placebo separation in RCTS: Site rater and computer outcomes

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Objective: High placebo response often hampers signal detection in randomised clinical trials. We used data from 4 recent failed studies to explore the impact of family history of mood disorder (FamHx) on signal detection.
Impact of Family History on Signal Detection: Active-Placebo at Endpoint

Methods: We examined outcomes from 4 failed double blind studies with 4 placebo groups and 7 active treatment groups that collected outcomes independently from site-based raters (SBR) and computer (Comp). Comparison groups were constructed based on subject report of family history of mood disorder (FamHx) collected by the computer. The studies were all powered to detect a drug-placebo difference (Signal) of 3–4 points on the primary outcome measure (change from baseline MADRS or HAMD). A priori, for these exploratory analyses FamHx was defined as Impactful if the difference in signal for FamHx(+) vs. FamHx(−) was ≥1 (≥25% of the estimated effect size).

Results: FamHx was impactful in all trials for all 7 comparisons based on both SBR and Comp outcomes. A trend favouring active treatment over placebo was found in all FamHx(+) subgroups. The difference in signal detection for FamHx(+) vs. FamHx(−) subgroups was large ranging in magnitude from 1.9–15.4 for SBR and 5.7–15.1 for the Comp ratings. A contrary trend favouring placebo over active treatment was found in 6 of the 7 FamHx(+) subgroups. In three of the four trials examined the drug-placebo difference for FamHx(+) reached statistical significance based on MADRS-COMP or HAMD-COMP, but not MADRS-SBR or HAMD-SBR.

Conclusion: The high rates of placebo response observed in subjects reporting no family history of mood disorder likely contributed to the failure of the clinical trials in this report. If this finding is replicated further study is needed to clarify the correlates of the FHx(−) subject status associated with high placebo response (e.g. diagnostic validity or enrolment rate).

Policy of full disclosure: Dr. Sachs and Mr. DeBonis are employees of Bracket Global.

P-14-055 Neural correlates of remission in major depressive disorder

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Objective: While overwhelming evidence points to alterations within emotional brain circuitries including the amygdala and the subgenual anterior cingulate cortex (sACC) in patients with concurrent major depressive episodes and under antidepressant treatment, neural mechanisms underlying stable remission are largely unknown. Hence, we aimed to investigate the neural dynamics between the amygdala and sACC in remitted and untreated Major Depressive Disorder (MDD) patients and healthy controls.

Methods: Within a multi-center, cross-sectional magnetic resonance imaging studying functional and structural local as well as brain systems level measures of the amygdala-sACC circuitry have been compared between thirty-eight adult, drug-free remitted MDD (rMDD) patients and 38 healthy controls without any psychiatric life-time diagnosis. Subjects underwent a functional block-design matching paradigm comprising emotional stimuli, angry/fearful faces or fearful/threatening scenes derived from the International Affective Picture System (IAPS). Based on our straight-forward a priori hypothesis, functional and structural local (BOLD, gray matter volume) as well as brain systems level measures (functional connectivity, structural covariance) have been analyzed restricted to the amygdalae and the cingulate cortex using AFNI, SPM8 and the DARTEL extension of SPM8.

Results: Decreased amygdala (right: t = −3.83, left: t = −3.13) and sACC (bilateral: t = −2.02) activation during conscious perception of unpleasant visual stimuli was found in rMDD patients in comparison to healthy controls. No structural differences could be found in both structures between groups. On a brain systems level, rMDD patients exhibited increased functional connectivity (t = 3.03) and structural connectivity (t = 3.84) between the amygdala and sACC compared to controls. In rMDD patients, functional coupling between amygdala and sACC was related to means of illness duration (P = 0.021).

Conclusion: This study demonstrates functional and morphometric differences within the amygdala-sACC circuitry between drug-free rMDD patients and healthy controls. Our findings suggest that remission of MDD cannot simply be interpreted as a disease-free condition from a neurobiological perspective.

P-14-056 Characteristics of the single event related [Oxy-Hb] changes in patients with depressive disorder

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Objective: The aim of this study was to examine characteristic of single event related Oxy-hemoglobin (Oxy-Hb) changes in patients with depressive disorder measured by multi-channel near-infrared spectroscopy (NIRS) during word generation task, Japanese ‘Shiritori’.

Methods: 26 patients with depression and 32 age and gender matched healthy subjects participated in the study. All the patients were...
right-handed and native Japanese speakers. Diagnosis of depression was made for ICD-10 by two experienced psychiatrist. In all patients psychiatric symptoms were evaluated using HAM-D (15.9 ± 5.3). The ethical committee of the Kurume University approved this study. All subjects gave written informed consent after a complete explanation of the study. The 44-multi-channel NIRS machine (ETG-4000, Hitachi) measures relative changes of [Oxy-Hb] and [deoxy-Hb]. The present study has segregated specific regions (ROI) in the prefrontal cortex associated with executive function (left 11Ch and right 12Ch). As word generation tasks, standard shiritori, vertebrae shiritori and word fluency were used in this study. The cognitive activation task induced a 12-s pre-task baseline and a single generation task of letter or word projected by TV monitor. The pre-tasks and tasks were performed repeatedly 20 times and the data was analyzed using average wave form.

Results: The changes of [Oxy-Hb] in patients with depressive disorder were significantly smaller than that of healthy subject during all word generation task. In both left 11Ch and right 12Ch (ROI), the changes of Oxy-Hb concentration in patients with depressive disorder were smaller than that of healthy subjects during vertebrae shiritori task, but there was not significantly difference between two groups during word fluency task.

Conclusion: These data suggested that the examination using word generation task measured by multi-channel NIRS were useful for a psycho-physiological index of patient with major depressive disorder.

P-14-057 | Medication taking behavior and its correlates in patients with comorbidity of depression and type 2 diabetes

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Objective: The objective of this study was to examine the differences between depressed and non-depressed patients with diagnosis of type 2 diabetes (T2DM) in sociodemographic, clinical characteristics, metabolic control and medication taking behavior as well as correlation between medication taking behavior and other examined variables.

Methods: A group of depressed diabetic patients comprising those with major depressive episode, first or repeated (ICD-10) and endocrinologist-diagnosed T2DM, duration ≥ 5 years on oral, insulin therapy or both (N = 35) and non-depressed ones (N = 32) (67 in total) of both genders (< 65 years) were included in this cross-sectional study. The Mini international Neuropsychiatric interview (MINI) were used to establish diagnosis. The Beck Depression Inventory (BDI; cut off ≥16) for self-assessment of depression severity, The Medical Adherence Questionnaire (MAQ) for self-assessment of medication taking behavior and The Problem Areas in Diabetes (PAID) for self-assessment of diabetes distress were also used. We performed laboratory and non-laboratory measures to assess metabolic control and the presence of metabolic syndrome. The exclusion criteria were determined.

Results: Significantly higher frequency of psychiatric heredity and neuropathy in depressed diabetic patients in comparison to non-depressed ones were found. Depressed diabetic patients had significantly higher MAQ (Mann-Whitney U test) and PAID score (Student’s t test) in relation to non-depressed ones. MAQ score significantly positively correlated with PAID score and number of metabolic components in depressed diabetic patients. In non-depressed diabetic patients significantly positive correlation between MAQ score and frequency of patients on oral hypoglycemic therapy and coronary artery diseases were found (Fpearson’s Correlation).

Conclusion: Depressed diabetic patients had significantly higher frequency of diabetic neurological complications, significantly more problematic medication taking behavior and significantly higher level of diabetes distress in comparison with non-depressed ones. Suboptimal medication adherence was significantly associated with elevated diabetes distress and metabolic risk in depressed diabetic patients.
Resistant depression in elderly

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Objective: Knowing the most effective therapeutic strategy used in Brief Hospitalization Unit (UHB) for elderly patients with depression who just entering after several treatments in the period between 2005 and 2010.

Methods: We performed a descriptive study using data based on medical records of patients over 65 years with a diagnosis of depression for those who have used therapeutic alternatives are not effective should be finally hospitalized in University Hospital Prince UHB de Asturias de Alcalá de Henares (Madrid). We use the variables: gender, age, socio-demographic data, previous antidepressant treatments, comorbidities, length of stay, type of therapeutic strategy used.

Results: We have found that treatment strategies are used ECT and augmentation with atypical antipsychotics.

Conclusion: We have found that treatment strategies are used ECT and augmentation with atypical antipsychotics.

BDNF, NTf3, NTf4 and GDNF neurotrophic factors

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Objective: Neurotrophic factors signaling disturbances have been implicated in the etiopathogenesis of mood disorders. Antidepressant treatment has been shown to influence neurotrophic factor expression in different brain areas. The aim of this study was to analyze Brain-Derived Neurotrophic Factor (BDNF), Neurotrophin 3 (NTF3), Neurotrophin 4 (NTF4) and Glial-Derived Neurotrophic Factor (GDNF) serum protein levels in first-episode drug-naïve depressed women during 8-weeks treatment with sertraline or venlafaxine. Correlations with clinical variables have been performed.

Methods: 30 drug-naïve first-episode women (mean age 38 years, SD 10.3) with depression episode were recruited. Diagnosis was made according to DSM-IV criteria using Structured Clinical Interview for DSM-IV SCID. Severity of depression was evaluated using 17-item Hamilton Depression Rating Scale (HDRS) at the beginning of antidepressant therapy and after 8 weeks of treatment. Patients were administered with sertraline (n = 16) or venlafaxine (n = 14). Control group consisted of 30 healthy, age-matched women. BDNF, NTf3, NTf4 and GDNF serum levels were measured using ELISA method.

Results: We have found lack of differences between BDNF, NTf3, NTf4 and GDNF serum levels in first-episode drug-naïve women compared to the control group. There were no changes in BDNF, NTf3, NTf4 and GDNF serum levels during 8-week treatment with sertraline or venlafaxine. No correlation have been found between BDNF, NTf3, NTf4 and GDNF serum levels and depression severity measured with Hamilton Depression Rating Scale as well as, age, BMI, smoking status, family history of mental illness, psychosocial stressor prior to onset and suicidal ideations. We have observed strong positive correlation in NTF3, NTF4 and GDNF serum protein levels in the studied group.

Conclusion: In our study we did not find differences in serum BDNF, NTf3, NTf4 and GDNF levels in first-episode drug-naïve depressed women during treatment nor correlations with clinical variables. Limitation of the study was relatively small sample size.

Magnetic deficiency induces anxiety- and depression-like behavior and metabolic dysfunction in C37Bl/6J mice

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Objective: There are indications that balance of magnesium (Mg) ions may regulate mood. Magnesium deficiency is also linked with altered glucose metabolism and an inflammatory response in the gut. In addition, mood disorders have been linked to a dysfunctional metabolism. In this study we investigated the involvement of Mg in regulating depression- and anxiety-like behaviour and metabolism, by using mice that have been deprived of dietary Mg and studying several behavioral and metabolic markers.

Methods: We examined the behavioural effects of Mg deficiency (deprivation of dietary Mg for 6 weeks) in mice through depression- and anxiety phenotyping experiments, namely the forced swim test and light-dark box respectively. We determined the behavioural effects 30 minutes after treatment with imipramine (20 mg·kg⁻¹), diazepam (2 mg·kg⁻¹) and ketamine (3 mg·kg⁻¹). The glucose tolerance test was used to assess metabolic function in Mg deficient mice.

Results: We found that, compared to control (n = 10), mice receiving Mg deficient diet (n = 10) (10% RDA), were more immobile in the forced swim test (p < 0.01), which suggested depression-like behavior...
which was significantly attenuated by imipramine and ketamine (p<0.001 and p<0.001 respectively). Mg deficient mice also displayed anxiety-like behavior in the light-dark box (p<0.01) compared to control, although diazepam did not significantly reverse this behaviour. The glucose tolerance test showed an elevation in glucose response after 30 minutes in Mg-deficient mice compared to the controls (p<0.05).

Conclusion: Insufficient dietary Mg may contribute to depressive and/or anxiety symptoms, as well as metabolic dysfunction. This data warrant further investigation into whether supplementation with Mg may relieve these disorders.

P-14-064 Effects of subanesthetic doses ketamine on the serotonergic neuronal system in conscious monkey brain

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Objective: The antidepressant effects of subanesthetic doses of ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist, are well known. The serotonin transporter is a target protein for many antidepressants. Hence, the aim of present study was to determine the effects of subanesthetic doses of ketamine on serotonergic activity in the conscious monkey brain.

Methods: The brains of three young adult monkeys were scanned using [11C]DASB for the serotonin transporter (SERT) and [18F]MPPF for the serotonin 1A receptor (5-HT1AR). Ketamine hydrochloride in doses of 1.5 and 1.5 mg/kg or vehicle was infused intravenously over 40 min. PET scans were taken after the end of ketamine infusion. Heart rate and blood pressure were monitored throughout the study. Arterial blood sampling was conducted during the PET scan. Time-activity curves (TAC) of metabolite-corrected arterial plasma were used as the arterial input function. Logan plot analysis for each TAC and each brain region was used for calculation of [11C]DASB and [18F]MPPF binding to SERT and 5-HT1AR, respectively.

Results: No significant changes in heart rate and blood pressure were observed with either dose of ketamine. Furthermore, ketamine infusion did not induce any substantial change in the plasma levels and metabolism of each radioligand. With ketamine infusion, the binding of [11C]DASB to SERT was reduced in a dose dependent manner. The binding of [18F]MPPF to 5-HT1AR tended to reduce compared with the control vehicle.

Conclusion: The present results from this conscious monkey PET study suggest that one of the mechanisms for the antidepressant efficacy of subanesthetic doses of ketamine is via modulation of the brain serotonergic neuronal system.

P-15. Animal Models

P-14-065 Comparison the efficacy between paroxetine and sertraline augmented with aripiprazole in patients with refractory major depressive disorder

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Objective: To determine the effects of subanesthetic doses of ketamine on serotonergic activity in the conscious monkey brain.

Methods: The brains of three young adult monkeys were scanned using [11C]DASB for the serotonin transporter (SERT) and [18F]MPPF for the serotonin 1A receptor (5-HT1AR). Ketamine hydrochloride in doses of 1.5 and 1.5 mg/kg or vehicle was infused intravenously over 40 min. PET scans were taken after the end of ketamine infusion. Heart rate and blood pressure were monitored throughout the study. Arterial blood sampling was conducted during the PET scan. Time-activity curves (TAC) of metabolite-corrected arterial plasma were used as the arterial input function. Logan plot analysis for each TAC and each brain region was used for calculation of [11C]DASB and [18F]MPPF binding to SERT and 5-HT1AR, respectively.

Results: No significant changes in heart rate and blood pressure were observed with either dose of ketamine. Furthermore, ketamine infusion did not induce any substantial change in the plasma levels and metabolism of each radioligand. With ketamine infusion, the binding of [11C]DASB to SERT was reduced in a dose dependent manner. The binding of [18F]MPPF to 5-HT1AR tended to reduce compared with the control vehicle.

Conclusion: The present results from this conscious monkey PET study suggest that one of the mechanisms for the antidepressant efficacy of subanesthetic doses of ketamine is via modulation of the brain serotonergic neuronal system.

P-14-066 Enhanced perception of negative emotion in depression: A preliminary study

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Objective: It has been hypothesized that biases in the processing of emotional stimuli may play an important role in interpersonal difficulties in patients with depression. A good interpersonal relationship requires capacity of context-based emotional processing. However, previous studies investigating emotion perception in patients with depression were mostly focused on perceiving facial or bodily expressions without social context. In the present study, we used movie scenes to examine context-based emotional processing of patients with depression.

Methods: A set of movie clips lasting 10 to 20 seconds with various emotional situations was presented to a total of 33 participants, grouped by depression (N=7) or healthy non-psychiatric individuals (N=16). The participants were asked to rate 5-point Likert scale, ranging from 0 (never expressed) to 5 (very highly expressed), on 11 kinds of emotions including happy, love, humor, sympathy, sorrow, fear, embarrassment, anxiety, anger, hatred, and greed. The symptom severity of depression was measured by PHQ-9. The degree of perception in each kind of emotion was compared between two groups using independent samples t-test.

Results: While there was no group difference for positive emotions, the patients with depression showed enhanced perception extensively for negative emotions including fear (p<0.01), anxiety (p<0.05), anger (p<0.05) and hatred (p=0.07) to the negative emotional scene.

Conclusion: The findings suggest that negatively biased emotional processing is a salient feature, which can explain interpersonal difficulties in depression.

P-15. Animal Models

P-15-001 Morphological studies on the distribution and expression of neuropeptide S and its receptor after REM sleep deprivation in rat

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Objective: The recently described 20 amino acid neuropeptide S (NPS) is involved in the modulation of arousal. Here we describe a detailed anatomical mapping of NPS expressing neurons in the rat brainstem, examining the expression of NPS and NPSR1 after a 72-hour REM-sleep deprivation and a subsequent 3-hour rebound sleep.

Methods: We applied the single-platform-on-water (flower pot) method. NPS and NPSR1 expression was detected by quantitative in situ hybridization. The NPS immunoreactivity (IR) was visualized by immunohistochemistry and quantified by densitometry.

Results: The highest expression of NPS was found in the peri-coerulear region and in a cell cluster close to the Kölliker-Fuse nucleus (KF cluster). A moderate expression level was detected in the lateral parabrachial nucleus and around the fourth ventricle. The NPS expression was significantly increased in the peri-coerulear cluster but not in the LPN or KF clusters after the deprivation. There was no such significant increase in the large pot (stress control) animals. The
expression level in the peri-coerulear cluster returned close to control levels after the 3-hour rebound sleep. The NPS IR fiber density was significantly decreased after the sleep deprivation in the preoptic region of the hypothalamus. The expression of NPSRI did not alter significantly in the preoptic region or in the rhomboid thalamic nucleus.

Conclusion: Our results suggest a differential response of NPS expressing neuron clusters after sleep deprivation and emphasize the role of the peri-coerulear cluster in the modulation of arousal. This modulation is, however, not associated with changes of NPSRI expression. The decreased NPS fiber density suggests extensive release of NPS in the preoptic region after sleep deprivation. As this is a sleep-promoting region, the release of NPS during the forced wakefulness raises the possibility that NPS facilitates the arousal by an inhibitory action here.

**P-15-002**

Modulation of biogenic amines, substance p and neuropilin factor produces chronic muscular pain and tactile allodynia accompanied by depression-a putative animal model of pain-depression dyad

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Objective: The present study was designed to investigate the effect of para-chlorophenylalanine (PCPA) on modulation of biogenic amines, Substance P and nerve growth factor on the pain-depression dyad to establish a new rodent model and support the possibility of a relationship and specifically address the neurogenic mechanism that might be involved in this syndrome.

Methods: Pain and depression was induced by the intraperitoneal administration of PCPA (350 mg/kg). The effects of different doses of duloxetine (3–30 mg/kg; p.o.), pregabalin (3–30 mg/kg; p.o.) and diloctenac (1–10 mg/kg; p.o.) treatment was evaluated for behavioural (pain and depression), neurochemical (dopamine, nor-epinephrine, and 5-hydroxytryptamine) and molecular alterations (Substance P and nerve growth factor) induced by PCPA.

Results: Administration of PCPA (350 mg/kg) led to a significant decrease in nociceptive threshold as evident from reduced paw withdrawal threshold in Randall Sellitto and von-Frey hair test as well as marked increase in immobility time in forced swim test. This behavioural deficit was integrated with decrease in biogenic amines (dopamine, nor-epinephrine, and 5-hydroxytryptamine) along with increased Substance P and nerve growth factor levels in both brain and serum of the PCPA administered rats. Pregabalin and duloxetine ameliorated the behavioural deficits associated with pain and depression by restoring behavioural, neurochemical and molecular alterations against PCPA-induced pain—depression dyad in rats.

Conclusion: The validity of the use of this PCPA model is demonstrated from three different aspects, i.e., face validity (manifestation of chronic pain and depression), construct validity (dysfunction of biogenic amines Substance P and nerve growth factor-mediated CNS pain control is involved), and predictive validity (similar responses to treatments used in pain and depression).

**P-15-003**

Substance P1-7-amide – a peptide-derived molecule with potential effects on chronic pain and opioid withdrawal

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Objective: The neuroactive peptide substance P (SP) is well recognized for its critical role in the regulation of many processes in the central nervous system. SP has received particular interest for its involvement in pain processing and the development of opioid tolerance and dependence. Following neurokinin NK-1 receptor activation SP is degraded into several fragments, some of which retain biological activity. One of its major bioactive metabolites, the N-terminal fragment SP1-7, is known to counteract several effects of SP. For instance, the heptapeptide opposes the SP-induced enhancement of pain transmission and expression of opioid withdrawal. In order to find suitable drugs capable of relieving pain and attenuate opioid withdrawal we have synthesized several analogues of SP1-7. One of these, the SP1-7 amide, exhibits higher affinity for the SP1-7 specific binding sites compared to the native heptapeptide, was investigated for its effects on chronic pain and opioid withdrawal using experimental animal models.

Methods: Hypersensitivity to thermal stimuli was investigated in streptozotocin (STZ)-induced diabetic mice. The expression of naloxone-induced opioid withdrawal was evaluated using morphine-tolerant rats.

Results: The results showed that the SP1-7 amide profoundly alleviates signs of thermal hyperalgesia when injected intrathecally in mice with STZ-induced diabetes. In addition, intracerebroventricular administration of the amidated heptapeptide prior to naloxone administration in rats reduced withdrawal signs in a dose-dependent manner. In both cases the effects surpassed those seen for native SP1-7.

Conclusion: To conclude, we have synthesized an analogue to the bioactive N-terminal SP fragment SP1-7 that significantly and more potently than the native compound attenuates the expression of opioid withdrawal and hyperalgesia in rodents through a mechanism that does not involve any neurokinin or opioid receptor. This finding opens for new possibilities to design and develop non-opioid and perhaps also non-peptide mimetics as potential drugs for the treatment of chronic pain and opioid dependence.

**P-15-004**

Stressful experience during peri-adolescent period induces depression-like phenotype in adult mouse

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Objective: Psychologists have long supposed that early life trauma can increase risk for psychiatric disorders. The observation that during early development individuals are susceptible to adverse environmental influences is confirmed by mouse studies. During mouse postnatal development, the third week (peri-adolescent age) represents a critical stage for the maturation of several brain functions. Moreover during this week it is possible to observe high levels of forebrain synaptogenesis. In terms of behavioral development the first rudimentary elements of social play are observable during this week. In spite of the relevance of this developmental period, there are no studies investigating if exposure to stressful experience during this week can induce long term changes on mouse behavior and brain functionality.

Methods: We exposed mouse pups to an adverse experience, consisting in social isolation in novel environment for 25 minutes per day from postnatal day 14 to 21. These mice were tested in the Social Interaction Test (SIT), Forced Swimming Test (FST), and Sucrose Preference Test (SPT) in adulthood.

Results: Stressed mice showed a depression-like phenotype characterized by increased social avoidance in SIT, behavioral despair in FST, and absence of sucrose preference in SPT. Moreover inspired by the hypothesis that environment has long term consequences on behavior, acting through changes at level of epigenetic mechanisms in the brain, we tried to protect the mouse pups from developing the pathological phenotype injecting them with drugs acting on these mechanisms. This pharmacological treatment was partially able to rescue the depression-like phenotype observed.

Conclusion: Our findings confirm that the peri-adolescent age is a critical period for the development of adult mouse behavior and exposure to stressful experiences during this period promotes depression-like phenotype in adulthood through modification of the epigenetic machinery in the brain.

**P-15-005**

Mitochondria plasticity of the hippocampus in a genetic rat depression model after antidepressant treatment

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Objective: A large body of data suggests that mitochondria may play an important role in the pathophysiology of depressive disorders and...
effects of antidepressant therapy. Here, we investigated whether chronic antidepressant treatment of rats induced changes of the mitochondrial number in hippocampus.

Methods: For this report, the effects of the tricyclic antidepressant imipramine were tested in two strains of rats; the Sprague–Dawley and the other strain from the Flinders sensitive line, which has been bred to a phenotype with certain “depressive-like” phenotype. Design-based stereological methods were used to estimate the number and the volume of mitochondria of mitochondria in CA1 stratum radiatum (CA1SR) of the hippocampus.

Results: The results showed that the number of mitochondria in CA1SR was significantly smaller in the FSL saline group compared to the FRL saline group. However, the mean volume of mitochondria was significantly larger in the FSL saline group compared to the FRL saline group. Following treatment, the FSL imipramine group showed a significant increase in the number of mitochondria compared to the FSL saline group. But treatment with imipramine did not induce significant differences in the number of CA1 mitochondria between the SD saline group and SD imipramine group.

Conclusion: In conclusion, our results support the mitochondrial plasticity hypothesis that depressive disorders and the pharmacological treatment thereof may be related to impairments of mitochondrial plasticity in the hippocampus and that antidepressant treatment may counteract the structural impairments.

P-15-006 | The role of the 5-HT1A receptor in the murine 5-HT-syndrome

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Objective: Despite a half century of clinical use and the recognized potential of benzodiazepine dependence, the mechanisms underlying benzodiazepine withdrawal remain insufficiently understood. The aim of the present study was to assess the influence of the non-selective antagonist (flumazenil) and the preferential 1b-subunit selective antagonist (CCt) on the anxiety level after diazepam withdrawal.

Methods: The male Wistar rats were protractedly treated during 21 days with diazepam (2 mg/kg) or solvent. On the testing day, 24 hours after the last injection, animals from the diazepam-treated groups received either antagonist (flumazenil or CCt) or solvent, and animals from the solvent-treated groups received solvent or diazepam. Twenty minutes after administration of treatment on the testing day, single animals were placed in the elevated plus maze in order to assess the level of anxiety.

Results: Two-way ANOVA revealed that animals withdrawn from diazepam spent significantly less time on the open arms than control animals (p=0.023). One-way ANOVA, followed by post hoc test, revealed that administration of flumazenil (10 mg/kg) or CCt (1.25, 5 or 20 mg/kg) reversed the diazepam withdrawal-induced anxiety (percentage of open arm time: p=0.003, p=0.032, p=0.031 and p=0.014 compared to the diazepam-withdrawn group, respectively). Concomitant administration of antagonists (10 mg/kg flumazenil, or 1.25, 5 or 20 mg/kg CCt) induced an anxiolytic effect comparable to that observed after acutely administered diazepam (percentage of open arm time: p=0.142, p=0.087, p=0.543 and p=0.200, respectively).

Conclusion: The present study demonstrated that administration of the 1b-selective antagonist CCt or non-selective antagonist flumazenil could prevent the withdrawal-induced anxiety and also induce an anxiolytic-like effect. Moreover, presented results have suggested that mechanism of preventing the withdrawal-induced anxiety involves the antagonism at 1b-containing GABAA receptors.

P-15-007 | Effects of novel dopaminergic derivates on depression-like behavior: A pilot study

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Objective: Recent evidences suggest that the dysfunction of the central dopaminergic pathways may be a critical component of the neurobiological basis of depression. The effects of novel dopaminergic substances, 3,4-dimethoxyphenylethylamine derivates, on experimental model of depression were studied in male rats after acute or chronic administration in comparison to those of the classical anti-depressant, clomipramine.

Methods: The novel DA derivates, PK-2111, PK-2112, PK-2123, PK-2126 (0.1, 1.0, 10.0 mg/kg, s.c.) and clomipramine (50.0 mg/kg) were injected acutely (1 h prior to behavioral testing) or chronically (for 21 days, the last injection being made 1 h prior to behavioral testing) in animals subjected to the forced swimming test (FST) and the locomotor activity test.

Results: In dose of 0.1 mg/kg, PK-2112 exerted depressant-like effect, while in doses of 1.0 or 10.0 mg/kg PK-2112 exerted anti-depressant-like effect as compared with the control group. Chronic treatment with PK-2123 or PK-2122 (0.1, 1.0 or 10.0 mg/kg) produced antidepressant-like effect which was significant as compared with control group and group treated with clomipramine. Also, chronic treatment of PK-2112 in high dose of 10.0 mg/kg induces anti-depressant-like effect as compared with the control group, and this effect was less effective than it in a doses of 0.1 and 1.0 mg/kg.

Conclusion: These results suggest that PK-2126 independently from dose and PK-2112 in the middle and high doses may be effective in experimental model of depression in rats when administered acutely, PK-2111, PK-2112 or PK-2123 may be effective in experimental model of depression in rats when administered repeated.
forms of cognitive flexibility remains unexplored. Here, we investigated the contribution of the NAc core and shell to probabilistic reversal learning, using an operant task developed for rats.

Methods: Over daily sessions of 200 discrete-choice trials, rats were required to press one of two levers for food reward. One lever initially designated ‘correct’, delivered reward 80% of the time, and the other ‘incorrect’ lever delivered reinforcement on only 20% of trials. After 8 consecutive ‘correct’ responses, reinforcement contingencies were reversed, and this pattern continued throughout the daily session. After ~10 days of training, rats received counterbalanced microinfusions of saline or GABA A/B agonists muscimol/baclofen into the NAc core or shell on separate test days.

Results: Inactivation of the shell markedly impaired probabilistic reversal performance, reducing the number of reversals completed and increasing errors. These effects were accompanied by a selective decrease in win-stay strategy, indicating a reduced sensitivity to positive reinforcement. In contrast, inactivation of NAc core did not impair reversal learning, but did increase the number of incomplete trials.

Conclusion: These results indicate that the NAc shell, but not core, plays a key role in facilitating reward sensitivity and cognitive flexibility in situations of reward uncertainty. Furthermore, they raise the possibility that impaired cognitive flexibility associated with depression may be due in part to abnormal function in the ventral striatum.

P-15-010 Growth hormone treatment improves spatial memory in rats

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Objective: Growth hormone (GH) is a polypeptide with a wide range of functions in the periphery and also in the brain. Replacement therapy with recombinant human GH (rhGH) has been demonstrated to alleviate cognitive deficiencies and improve memory in patients with growth hormone deficiency. Furthermore, GH has been suggested to be involved in neuroprotection and neuroregeneration and has recently been shown to counteract opioid-induced apoptosis in hippocampal cells. Anabolic androgenic steroids (AAS) have been demonstrated to affect several peripheral organs and also several CNS-related behaviors such as aggression, anxiety, depression and cognitive functions. In the present study, we investigated the effects of GH on rats treated with nandrolone decanoate.

Methods: Male Wistar rats received the steroid (15 mg/kg) or peanut oil every third day for three weeks and were subsequently treated with rhGH (1.0 IU/kg) or saline for ten consecutive days. During the GH/saline treatment spatial learning and memory were tested in the Morris water maze (MWM), where the rats had five training days with four swims each day. Two days after the last training session a probe trial was performed.

Results: The results demonstrated a significant impact of GH on spatial memory. In general, the behavior of the AAS animals was unaffected by GH treatment suggesting that the underlying mechanisms does not seem to be directly coupled to the GH signaling system. Both GH and AAS demonstrated important effects on body weight gain and GH was able to counteract the reduction of weight gain induced by AAS.

Conclusion: To conclude, GH improved performance in the MWM, suggesting an important impact of GH on memory functions.

P-15-011 Effects of gastrodia elata blume on spatial memory and choline acetyltransferase and acetylcholinesterase in a rat model of Alzheimer’s disease

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Objective: Gastrodia elata Blume (GEB) is a herb used in traditional Chinese medicine to treat dizziness, paralysis, and epilepsy. Here, we investigated the effects of GEB on spatial memory in a rat model of Alzheimer’s disease (AD) and on choline acetyltransferase (ChAT) expression and acetylcholinesterase (AChE) activity in several regions of the model rat brain.

Methods: A rat AD model was established by bilateral injection of amyloid-beta peptide (Aβ25-35) into the hippocampus. The AD model rats were subsequently treated daily either with 0.5% cellulose (Aβ25-35/cellulose group), with 500 mg/kg GEB (Aβ25-35/GEB500 group), or with 1000 mg/kg GEB (Aβ25-35/GEB1000 group). Vehicle rats received saline injection followed by daily treatment with 0.5% cellulose. After 6 weeks, spatial memory was assessed using the Morris water maze test, and ChAT expression and AChE activity in the prefrontal cortex, medial septum, and hippocampus were measured using Western blotting and a commercial AChE assay kit, respectively.

Results: In the probe trial, significant differences between the Aβ25-35/cellulose group and the vehicle, Aβ25-35/GEB500, and Aβ25-35/GEB1000 groups were observed in terms of both time spent and distance traveled in the target quadrant. The Aβ25-35/cellulose rats also had significantly lower ChAT protein levels in the hippocampus and higher AChE activity levels in the prefrontal cortex, medial septum, and hippocampus than the other rats.

Conclusion: Intrahippocampal injection of Aβ25-35 peptide impairs spatial reference memory and has detrimental effects on ChAT expression and AChE activity in the brain. The long-term administration of GEB acts to reverse these effects, suggesting that it has potential as a treatment for AD.
abnormalities, most of which were reversed by atypical antipsychotic drugs, and that PACAP gene SNPs were associated with schizophrenia. These results suggest that PACAP might be a risk factor for psychiatric disorders including schizophrenia, however, a pathogenic pathway involving PACAP signaling remains unknown. Recent evidence implicates abnormal spine morphology in the pathogenesis of psychiatric disorders. In this study, we therefore examined if PACAP-/- mice have such an abnormality. In addition, since serotonin (5-HT7) receptors have been implicated in psychiatric disorders and as a promising novel target of antipsychotic drugs, we also examined if a similar feature of 5-HT7 antagonism is observed in PACAP-/- mice to address predictive validity of the mutants as a model for psychiatric disorders.

Methods: After Golgi staining, dendritic spine morphology was analyzed in hippocampal CA1 neurons in PACAP-/- and wild-type littermate mice. The number of postsynaptic density protein (PSD)-95-immunolabeled synaptic puncta was determined in primary cultured hippocampal neurons from both genotypes. For behavioral analyses, mice were subjected to an open field test, the Porsolt forced swimming test, and a Y-maze working memory task.

Results: Golgi staining of hippocampal CA1 neurons revealed dendritic spines are morphologically immature in PACAP-/- mice. In primary cultured neurons from the mutant mice, the volume of PSD-95-labeled synaptic puncta was decreased. SB-269970, a selective 5-HT7 antagonist, significantly ameliorated the abnormal psycho-motor behavior and impaired working memory performance in PACAP-/- mice.

Conclusion: The present results implicate PACAP signaling in synaptic pathology and provide predictive validity of PACAP-/- mice in modeling psychiatric disorders. Taken together, it is suggested that the PACAP signaling pathway may emerge as a potential therapeutic target for psychiatric disorders.

P-15-014 Toxicity effect of cisplatin-treatment on cerebellar purkinje cells at during lactovirus in neonate mice
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Objective: Cisplatin is a Vina Alkaloid which is a cell-cycle-specific agent and blocks. Cisplatin is a drug to treat certain types of cancer. Although genetic neoplasia can be supposed soon after cisplatin treatment, its side effects, although uncommon, may prevent the drug from becoming a standard of therapy. At lactation period, it is not known whether this drug is excreted in breast milk. In this research we studied the effect of cisplatin on Cerebellar Purkinje cells at During Lactovirus in Neonate Mice.

Methods: 50 Female Mice at lactation period divided randomly to control & experimental groups. Mice of experimental group were injected by cisplatin (10 mg/kg/IV for one dose on days 1th, 8th, 15th of lactation period. One week after the inject, neonate brains (21days old) fixed with perfusion procedure & removed from skull. Then cerebellum embedded in 10% formalin solution. The 5-micron sections taken from cerebellum of neonate were stain by H&E & Gold chloride. Density & volume of purkinje cells & distance of cells from each other studied with light microscopy & digital camera. One other way, T-Test were used for analysis (P <0.05).

Results: The body weight in experimental group reduced in contrast to control group. The volume of purkinje cells in experimental group were increased than the control group. The number of cells were a few decreased and the distance of cells in experimental group a few increased.

Conclusion: Cisplatin effect on neonate purkinje cells is excreted in breast milk with histopathologic changes and decrease of number of the purkinje cells.

P-15-015 Toxicity effect of cisplatin-treatment on mice cerebellum formation
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Objective: Cisplatin is an alkald that is administered to inhibit the division of malignant tumor cells. Occurrence of malformation in embryos has been proved in treated pregnant mothers. However, there was no adequate information about its toxic effect on cerebellar structures of newborns. Considering the passage through the Blood Brain Barrier and its cytotoxic effect, the destructive effects of cisplatine on the formation of cerebellum in newborns was demonstrated.

Methods: In this study 30 pregnant female mice were randomly divided in two groups (control and experimental). The treated group received 10 mg/kg at days 8 and 13 of pregnancy (I.P). At the end of pregnancy, 60 newborns (control and experimental groups) were selected for examination by H&E staining. T-test and SPSS software were used to analyze data obtained from quantifying parameters.

Results: Morphologic observations showed significant decrease in weight, skull size and newborn growth (P<0.05). On microscopic observation, cerebellar white matter of cerebellum showed decreased compaction of glial cells accompanied by deficiency in myelination of nervous fibers. Occurrence of apoptosis was seen in epithelial cells of choroid plexus and in white matter glial cells.

Conclusion: Based on these results, we can conclude that the effects of anti-mitosis drugs can include inhibitory activity on the proliferation of cerebellar cortical cells. The results also show induction of apoptosis in choroid plexus cells and cerebellum.

P-15-016 Protective effects of betaine on lipopolysaccharide-induced memory impairment in mice and the involvement of GABA transporter 2
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Objective: Betaine (glycine betaine or trimethylglycine) plays important roles as an osmoregulator and a methyl donor in animals. While betaine is reported to suppress expression of proinflammatory molecules, glial markers, and GABA transporter 2 and reduce oxidative stress in aged rat kidney, the effects of betaine on the central nervous system are not well known. In this study, we investigated the effects of betaine on lipopolysaccharide (LPS)-induced memory impairment and on mRNA expression levels of proinflammatory molecules, glial markers, and GABA transporter 2 (GAT2), a betaine/GABA transporter.

Methods: Mice were continuously treated with betaine for 13 days starting 1 day before they were injected with LPS, or received subacute or acute administration of betaine shortly before or after LPS injection. Then, their memory function was evaluated using Y-maze and novel object recognition tests 7 and 10–12 days after LPS injection (3 μg/mouse, i.c.v.), respectively. In addition, mRNA expression levels in hippocampus were measured by real-time RT-PCR at different time points.

Results: Repeated administration of betaine (0.163 mmol/kg, s.c.) prevented LPS-induced memory impairment. GAT2 mRNA levels were significantly increased in hippocampus 24 hr after LPS injection, and administration of betaine blocked this increase. However, betaine did not affect LPS-induced increases in levels of mRNA related to inflammatory responses. Both subacute administration (1 hr before, and 1 and 24 hr after LPS injection) and acute administration (1 hr after LPS injection) of betaine also prevented LPS-induced memory impairment in the Y-maze test.

Conclusion: These data suggest that betaine has protective effects against LPS-induced memory impairment and that prevention of LPS-induced changes in GAT2 mRNA expression is crucial to this ameliorating effect.

P-15-017 Behavioral profiling for voluntary ethanol intake and ethanol seeking in male outbred rats
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Objective: The development of alcohol use disorder (AUD) is dependent on the interaction between genetics and environment, mirrored by the individual variation in voluntary ethanol intake and seeking between, and within, outbred rat strains. We used the Novel Cage Test (NCT) to evaluate the emotional reactivity and stress coping styles in relation to ethanol consumption in Rcc Wistar, Lister Hooded and Long Evans rats.

Methods: The latency time, frequency and duration of locomotor, explorative, risk assessment and anxiety-like behaviors were calculated from 5 min of spontaneous behavior in a box. The rats were...
**P-15-018** Effect of hemantane on depressive-like behavior and memory in rat model of parkinson’s disease

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**Objective**: Non-motor symptoms precede motor disturbances in Parkinson’s disease. The aim of the study was to evaluate the effects of the novel antiparkinsonian drug, Hemantane (N-(5-hydroxy-nicotinoyl)-L-glutamate) and Amantadine sulinate in methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned rats, a model of the pre-motor stage of Parkinson’s disease.

**Methods**: Male white outbred rats were distributed into four groups: 1st – sham operated, 2nd – MPTP-lesioned, animals of the 3rd and 4th groups were injected intraperitoneally with Hemantane (10 mg/kg) or Amantadine (20 mg/kg) daily starting 5 days before the MPTP infusion and throughout the study. MPTP (100 µg/1 µl) was infused bilaterally into substantia nigra pars compacts (SNc). Three weeks after surgery, rotarod, modified forced swimming and passive avoidance tests were performed.

**Results**: No motor alterations were determined in the rotarod test in animals of all groups. In the swimming test, animals of group 2 presented depressive-like behavior; swimming activity was significantly reduced (38%), and immobility increased 10-fold compared to group 1. Hemantane completely normalized immobility and swimming duration. Amantadine significantly decreased immobility. But its effect was 3 times less than that of Hemantane. In passive avoidance test, impairment of the hole relex was determined in 50% of MPTP-lesioned rats, which did not enter the dark compartment at the training session. The other group 2 animals demonstrated impaired acquisition in retention trial. Hemantane and Amantadine prevented these alterations.

**Conclusion**: Bilateral injection of MPTP into the SNc induced depressive-like behavior and impaired learning and memory in rats. Hemantane and Amantadine are able to prevent or reduce these disturbances. The effect of Hemantane was more pronounced than that of Amantadine.

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**P-15-019** Perinatal NMDA receptor blockade causes lasting impairments to the synaptic and intrinsic physiology of fast-spiking interneurons in a developmental model of schizophrenia

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**Objective**: NMDA antagonists induce psychotic states that closely resemble schizophrenic symptoms and are therefore widely used to model schizophrenia (SZ). Neonatal mice sub-chronically treated with NMDA antagonists incur long-lasting behavioral deficits, and repeated exposure decreases staining of biochemical markers of inhibition. However, the impact on inhibitory physiology is less clear. Thus, the aim of this study is to determine the impact of perinatal NMDA receptor blockade on cortical inhibitory neurotransmission.

**Methods**: Whole-cell patch clamp electrophysiology was performed on fast-spiking/parvalbumin-positive interneurons (FS cells) from cortical brain slices of adult animals treated with the MK-801 as neonates. Immunohistochemical analyses was also performed.

**Results**: Neonatal MK-801 treatment caused a four-fold reduction in near-threshold spike latency of FS cells; a 61% increase in membrane resistance; and a 23% increase in AP 1/2 width. The AP threshold of FS cells from MK-801 treated animals was strongly dependent on the amplitude of the depolarizing current, which did not occur in vehicle treated animals. Consistent with these findings, immunohistochemical analysis revealed dramatic reductions in the somatic expression of the potassium channel, Kv1.1. MK-801 treatment also disrupted excitatory synaptic input to FS cells. We found that thalamo-cortical synapses on FS cells were twice as likely to express functional NMDA current in MK-801 treated animals (80% MK-treated vs. 40% vehicle-treated), and immunohistochemical analyses revealed a substantial increase in the expression of the NR2B subunit in the soma of FS cells. Electrically evoked responses from the thalamocortical synapses of MK-801-treated animals contained 300% more NR2B-mediated current than vehicle-treated controls.

**Conclusion**: Together these data demonstrate that transient NMDA receptor blockade during early development elicits changes in the physiology of cortical FS cells that persist into adulthood, and may provide a physiological basis for the behavioral deficits observed in this model.

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**P-15-020** Cognition improving and antioxidant effects of asparagus racemosus wild in mice

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**Objective**: In the present study, nootropic activity of aqueous extract of roots of A. racemosus (AR) was studied in mice.

**Methods**: Elevated plus maze and passive avoidance paradigm were employed to evaluate learning and memory. Scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) were used to induce amnesia in mice. AR (50 and 100 mg/kg, p.o.) significantly attenuated amnesic deficits induced by scopolamine, diazepam and natural aging. To delineate the possible mechanism through which A. racemosus elicits anti-amnesic activity, effects on whole brain acetylcholinesterase activity, brain lipid peroxide levels and antioxidant enzymes activity were estimated.

**Results**: AR significantly decreased acetylcholinesterase activity and increased brain levels of thiothreitol acid reactive substances and glutathione peroxidase activity. These findings suggest that the roots of A. racemosus exert a preventive effect against cognitive deficits induced by scopolamine, diazepam and natural aging.

**Conclusion**: The memory improving activity of A. racemosus may be attributed to its antioxidant, neuroprotective, pro-cholinergic and anti-acetylcholinesterase properties and can be of enormous use in delaying the onset and reducing the severity of Alzheimer's disease.

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**P-15-021** Behavioral and neurochemical effects of calcium salt of N-(5-hydroxy-nicotinoyl)-L-glutamate in accelerated aging male mice SAMP10

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**Objective**: Senescence-accelerated mouse prone 10 (SAMP10) strain is one of the models for study of neurodegeneration associated with aging. It is known that SAMP10 mouse over 6 mo exhibits behavioral disorders (memory deficiency, increased anxiety, depressive-like responses) and shifts of neurotransmitter contents in brain structures. Novel neuroprotective substance calcium salt of N-(5-hydroxy-nicotinoyl)-L-glutamate (Ampassae®) (AMPS) modulates an activity of the glutamate receptors AMPA-subtype and possesses anti-hypoxic, anti-ischemic and anti-aminergic activities in standard rodent’s tests.
**P-15. Animal Models**

**Methods:** The aim of the study was to investigate AMPs (5–20 mg/kg) effects on behavior and neurotransmitter amino acids contents in male SAMP10 of 9–16 mo. In behavioral experiments memantine (2 mg/kg), a low-affinity noncompetitive antagonist of glutamate receptors NMDA-subtype, used as reference drug. The substances were injected intraperitoneally once per day 30 min before testing. Memory was studied in one-trail passive avoidance step-through paradigm, anxiety − elevated plus maze, depression-like response − in the Porsolt’s forced swimming test. In the neurochemical assay AMPs (5 mg/kg) was administered intraperitoneally for 5 days, the last injection − 30 min before the animals were decapitated. The neurotransmitter amino acids glutamate, aspartate, taurine, glycine and gamma-aminobutyric acid contents were determined in frontal cortex, hypothalamus, striatum, hippocampus by HPLC/PD.

**Results:** AMPs (20 mg/kg) completely eliminated the memory deficiency and anxiety and had no effect on the animal’s depression-like behavior. Memantine provided a greater corrective action on emotion than on the memory in the mice. AMPs increased the level of all recorded amino acids in striatum and glutamic acid and glycine levels in hypothalamus.

**Conclusion:** Thus, AMPs decreases neurochemical shifts in the animal brain, especially in striatum, one of the structures most prone to atrophy in mice SAMP10, and the mechanism may at least partly underlie its neuroprotective effects in SAMP10.

**P-15-022** Local GluN2B antagonism in responses to stress and anxiety- and depression-related behavior

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**Objective:** Increasing evidence points to a role for N-methyl-D-aspartate receptors (NMDARs) in the treatment of mood and anxiety disorders. Systemic administration of drugs acting as antagonists at the GluN2B subunit of the NMDAR has fast-acting clinical efficacy in depression, and reduces anxiety- and depression-related behaviors in rodent preclinical assays. However, the specific brain regions mediating these effects remain to be determined. Prior studies have shown that acute antidepressant-related effects of systemically-delivered GluN2B antagonists parallel synaptic changes in the medial prefrontal cortex (mPFC) (Li et al., 2010), while gene deletion of GluN2B in corticohippocampal principal neurons attenuates depression-related responses to repeated swim stress (Kiselyczynk et al., 2011). Here we examined the role of GluN2B localized in the mPFC and basolateral amygdala (BLA) in mediating depression- and anxiety-like behaviors.

**Methods:** Male C57BL/6J mice were cannulated to bilaterally infuse the GluN2B-selective antagonist, Ro 25−6981, into either mPFC or BLA prior to testing in the light/dark exploration test for anxiety-like behavior or the forced swim test for depression-related behavior. To compliment these pharmacological studies, mPFC GluN2B expression was reduced via lenti viral-mediated knockdown and mice were tested for depression-related responses to repeated swim stress.

**Results:** Results showed that Ro 25–6981 infused into mPFC, but not BLA, reduced depression-related behavior. By contrast, there were minimal effects of Ro 25–6981 infused into mPFC or BLA on anxiety-like behavior.

**Conclusion:** Collectively, these data are consistent with the mPFC as a major effect-locus for the antidepressant-like effects of GluN2B antagonists. This has implications for understanding the mechanisms underlying the fact-acting antidepressant effects of these drugs in human patients.

**P-15-023** The influence of selective serotonin reuptake inhibitors (SSRI) and 3,4-methylenedioxymethamphetamine (MDMA) on neurogenesis in the adult rat hippocampus

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**Objective:** There are two regions of high density cell division in the adult mammalian brain that produce new neurons throughout adulthood: the subventricular zone of the lateral ventricle (SVZ) and the subgranular zone of the dentate gyrus in the hippocampus (SGZ). We examined the influence of two serotonin reuptake inhibitors (SSRI – fluoxetine, citalopram) and a serotonin releaser 3,4-methylendioxymethamphetamine (MDMA) on proliferation and maturation of neuronal cells in the hippocampus of adult rats.

**Methods:** Adult male Wistar rats were administrated with the tested substances (citalopram 10 mg/kg i.p., fluoxetine 5 mg/kg i.p., MDMA 5 mg/kg i.p., saline) for 3 (proliferation) or 21 (maturation) days. Newly generated cells were labeled with 5-bromo-2-deoxy-uridine (BrdU; 3 × 50 mg/kg s.c.) one day before (maturation) or after (proliferation) drug treatment. Rat brains were perfused (4% paraformaldehyde), sliced (40 μm) and every 6th section was immunohistochemically stained (rat anti-BrdU, Serotec OBT0030). The number of BrdU positive cells was counted under a light microscope (Zeiss Axios Imager Z1).

**Results:** Acute administration of SSRi and MDMA nonsignificantly increased the number of BrdU positive cells in the dentate gyrus compared to the controls. We detect no statistically significant difference in the number of BrdU positive cells after chronic drug administration among the tested groups.

**Conclusion:** According to our result, proliferation of new hippocampal cells is not dependent on the way the serotonin system is stimulated. However, it seems that maturation of neurons is not influenced by the serotonin system, which is in conflict with various studies. These data have an implication for neurogenesis in depression as an underlying factor of antidepressant effect. This study was supported by the grants IGA MHLR NS 10374-3, NS 10375-3, MEYS CR 1MD15715, MHLR MZO58P2005, VG2VS/200 and VG2VS/271.

**P-15-025** Modulation of ketamine-induced oxygen amperometry signals in awake rats − a translational imaging biomarker for novel antipsychotics

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**Objective:** Human functional imaging has had a major impact on cognitive neuroscience, linking brain structure to function. The technique is translatable but rodent fMRI is limited to anaesthetised or restrained animals. In vivo oxygen amperometry is an alternative approach that can measure oxygen changes related to behaviour since it allows real time monitoring of extracellular tissue oxygen in freely-moving animals. Neuroimaging techniques have previously been used to determine the effects of NMDA antagonists on brain activation in humans and animals; these compounds have been shown to be psychotrophic and to induce cognitive disturbances. Pharmacological reversal of the NMDA antagonist-induced amperometric response may represent antipsychotic activity, as previously seen with mGlu2/3 agonists. Here, we compared the effect of i.v. ketamine challenge on neuroimaging signals in healthy volunteers and anaesthetised rats to the oxygen response in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC) of freely-moving rats using in vivo oxygen amperometry. The modulation of the oxygen amperometric ketamine response by the mGlu2/3 agonist LY379268 was also assessed.

**Methods:** For the oxygen amperometry, rats were implanted with oxygen sensors in the mPFC and dHPC and were given a 1 mg/kg i.v. infusion of ketamine over 2 minutes. For the mGlu2/3 agonist modulation studies, LY379268 (1, 3, and 10 mg/kg) was dosed i.p. 30 minutes before ketamine was administered.

**Results:** Our results show a translational response to i.v. ketamine challenge, with the human fMRI, anaesthetised rat CBV imaging, and freely-moving rat oxygen amperometry showing similar increases in activation in the cingulate/mPFC. Pretreatment with LY379268 caused a dose-dependent reversal of the ketamine response in the oxygen signal in freely-moving rats.

**Conclusion:** We show that oxygen amperometry may be a good translational surrogate for imaging studies in freely-moving animals, and modulation of the oxygen ketamine response may provide a translational neuropharmacological biomarker of antipsychotic activity.
Objective: Hypothalamic circuitys responsible for the homeostatic control of essential body functions can be permanently affected by the early-life environment. A single episode of maternal deprivation (MD, 24 h on postnatal day, pnd, 9) compromises metabolic and endocrine homeostasis, and provokes behavioral outcomes that resemble symptoms frequently observed in neuropsychiatric disorders. In humans, the pharmacological management of such disorders includes administration of atypical antipsychotics, i.e. olanzapine (Olan), often prescribed to children and adolescents despite adverse side-effects. We aimed to investigate the long-lasting effects of these manipulations on hypothalamic key hormonal systems controlling reproduction and energy balance, namely Kiss1/Gpr54 and GnIH/Gpr147.

Methods: Male and female Wistar rats exposed to MD or left undisturbed were orally administered with Olan (7.5 mg/kg/day) or vehicle (1 mM acetic acid) from pnd 28 to 49 and hypothalamic mRNA expression of Kiss1/Gpr54 and GnIH/Gpr147 was analyzed in adult animals.

Results: MD resulted in a persistent decrease in body weight that extended to adolescence in males and to adulthood in females. MD induced sex-dependent alterations in the kisspeptin system; decreased Kiss1 levels in males and Gpr54 expression in females. Olan only induced a subtle reduction in body weight gain among females together with a reduction in Kiss1 levels in males that was exacerbated by prior exposure to MD. Male animals exposed to both MD and Olan exhibited the lowest levels of Gpr54 and GnIH/Gpr147. In females, Olan reduced Gpr147 expression whereas Kiss1/Gpr54 seemed not to be affected. The combination of both manipulations also diminished hypothalamic GnIH level among females.

Conclusion: Present data indicate that MD critically interferes with hypothalamic developmental programming in a sex-dependent manner, mainly through modulation of the Kiss1/Gpr54 system. Adolescence is also suggested as a sensitive period for pharmacological hypothalamic modulation. Further research on the long lasting effects of antipsychotic drugs and their interaction with early life events is urgently needed.

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Objective: Evaluation of the neuroprotective role of rivastigmine in the treatment with haloperidol (animal model)

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The neuroprotective role of rivastigmine in the treatment with haloperidol (animal model)

Methods: Animal model study, on two lots consisting of 5 Wistar rats each, male adults, weight 200–250 g, held during the study in temperature, humidity, food and ambient stressless conditions. On N1 lot, from day 1 to 14 has been administered saline solution through stomach tube, and from day 15 to 28 has been administered haloperidol (0.2 mg/kg/day) and saline solution. On N2 lot, from day 1 to 14 has been administered rivastigmine through stomach tube (equivalent to 0.5 mg/kg/day), and from day 15 to 28 has been administered haloperidol intraperitoneally (equivalent to 0.20 mg/kg/day) and rivastigmine (equivalent to 0.5 mg/kg/day). In the day 29 the rats were sacrificed. The sample brain (frontal cortex, hippocampus, striatum, Meynert nucleus, white matter) was histopathologically processed: formalin (10%) and ethyl alcohol (96%) fixation and paraffin embedded. Microtome slices were stained in hematoxyline-eosine, trichromic GS, PAS-hematoxyline, toluidine blue, methylene blue for Nielse corpuscles and argentimpregnation for neurofibres. The obtained slices were studied with optical microscope.

Results: Haloperidol significantly alter the neural structures and white substance (neuronal apoptosis and vacuolations). Rivastigmine exercise neuroprotepection on N2 lot by reducing neuronal loss in the frontal cortex and hippocampus and reduction in neuronal changes of striatum and Meynert nucleus. Rivastigmine ensures high protection for the white substance, with minimum number of vacuolations.

Conclusion: Rivastigmine presents neuroprotective qualities, both for the gray substance and white substance on brain structures involved in the cognitive process (hippocampus, frontal cortex, striatum, Meynert nucleus) under the treatment with haloperidol.

Objective: Genetic association studies have linked the neuregulin1 (NRG1) and its ErbB4 receptor to schizophrenia. Altered NRG1/ErbB4 signaling has also been shown to result in hypofunction of glutamatergic system. We hypothesized that NRG1/ErbB4 pathway interacts with glutamatergic receptors pathways by homeostatic mechanisms in a way that the deficits in one of the pathways could result in adaptive changes in others.

Methods: To analyze primary changes in NRG1/ErbB4 pathway we used knockout mice that lack beta-site APP cleavage enzyme 1 (BACE1). BACE1 participates in the proteolytic processing of NRG1 and its deletion results in multiple endophenotypes related to schizophrenia as observed in BACE1ko mice. For analysis of secondary changes in NRG1/ErbB4 signaling we used sub-chronic phenylclidine treatment (PCP), a non-competitive antagonist of the NMDA receptors, on postnatal days (PND) 7, 9, and 11 (10 mg/kg, i.p). Wild type (WT) and BACE1ko mice were behaviorally tested at PND 28–30.

Results: As expected, WT-PCP mice developed numerous schizophrenia-like behavioral traits such as deficits in prepulse inhibition, spatial recognition memory, and increased sensitivity to MK-801. BACE1ko mice demonstrated similar deficits on the vehicle treatment. Interestingly, PCP administration in BACE1ko mice resulted in the amelioration of some of the deficits. Western blot analyses showed decreased levels of BACE1 protein in WT mice after PCP treatment. The levels of two major substrates of BACE1, APP and NRG1, as well as phosphorylation of NRG1 receptor, ErbB4, were modified. In addition, PCP treatment in WT mice resulted in reduced levels of myelin basic protein (MBP), one of the down stream markers of NRG1/ErbB4 pathway activity. In contrast, PCP-treated BACE1ko mice showed some recovery of low levels of MBP, a marker of central hypomyelination in these mice.

Conclusion: Results of this study indicate that the perinatal PCP treatment modify activity of the BACE1/NRG1 pathway implicating the interactions of these pathways during development.
P-15. Animal Models

Expression of serotonergic genes in the raphe nuclei associated with anxiety-related behaviour in rats

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Objective: Numerous genetic studies imply variation in brain serotonergic neurotransmission as a determinant of differences in temperament in humans. Since the biochemical underpinnings of such associations are difficult to study in man, it is of interest to explore if similar associations are at hand also in experimental animals. To this end, this study aimed at investigating (in rat) the possible association between inter-individual differences in anxiety-like behaviour on the one hand, and the expression of a number of genes important for serotonergic transmission on the other.

Methods: 30 male Wistar rats were used. Inter-individual differences in anxiety-like behaviour were assessed using the elevated plus-maze. Three weeks later, the animals were sacrificed and the brains were extracted. Expression of serotonergic genes in the raphe nuclei was measured using RTDA cards.

Results: Animals exhibiting high levels of anxiety-like behaviour had significantly higher mRNA levels for several of the genes normally expressed by serotonergic neurons, such as those encoding tryptophan hydroxylase 2, amino acid decarboxylase and the serotonin transporter.

Conclusion: The results suggest that the expression of serotonergic genes in the raphe nuclei is associated with anxiety-like activity. kindness in specific brain regions may contribute to the lingering behavioral suppression induced by considerable dose of LPS. Our findings suggest that memantine may be an off-label effective drug for the treatment of MDMA-induced hyperthermia in humans.

P-15-033 Effect of L-carnosine on repeated social defeat stress-induced behavioral and neurochemical changes in mice

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Objective: Mood and anxiety disorders are two major mental illness, and more than one-third people reported the symptoms of these disorders in their life. Since current treatments are poorly effective, new curatives are greatly needed. Mice experiencing repeated social defeat stress (SDS) develop a persisted aversion to social contact. This aversion can be normalized by chronic treatment with antidepressants, which resemble depression in human. Previous studies indicated that dipeptide L-carnosine produced many effects in nervous systems, such as antiinocceptive and hypnotic actions. The present study was, then, designed to investigate the antidepressive-like activity of L-carnosine on repeated SDS model in mice.

Methods: Mice were subjected to daily social defeat, and then separated from the aggressor behind a protective wire mesh barrier, which allowed for sensory contact, for the remainder of the day.

P-15-030 Memantine attenuates and reverses hyperthermia induced by 3,4-methylenedioxymethamphetamine (MDMA) in rats

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Objective: Life-threatening hyperthermia occurs in some individuals consuming 3,4-methylenedioxymethamphetamine (MDMA). No effective pharmacological treatment for MDMA-induced hyperthermia has yet been established. In the present study, we evaluated the effectiveness of memantine, a non-competitive NMDA receptor antagonist and α7 nicotinic ACh receptor antagonist, in treating MDMA-induced hyperthermia. We also examined the pharmacological effects of MDMA using in vivo microdialysis.

Methods: MDMA (10 mg/kg) was injected and the dopamine and serotonin levels in rat hypothalamus were measured by the microdialysis method. In the prior-administration experiment, saline, memantine (10 mg/kg or 20 mg/kg), MK 801 (0.5 mg/kg), CGS 19755 (5 mg/kg), or methyllycaconitine (6 mg/kg) was injected intraperitoneally. MDMA (10 mg/kg) was then injected subcutaneously 30 minutes later. Rectal temperature was measured every 30 minutes. In the post-administration experiment, MDMA was injected and then memantine (10 mg/kg and 20 mg/kg) was injected intraperitoneally 30 minutes later.

Results: The extracellular concentrations of serotonin (5-HT) and dopamine (DA) in rat anterior hypothalamus were increased 50- and 15-fold, respectively, compared with their respective pretreatment levels after administration of MDMA. Pretreatment and post-treatment with memantine each inhibited the peak increase in body temperature. Although pretreatment with the NMDA receptor antagonists MK801 and CGS 19755 suppressed the increase in body temperature induced by MDMA, pretreatment with methyllycaconitine did not suppress the hyperthermia induced by MDMA. These findings suggest that MDMA increases the concentrations of 5-HT and DA in the hypothalamus, and that memantine suppresses MDMA-induced hyperthermia via its NMDA receptor-antagonistic effect.

Conclusion: Our findings suggest that memantine may be an off-label effective drug for the treatment of MDMA-induced hyperthermia in humans.
Mice were exposed to a different aggressor each day for 10 days, and were then examined for social behavior. Mice showed aversion to social contact at 1 day after SDS was used. Imipramine or L-carnosine treatment was started from 1 day after SDS for 10 days.

Results: Repeated social defeat stress-induced aversion to social contact was attenuated by the repeated, but not acute, treatment with imipramine or L-carnosine. We also examined the changes of the glutamate receptors in anterior cingulate cortex (ACC) where modulates emotions responses. The expressions of NR2B NMDA receptor subunit and GluA1 and GluA2 AMPA receptor subunits were increased in the ACC of SDS mice. These increases were attenuated by imipramine or L-carnosine treatment.

Conclusion: Our present results suggest that L-carnosine might be effective for long-lasting behavioral plasticity in response to aversive social experience. We also hypothesized that enhanced glutamatergic functions in ACC might be involved in the avoidance of social contact after repeated SDS.

P-15-034 The effects of mGlu3 agonist on neurochemical and electrophysiological changes induced by hallucinogen 4-bromo-2,5-dimethoxyphenethylamine (2C-B)

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Objective: Increases in the release of glutamate in the prefrontal cortex (PFC) and disrupted functional connectivity induced by hallucinogenic drugs have been proposed to be linked to hallucinogen-effects and psychotic symptoms. Therefore we examined whether inhibition of this release by the metabolotropic glutamate 2/3 (mGlu2/3) receptor agonist (LY379268), will normalize the neurochemical and electrophysiological effects of the hallucinogen 4-bromo-2,5-dimethoxyphenethylamine (2C-B). We concentrated on neurotransmission in the prefrontal cortex (PFC) and cortical functional connectivity (EEG spectra and coherence).

Methods: Male Wistar rats were used in all experiments. Microdialysis of PFC was performed to measure levels of dopamine, serotonin and their metabolites, and of glutamate and GABA. Cortical EEG was recorded from 6 pairs of electrodes on each hemisphere above the frontal, parietal and temporal cortex in freely moving rats. EEG power spectra and coherence in EEG traces that correspond to behavioral inactivity were subsequently analyzed in Neuroguide Deluxe v.2.6 software.

Results: 2C-B increased the levels of dopamine, serotonin and glutamate and decreased the levels of GABA in PFC. LY379268 normalized the effects of 2C-B on glutamatergic neurotransmission, slightly potentiated the release of dopamine and serotonin and had no effect on GABA. 2C-B induced EEG power decreases except in theta and alpha bands and globally decreased coherence. LY379268 normalized 2C-B induced a power decrease in delta, potentiated the effect on GABA. 2C-B induced EEG power decreases except in theta slightly potentiated the release of dopamine and serotonin and had no potential. Our data have implications for serotonin-glutamate interactions in psychoses and hallucinogenesis. This study was supported by the grants IGAMHCR NS10374-3, NS 10375-3, MEYSCR1M0517, MHCRMZO/PCP2005, MICR VGZS/200 and VGZS/271.

Conclusion: Our present results suggest that L-carnosine might be effective for long-lasting behavioral plasticity in response to aversive social experience. We also hypothesized that enhanced glutamatergic functions in ACC might be involved in the avoidance of social contact after repeated SDS.

P-15-036 Sexually dimorphic dopaminergic dysfunction in a mouse model of Huntington’s disease and depression

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Objective: Depression is the most common psychiatric disorder in Huntington’s disease (HD) patients. There is yet to be a study of sexual dimorphism in the development and presentation of depression in HD patients. Interestingly, we have previously reported a female-specific depression-like phenotype in the R6/1 transgenic mouse model of HD associated with serotonergic system alterations. We now extend these findings to include sex-dimorphic dopaminergic (DA) dysfunction at an early pre-motor symptomatic disease stage.

Methods: In order to investigate whether transgenic HD mice display depressive-like endophenotypes associated with dopaminergic impairments, we assessed the effect of several dopaminergic ligands (including the DA transporter inhibitor bupropion, as well as SKF-81297 and ropinirole, respectively D1 and D2/D3 receptor agonists) on the forced-swim test (FST) and on locomotor activity in 8–12-week-old male and female HD mice.

Results: Overall we found that compared to female animals, males were more sensitive to the locomotor stimulating effects of bupropion at both 8 and 12 weeks of age, which were successfully attenuated with the selective D1 antagonist SCH-23390. In addition, 8-week-old HD females but not male showed an impaired locomotor response to bupropion. The HD mutation also resulted in a decrease of locomotor response to the D1 agonist SKF-81297. In contrast, the selective D2/D3 agonist ropinirole significantly reduced locomotor activity in all animals. However, this effect seemed dose-dependently reduced in HD compared to WT mice. Finally, the depressive-like behavior exhibited by female HD mice in the FST was rescued by acute bupropion, possibly through a mechanism involving D2/D3 receptor signaling.

Conclusion: Our data suggest a crucial role for disrupted dopaminergic signaling in mediating the sexually dimorphic depression-like phenotype in HD mice and provide evidence suggesting that bupropion could be explored as a potential antidepressant in HD.
P-15. Animal Models

P-15-037 Pharmacological characterization of the glycine transporter-I inhibitors RC1678 and SSR504734 in rodent models for treatment of cognitive and positive symptoms in schizophrenia

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Objective: Evidence from clinical and preclinical studies has led to the hypothesis that hypofunction of N-methyl-D-aspartate (NMDA) receptors play an important role in the pathophysiology of schizophrenia involving positive, negative and cognitive symptoms. One approach to counteract NMDA receptor hypofunction is the extracellular increase of the NMDA receptor co-agonist glycine by glycine transporter-1 (GlyT1) inhibitors. Thus, by strengthening glutamatergic neurotransmission, GlyT1 has the potential for treatment of positive and cognitive symptoms of schizophrenia, besides the shown efficacy on negative symptoms in a recent clinical trial (Umbricht et al., 2011). In the present study, the GlyT1-inhibitors RC1678 (Umbricht et al., 2011) and SSR504734 (Depoortere et al., 2005) were evaluated in models of positive and cognitive symptoms in rodents.

Methods: Adult male rats were administered with two different GlyT1-inhibitors, SSR504734 (as racemate) or RC1678, and the increase of glycine in CSF was determined via LC/MS-MS analysis. Regarding antipsychotic and memory enhancing efficacy, both compounds were tested for reversal of ketamine induced hyperlocomotion in rats and for reversal of MK-801 induced memory impairment in the mouse T-maze spontaneous alternation task.

Results: RC1678 and SSR504734 led to a dose-dependent increase of glycine in rat CSF. Both compounds also showed antipsychotic-like and pro-cognitive efficacy in the hyperlocomotion test and T-maze task, respectively. However, the efficacious dose/exposure range in T-maze was 5–10-fold lower than in hyperlocomotion test.

Conclusion: The results of this study demonstrate preclinical efficacy of GlyT1-inhibitors in rodent models for positive and cognitive symptoms of schizophrenia confirming previous findings (Depoortere et al., 2005). The marked difference of efficacious doses between antipsychotic and pro-cognitive activity might indicate that different levels of NMDA receptor potentiation via glycine increase are needed for the treatment of positive or cognitive symptoms.

P-15-038 Behavioral analysis of LRP1 mediated brain adaptation

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Objective: Several lines of evidence positioned the LDL receptor gene family as one of the key players in homeostasis of neuronal signalling. The Low Density Lipoprotein Receptor-Related Protein 1 (LRP1) is well recognized as a receptor for amyloid β (Aβ) and its modulation a possibility in Alzheimer's disease therapy. But recently, a new interaction between LRP1 and the NMDA receptor has been found. It was demonstrated that knock-in mutations in the C-termius of LRP1 directly influence NMDA receptor function. The in vivo relevance of that mechanism is unknown.

Methods: To analyse the effect of a perturbed LRP1 function on the NMDA receptor due to the knock-in mutation in the LRP1 gene we compared transgenic LRP1 KI mice to wild type littermates for a behavioural phenotype. Animals were tested with respect to activity (open field), anxiety (elevated plus maze, light dark chamber), learning and memory (object recognition, Morris Water maze) as well as locomotion (Rotarod).

Results: The open field paradigm revealed a tendency to hyperactivity in LRP1 KI mice. No differences between genotypes were seen with respect to anxiety-related behaviours. Learning and memory related behaviours in the MWM test indicated that wild type mice learned the position of the hidden platform faster and more accurately compared to LRP1 KI mice. Similarly in a releaming paradigm and with respect to emotional memory wildtype mice were superior. However LRP1 KI mice outperformed wild type littermates on the Rotarod task for locomotion.

Conclusion: Presently those behavioural alterations in form of hyperactivity and altered spatial learning parallel effects seen in conditional knock out of LRP1 but also after antagonism of the NMDA receptor giving a first in vivo indication of a reduced LRP1 NMDA receptor-related interaction in those transgenic mice. This opens new possibilities for NMDA receptor modulation under pathological conditions.

P-15-039 Risperidone attenuated serotonin syndrome animal model induced extracellular nitric oxide and glutamate

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Objective: As serotonergic agents prescription has increasing, serotonin syndrome has been major and important health issue. Recently, several studies reported that glutamate and nitric oxide (NO) play a role in psychostimulant drugs-induced hyperthermia which related to neurotoxicity. Therefore we hypothesized that serotonin animal model can raise glutamate and NO concentration and those increasing may be attenuated by risperidone (potent 5-HT2A and D1 receptor antagonist) treatment. We therefore measured the changes in the levels of glutamate and NO metabolites in the anterior hypothalamus by using microdialysis method.

Methods: Male Wistar rats were used in this study. All the animal procedures employed were approved by the Animal Investigation Committee of our School and were in strict accordance with the NIH Guide for the Care and Use of Laboratory Animals. Two different serotonin syndrome animal models were prepared. In the first model, tranylcypromine (3.5 mg/kg) and fluoxetine (10 mg/kg) were simultaneously intraperitonially (i.p.) administered to rats. We simultaneously administrated clorgyline (1.2 mg/kg) and 5-HTP (80 mg/kg) i.p. to rats in the second model. The perfusate was collected and injected into a HPLC unit by using an automatic injector and the levels of glutamate and NO metabolites (NOx) were immediately determined.

Results: In the both animal models induced NOx levels increasing and each increasing were attenuated by risperidone (0.5 mg/kg) pretreatment. Extracellular levels of glutamate were increased in the first animal model, but not second animal model, and risperidone pre-administration attenuated which increasing.

Conclusion: Previous studies have reported that D1 receptor activation induces glutamate levels increasing and D1 and 5-HT2A receptors activation increase the NOx synthesis, therefore risperidone’s D1 and 5-HT2A receptors antagonistic effect were assumed to suppress glutamate and NOX increasing.

P-15-040 Blockade of the nmda-no pathway in the ventromedial prefrontal cortex (vmPFC) induces antidepressant-like effects

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Objective: Stress exposition enhances glutamate and nitric oxide (NO) levels into the central nervous system. Depressed individuals show enhanced levels of glutamate and neuronal nitric oxide synthase (nNOS) in limbic structures. Administration of antagonists of glutamate NMDA receptors or inhibitors of NO synthesis induces anti-depressant-like effects. The aim of the present study was to evaluate the participation of the glutamatergic and nitrigenic systems of the vmPFC over the behavioral consequences induced by forced swimming (FS), an animal model of depression.

Methods: Male Wistar rats (230–260 g) with guide cannulas aimed at the prelamic (PL) region of vmPFC were submitted to a 15 min session of FS and, 24 h later, they were submitted to a 5 min session of the FS test when the immobility time was measured. Injection of LY225996 (LY; NMDA antagonist at 1, 3 and 10 nmol/0.2μL), NPA (nNOS inhibitor at 0.01 nmol/0.2 μL), cPTIO (NO scavenger at 1.0 nmol/0.2 μL), ODQ (solute guanylyl cyclase-SCG – inhibitor at 1.0 nmol/0.2 μL) or vehicle was realized 5 min before the test.

Conclusion: The behavior of the rats injected with LY and NPA showed a significant decrease of the immobility time in the first session of the FS test and also in the second session. ODQ showed a significant decrease of the immobility time in the second session. The antagonist cPTIO did not show any significant effect. These results suggest that a blockade of the NMDA or NO pathways might be important for the antidepressant-like effects induced by the forced swimming test.

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session. All data were analyzed by ANOVA followed by Dunnett’s post-hoc test.

Results: LY administration into vmPFC-PL reduced the immobility time (Mean ± SEM: vehicle: 116.3 ± 21.17; LY 1 nmol: 164.4 ± 18.92; LY 3 nmol: 28.71 ± 10.21;*p < 0.05 from control group). NPA, c-PTIO and ODQ induced similar effects (Mean ± SEM: vehicle: 140.1 ± 15.23; NPA: 47.57 ± 10.42; c-PTIO: 56.86 ± 10.62; ODQ: 81.20 ± 15.99; *p < 0.05 from control group).

Conclusion: These results show for the first time that the blockade of NMDA receptors, NO synthesis or sgc activity in the vmPFC-PL induces antidepressant-like effects. Therefore, the activation of the NMDA-NO-cGMP pathway in the vmPFC in response to stress may facilitate the development of its behavioral/emotional outcomes.

P-15-041 The role of dopamine signalling in the GABAergic neuron development and motor behavior in zebrafish larvae
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Objective: An imbalance in dopamine-mediated neurotransmission and neurodevelopmental abnormalities are features of schizophrenia. The main target of antipsychotics, the dopamine D2 receptor, modulates the activity of Akt and DARPP-32, which are downregulated in the brain of schizophrenic patients. To investigate if altered D2-dependent signalling leads to abnormal neurodevelopment, we first evaluated if dopamine modulates Akt and DARPP-32 signalling in the developing brain. Later, we investigated the role of dopamine in the development of GABAergic neurons and the effects in the motor behavior.

Methods: Since the zebrafish development is external, we used zebrafish as experimental model. We treated 3 dpf larvae with dopamine agonists and antagonists to evaluate the dopaminergic intracellular pathways. In order to investigate the role of dopamine in the neurodevelopment, we examined dopamine levels and GABAergic neurons, chronically exposed to dopamine. Ultimately, we recorded and analyzed the motor behavior of the larvae.

Results: We observed dephosphorylation of Akt at threonine 308 (T308) and DARPP-32 at threonine 54 (T54) through D2 receptors. Chronic exposure to dopamine resulted in region-specific alterations in the number of GABAergic neurons, but not the total number of cells. Furthermore, we observed that dopamine affects motor behaviour in 3-5 dpf larvae.

Conclusion: Together, our data suggest that dopamine signalling represses Akt and DARPP-32 signalling in the developing brain and leads to defects in GABAergic neuronal differentiation in the zebrafish larval brain. Furthermore, the alterations in forebrain GABAergic neurons are correlated with altered context-dependent motor behaviour. Thus, with this model system, we could holistically assay the pharmacological sensitivity of these assays, leaving there utility for the drug discovery process largely unexplored. Here we attempt to demonstrate that a touchscreen test of visuo-spatial paired associates learning (PAL) can be selectively impaired by a pharmacological model of schizophrenia, and that this impairment can be reversed.

Methods: Rats (male lister-hooded, Harlan) were trained in a PAL task (Talpos et al., 2009, Psychopharmacology) performed in Med Associates operant boxes run by K-Limbic software (Conclusive Solutions). Once the task was acquired 0.5 mg/kg of amphetamine was used to disrupt recall. We then attempted to reverse this disruption with common antipsychotics including risperidone (0.04–0.16 mg/kg) and haloperidol (0.01–0.04 mg/kg) given 30 min prior to testing, a dose known to selectively impair accuracy, was used to disrupt recall. We then attempted to reverse this disruption with common antipsychotics including risperidone (0.04–0.16 mg/kg) and haloperidol (0.01–0.04 mg/kg) given 30 min prior to behavioral testing.

Results: Haloperidol and risperidone were both shown to dose dependently lessen the amphetamine induced impairment without substantially altering response latencies.

Conclusion: A “low” dose of amphetamine consistently induced a selective impairment in performance of an object-in-place PAL task. This impairment was partially reversed by administration of common antipsychotics risperidone (0.04–0.16 mg/kg) and haloperidol (0.01–0.04 mg/kg) given 30 min prior to behavioral testing.

P-15-043 The effects of antipsychotics on amphetamine induced recall impairments in a visuo-spatial paired associates learning task using touchscreen equipped operant boxes
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Objective: The use of operant boxes equipped with touchsensitive computer monitors for the testing of cognition in rodents is becoming increasingly popular. However to date the majority of published work has focused on task validation via lesions or direct administration of compounds to areas of interest. Little work has been done demonstrating the pharmacological sensitivity of these assays, leaving there utility for the drug discovery process largely unexplored. Here we attempt to demonstrate that a touchscreen test of visuo-spatial paired associates learning (PAL) can be selectively impaired by a pharmacological model of schizophrenia, and that this impairment can be reversed.

Methods: Rats (male lister-hooded, Harlan) were trained in a PAL task (Talpos et al., 2009, Psychopharmacology) performed in Med Associates operant boxes run by K-Limbic software (Conclusive Solutions). Once the task was acquired 0.5 mg/kg of amphetamine given 60 minutes prior to testing, a dose known to selectively impair accuracy, was used to disrupt recall. We then attempted to reverse this disruption with common antipsychotics including risperidone (0.04–0.16 mg/kg) and haloperidol (0.01–0.04 mg/kg) given 30 min prior to behavioral testing.

Results: Haloperidol and risperidone were both shown to dose dependently lessen the amphetamine induced impairment without substantially altering response latencies.

Conclusion: A “low” dose of amphetamine consistently induced a selective impairment in performance of an object-in-place PAL task. This impairment was partially reversed by administration of common antipsychotics risperidone (0.04–0.16 mg/kg) and haloperidol. While additional work will be required to see if this model has utility in exploring mechanisms beyond D2 receptor antagonism, these data demonstrate the potential utility of this assay and challenge model for pharmacological research. These results and additional data will be discussed, along with the translational value of this approach.

Policy of full disclosure: All authors work for Janssen pharmaceutical companies of Johnson and Johnson, makers of risperidone and haloperidol.

P-15-044 Social-cooperation is associated with increased levels of hypothalamic nor-epinephrine and striatal serotonin – evidence from a laboratory rat model
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Objective: Explanations and models of cooperation usually focus on the ‘economics’ of individual’s ‘invested efforts’ and ‘outcomes’ while down-playing adjacent social dimensions of naturally occurring cooperation. This study examined whether cooperative and
individual behaviors differ in monoaminergic function in a manner that may explain the reported ‘bias for cooperation’ even in situations where there is no immediate economic gain.

**Methods**: Cooperation, represented by pairs of rats reinforced for coordinated shuttles within a shared chamber (COOP), was compared with individual rats shuttleting for reinforcements (IND), and behaviorally naive rats (NAIVE). Following training, the hypothalamus and striata were sampled and the activity pattern of the noradrenergic, serotonergic and dopaminergic systems were assessed using HPLC analyses.

**Results**: Since rates of shuttling and reinforcements were controlled, COOP and IND rats did not differ at the individual level in either ‘invested effort’ (shuttles) or ‘outcomes’ (reinforcements). Nevertheless, differences were evident in monoaminergic functions. COOP rats exhibited significantly higher hypothalamic noradrenaline levels than IND and NAIVE rats. Compared to IND rats, COOP rats exhibited significantly higher striatal serotonin levels. Differences in levels of dopaminergic metabolites were restricted to the right striatum; compared to IND rats COOP rats exhibited significantly higher levels of HVA, whereas NAIVE rats exhibited significantly higher DOPAC levels.

**Conclusion**: These differences are dissociated from the ‘economics’ of ‘effort’ and ‘outcomes’ and thus highlight the importance of social behaviors in the reported ‘bias for cooperation’ as they demonstrate a relationship between social cooperation and a distinct activity pattern in brain mechanisms that were related with arousal, goal directed behaviors and motivation.

**P-15-045** A comparison of electroencephalographic activity in serotonergic and glutamatergic models of psychosis

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**Psychiatric Centre Prague, Czech Republic**

**Objective**: We focused on the electrophysiological changes in the EEG coherence across the whole spectrum with most prominent gamma band; a discrete decrease in theta and beta band after MK-801 was also observed. Both substances induced a significant reduction of gamma band; a discrete decrease in theta and beta band after MK-801 was also observed. Differences were evident in monoaminergic functions. COOP rats exhibited significantly higher hypothalamic noradrenaline levels than IND and NAIVE rats. Compared to IND rats, COOP rats exhibited significantly higher striatal serotonin levels. Differences in levels of dopaminergic metabolites were restricted to the right striatum; compared to IND rats COOP rats exhibited significantly higher levels of HVA, whereas NAIVE rats exhibited significantly higher DOPAC levels.

**Conclusion**: These differences are dissociated from the ‘economics’ of ‘effort’ and ‘outcomes’ and thus highlight the importance of social behaviors in the reported ‘bias for cooperation’ as they demonstrate a relationship between social cooperation and a distinct activity pattern in brain mechanisms that were related with arousal, goal directed behaviors and motivation.

**P-15-046** Effect of transient blockade of N-methyl-D-aspartate receptors at neonatal stage on stress-induced lactate metabolism in the medial prefrontal cortex of adult rats: Role of serotonin-1A receptor agonism

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**Objective**: Decreased activity of the prefrontal cortex (PFC) has been considered to provide a basis for the pathophysiology of schizophrenia, an illness associated with a neurodevelopmental origin. Evidence from preclinical and clinical studies indicates serotonin (5-HT1A) receptors play a crucial role in energy metabolism of the PFC. The present study was undertaken to determine 1) if transient blockade of N-methyl-D-aspartate (NMDA) receptors during the neonatal stage inhibit energy demands in response to stress, as measured by extracellular lactate concentrations, in the medial PFC (mPFC) at the young adult stage, and 2) if tandospirone, a 5-HT1A partial agonist, reverses the effect of the neonatal insult on energy metabolism.

**Methods**: The procedures complied with the National Institutes of Health Guidance for the care and use of Laboratory animals. All experiments were reviewed and approved by the Committee of Animal Research, University of Toyama. Male pups received MK-801 (0.20 mg/kg) on postnatal day (PD) 7 through 10. On PD 63, footshock stress-induced lactate levels were measured using in vivo microdialysis technique. Tandospirone (0.1, 1.0, 5.0 mg/kg) was administered once daily for 14 days before the measurement of lactate levels.

**Results**: Neonatal MK-801 treatment suppressed footshock stress-induced lactate production in the mPFC, but not caudate-putamen (CPu), whereas basal lactate levels were not significantly changed in either brain region. The MK-801-induced suppression of footshock stress-induced lactate production in the mPFC was attenuated by tandospirone at 1.0 mg/kg/day, but not 0.1 or 5.0 mg/kg/day, an effect antagonized by co-administration of WAY-100635, a selective 5-HT1A antagonist.

**Conclusion**: These results suggest a role for impaired lactate metabolism in negative symptoms and cognitive deficits of schizophrenia, and provide a novel insight into the ability of 5-HT1A receptor agonists to treat these symptoms.
 compose the neuron circuits and molecular cascades, respectively, which might be involved in the pathophysiology of schizophrenia.

P-15-048 Effects of chronic social defeat stress on behavior in adult mice and expression on ChAT

T. Zhao¹, C.B. Huang², S. Shrestha Mura³, Y.-C. Chung¹. ¹Chonbuk National University, Jeonju, Republic of Korea

Objective: Because social factors play a key role in human stress precipitated brain disorders, social defeat stress is widely used in biomedical research to model various psychiatric disorders in animals. The purpose of the present studies was to observe the behavior of the adult mice and expression on choline acetyltransferase (ChAT) after social stress.

Methods: Male C57BL/6J mice were divided into two groups (susceptible and unsusceptible groups) after 10 days of social defeat stress. Next, we measured spontaneous locomotion and social interaction test, dark/light test, Morris water maze test, novel object recognition test (NORT) and forced swimming test (FST). Choline acetyltransferase (ChAT) expression was measured in the mouse prefrontal cortex (PFC), amygdala and hippocampus using Western blotting.

Results: There was no difference in locomotor activity between control, susceptible and unsusceptible groups. In dark/light test, the defeated mice spent much more time in the dark box than control group and took longer to emerge from the dark box than control group. However, between susceptible group and unsusceptible group, there was no significant difference. Susceptible group displayed significant impairment of memory for the novel object recognition and decreased social sniffing compared with control group in NORT and social interaction test, respectively. On the other hand, in Morris water maze, there was no difference of escape latency and spent time in the target quadrant between control and defeated groups. In FST, susceptible group displayed significantly more immobility time compared with control and unsusceptible groups. ChAT expression in the PFC, amygdala and hippocampus was significantly decreased in susceptible group as compared to control.

Conclusions: Our results suggest that chronic social defeat stress in mice produces significant decrease of social interaction, impairment of memory for novel object, increase of immobility and significant decreased expression of ChAT in the PFC and hippocampus. The clinical implications of these findings should be discussed with regard to environmental causes for mental disorders.

P-16. Imaging

P-16-001 Quantitative immunohistochemical mapping of neurochemicals in the human brain

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Objective: We developed a human brain mapping analyzer to determine quantitative immunohistochemical distributions of neurochemicals in a large tissue slice at the cellular or near-cellular level (Sutoo et al., 1998). In this study, the distributions of choline acetyltransferase, tyrosine hydroxylase, dopamine-beta-hydroxylase, glutamate decarboxylase, glutamate dehydrogenase, calmodulin and substance P in the human brain were analyzed using this analyzer.

Methods: The brains of three male adults (age range: 50-70) with no history of neurological or psychiatric disorders were perfused with ice-cold fixative within 8 h following death. After fixation, the right hemisphere was sectioned at a thickness of 20 micron, and consecutive coronal slices were stained fluorescent immunohistochemically. Each stained slice was divided into approximately 3 million microareas at 50 micron intervals, and the fluorescence intensities in the microareas were measured quantitatively.

Results: Autofluorescence in the brain slice was eliminated photometrically, and pure immunohistochemical distribution was obtained (Sutoo et al., 1998, 1999, 2000, 2001). Its quantitative linearity surpasses that of the image analyzers used with TV cameras, and the sensitivity is greater than that of HPLC. Also, the measuring area is far larger than that of laser confocal microscopes.

Conclusion: This method is a powerful technique for quantitative and comparative analysis of the distributions of neurochemicals in the whole brain slices, and we believe that it will facilitate the investigation of the functions of the central nervous system and disorders thereof in various diseases.

References


P-16-002 Reduced hippocampal grey matter in depression: Effect of state and short-term antidepressant treatment

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Objective: Loss of grey matter volume in the hippocampus is one of the most replicated structural changes in depression. Antidepressants induce neurplastic effects in the hippocampus in animal but effects of antidepressants in this region have not been demonstrated in humans. In this study we aimed to determine (1) whether grey matter loss in the hippocampus in depression is a current state or trait abnormality and (2) whether rapid change can be detected following antidepressant treatment and associated clinical improvement.

Methods: We recruited 64 medication free unipolar depressed patients (39 currently depressed and 25 in remission) and 66 healthy controls who underwent structural magnetic resonance imaging. Thirty-two currently depressed participants were treated with the antidepressant citalopram for 8 weeks. Adherence to treatment was evaluated by measuring plasma citalopram concentration. We measured regional variation of grey matter concentration by using voxel-based morphometry (VBM-DARTEL).

Results: In the cross sectional study patients with current depression had reduced grey matter concentration in the hippocampus vs. healthy controls (L: -28, -16, -23; R: 28, -23, -24, both whole-brain FWE p=0.001) and vs. untreated patients in stable remission (L: -29, -27, -22; FWE < 0.01 and R: 34, -29, -24, whole brain FWE p = 0.013). In the longitudinal analysis, after treatment, there was bilateral hippocampal grey matter increase in currently depressed participants (L: -24, -4, -25; R: 19, -15, -25, both FWE p=0.010) but not in healthy controls, although post-treatment grey matter still remained lower than in controls.

Conclusion: Our results confirm grey matter reduction in the hippocampus in currently depressed patient that is not present in those with long-term remission. Short-term, successful antidepressant treatment partially reverses this abnormality suggesting that this may be a state-markers for depression.

P-16-003 Global decrease of serotonin-1A receptor binding after electroconvulsive therapy in major depression

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Objective: Electroconvulsive therapy (ECT) has been successfully applied as first-line approach for treatment-resistant depression. However, the neurobiological mechanisms underlying its effectiveness remain unclear, although numerous preclinical studies point towards a significant involvement of the serotonergic system,
particularly the serotonin-1A receptor (5-HT1A). Considering the consistently reported 5-HT1A alterations in depression, this study aims to investigate molecular mechanisms of ECT using positron emission tomography (PET).

**Methods:** 12 subjects (8 female, mean age ± SD = 47.83 ± 11.12 years) with severe unipolar depression (HAM-D7 score ≥ 23), participated in this study. Patients underwent 3 PET scans using [carbon-11]WAY-100635, two before (test-retest reliability) and one after completed ECT. ECT was carried out according to international standards, resulting in 10.08 ± 2.35 sessions. Medications remained in steady-state during the investigation, drugs targeting the 5-HT1A receptor were discontinued prior inclusion. PET scans were normalized to MNI-space (SPM8). Quantification of 5-HT1A receptor binding potential (BPND) was carried out in PMOD 3.3 using MRTM2 and the cerebellar grey as reference.

**Results:** Paired-samples t-test showed a significant decrease (t = 9.16, p < 0.001; mean = 17.58 ± 6.65) of HAM-D values after ECT. Voxel-wise repeated-measures ANOVA revealed a global decrease of 5-HT1A BPND (p < 0.05, FDR-corrected) comparing PET2/PET3, corresponding to one interconnected cluster (436 cm³) with peak areas in the anterior cingulate cortex (ACC: t = 4.58, x/y/z = 2/40/20 mm MNI space), its subgenual part (sgACC: t = 3.77, x/y/z = 6/36/-8) and the amygdala (t = 3.91, x/y/z = −26/4/26 mm). There was no significant difference comparing PET1/PET2.

**Conclusion:** Our results substantiate the effectiveness of ECT in depression. Furthermore, we showed a significant decrease of 5-HT1A BPND in depressed patients after ECT affecting virtually the whole cortex. More precisely, these findings include brain regions, consistently reported to present functional and morphological alterations in subjects suffering from affective disorders.

**P-16-004** Functional abnormalities within the working memory network in remitted major depressive disorder

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**Objective:** Highly variable severity and course as well as a heterogeneous clinical picture comprising emotional, vegetative, psychomotor and cognitive symptoms characterize Major Depressive Disorder (MDD). Previous neuroimaging studies investigated predominantly MDD patients with a concurrent depressive episode compared to healthy controls and repeatedly observed activation increases within emotion as well as cognition brain circuits. While limited evidence is available regarding neural alterations in cognition-related circuits during symptomatic MDD, literally nothing is known concerning the functionality of working memory (WM) networks during stable remission.

**Methods:** Hence, we conducted a cross-sectional functional magnetic resonance imaging (fMRI) study with the goal to determine if WM function and associated neural activation differ between fully remitted medication-free MDD patients (N = 61) and healthy subjects (N = 84) without any previous psychiatric life-time diagnosis. We employed the so-called n-back WM paradigm.

**Results:** While no significant differences in task performance were detected between the groups, activation increases in extended frontal, parietal and cingulate areas, with punctum maximum in the frontal gyrus, were identified in both, remitted MDD (rMDD) patients as well as controls, during the 2-back versus 0-back condition. Moreover, relative to controls, rMDD patients showed greater activation in the left frontal cortex, including inferior and middle frontal gyrus as well as adjacent areas such as the medial frontal and insular cortex, with the peak of activation differences between the left inferior frontal and precentral gyrus (Z = 3.71, p < 0.001, uncorrected; x = −62, y = 12, z = 12).

**Conclusion:** Our finding of increased WM-related neural activation in rMDD patients in comparison to controls in the absence of any behavioral differences suggest, that rMDD patients have to compensate underlying deficits in cognitive networks by increasing neural processing within the same neural circuits in order to maintain a comparable level of WM performance. Moreover, our results point towards persisting functional alterations in the cognitive networks even after a full recovery of MDD.

**P-16-005** Impaired to P-down processing in schizophrenia in the perception of a hollow mask revealed with fMRI and event related potentials

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**Objective:** Visual illusions can reveal mechanisms of perception that try to make our world around us meaningful. In order to perceive our environment around us as meaningful the interaction between bottom-up and top-down processing has to be intact. In this study we use the principles of the ‘hollow-mask illusion’ to investigate this interaction. The hollow-mask illusion occurs when a hollow mask is perceived (incorrectly) as a normal face. It is understood to be a process that involves the generation of hypotheses about the three-dimensional shape of faces by interpreting the bottom-up signals received from the eyes using conceptual and perceptual knowledge (top-down processing). Healthy volunteers perceive a hollow mask as a normal face, presumably due to the strength of constraining top-down influences, while patients with schizophrenia do not. However, the neural mechanisms underpinning this effect remain poorly understood.

**Methods:** We used functional magnetic resonance imaging and event related potentials to investigate the hollow-mask illusion in schizophrenic patients and healthy controls. The primary aim of this study was to use measures effective connectivity arising from dynamic causal modelling (DCM).

**Results:** We identified differences between the two groups in effective connectivity. In particular, there was a strengthening of bottom-up processes, and weakening of top-down influences, while presenting ‘hollow’ faces for the patients. In contrast, the controls exhibited a strengthening of top-down processes when perceiving the same stimuli.

**Conclusion:** These findings suggest that schizophrenic patients rely on stimulus-driven processing and are less able to employ conceptually-driven top-down strategies during perception, where incoming sensory data are constrained with reference to a generative model that entails stored information from past experience.
Objective: To evaluate the hypothesis that [11C]yohimbine, a selective antagonist of the alpha 2a receptors in tracer dose, may be used to assess in vivo changes in synaptic noradrenaline (NA) during acute pharmacological challenges.

Methods: Isoflurane-anesthetised Gottingen minipigs were positioned in a stereotaxic headholder and a high resolution CT performed. In a Siemens PET/CT. Microdialysis probes (CMA70) were placed stereotaxically in thalamus, striatum and cortex and perfused with artificial CSF (2 μL/min). Samples were collected every 10 min throughout the course of the experiment and immediately frozen until assay. After a 2–3 h equilibrium period, three 90 min [11C]Yohimbine (200–300 MBq in 10 mL, injected mass<1 μg) scans were obtained: the first (baseline) scan was followed by a pharmacological intervention (amphetamine (1–10 μg/kg), a non specific NA/DA releaser or nisoxetine (1 mg/kg), a specific NET inhibitor) and scans at 30 and 150 min after challenge. Vital signs were monitored throughout the course of the study. The animal was humanely euthanized at the end of the experiment to verify probe integrity and location. Samples were analyzed by HPLC for NA and DA and their metabolites. Yohimbine total distribution volume (DVT) were obtained from thalamus, striatum and several cortical regions as previously described.

Results: Both pharmacological challenges induced a significant decrease in yohimbine binding, presumably from competition by the endogenous ligand: cortical and thalamic regions showed the greatest decrease (>20%) while the striatum had a more moderate decrease (8-15%) consistent with reduced striatal NA innervation. Dialysis samples revealed a significant increase in NA extracellular concentrations after challenge. DA was also significantly increased after amphetamine challenge.

Conclusion: This data suggest that [11C]yohimbine may be a potential tracer to evaluate acute variations in synaptic NA concentrations after pharmacological challenges.

Objective: We conducted functional MRI studies in healthy subjects, patients with schizophrenia and affective disorders and in their healthy first-degree relatives. The functional integrity of the whole DMN as seed region. A repeated-measures ANOVA was used to search the genome for genetic factors that may be involved in the occurrence of these endophenotypic markers.

Methods: In most studies of bipolar patients may reflect putative neuroprotective effects of lithium (Li).

Objective: To investigate [11C]yohimbine in bipolar disorders (BD) while controlling for Li exposure, we performed a meta-analysis of neuroimaging studies which subdivided BD patients based on the presence or absence of current Li treatment. Hippocampal volumes were compared by combining standardized differences in means (Cohen’s d) from individual studies using random effect models.

Results: Overall, we meta-analyzed data from 101 Li treated BD subjects, 245 BD subjects not treated with Li (non-Li group) and 456 controls from 16 studies. Both the left and right hippocampal volumes were significantly larger in the Li treated BD subjects than in controls (Cohen’s d = 0.53, 95% CI = 0.18; 0.88; Cohen’s d = 0.51; 95% CI = 0.21; 0.81, respectively) or the non-Li group (Cohen’s d = 0.93; 95% CI = 0.56; 1.31; Cohen’s d = 1.07, 95% CI = 0.70; 1.45, respectively), which had smaller bilateral hippocampal volumes than the controls (Cohen’s d = 0.36, 95% CI = 0.55; 0.37; Cohen’s d = 0.38, 95% CI = 0.63; 0.13, for the left and right hippocampal volumes respectively). There was no evidence of publication bias.

Conclusion: Considering the opposite direction of findings in subjects with versus without exposure to Li, the preserved hippocampal volumes among BD subjects in the majority of individual studies and all previous meta-analyses were most likely related to the inclusion of Li-treated subjects. Our findings provide indirect support for the neuroprotective effects of Li and for the negative effects of bipolar disorders on hippocampal volumes.

Objective: To evaluate the hypothesis that [11C]yohimbine, a selective antagonist of the alpha 2a receptors in tracer dose, may be used to assess in vivo changes in synaptic noradrenaline (NA) during acute pharmacological challenges.

Methods: Isoflurane-anesthetised Gottingen minipigs were positioned in a stereotaxic headholder and a high resolution CT performed. In a Siemens PET/CT. Microdialysis probes (CMA70) were placed stereotaxically in thalamus, striatum and cortex and perfused with artificial CSF (2 μL/min). Samples were collected every 10 min throughout the course of the experiment and immediately frozen until assay. After a 2–3 h equilibrium period, three 90 min [11C]Yohimbine (200–300 MBq in 10 mL, injected mass<1 μg) scans were obtained: the first (baseline) scan was followed by a pharmacological intervention (amphetamine (1–10 μg/kg), a non specific NA/DA releaser or nisoxetine (1 mg/kg), a specific NET inhibitor) and scans at 30 and 150 min after challenge. Vital signs were monitored throughout the course of the study. The animal was humanely euthanized at the end of the experiment to verify probe integrity and location. Samples were analyzed by HPLC for NA and DA and their metabolites. Yohimbine total distribution volume (DVT) were obtained from thalamus, striatum and several cortical regions as previously described.

Results: Both pharmacological challenges induced a significant decrease in yohimbine binding, presumably from competition by the endogenous ligand: cortical and thalamic regions showed the greatest decrease (>20%) while the striatum had a more moderate decrease (8-15%) consistent with reduced striatal NA innervation. Dialysis samples revealed a significant increase in NA extracellular concentrations after challenge. DA was also significantly increased after amphetamine challenge.

Conclusion: This data suggest that [11C]yohimbine may be a potential tracer to evaluate acute variations in synaptic NA concentrations after pharmacological challenges.

Objective: We conducted functional MRI studies in healthy subjects, patients with schizophrenia and affective disorders and in their healthy first-degree relatives. This combination of investigations permits to identify pathophysiological abnormalities in brain circuits of psychiatric patients, to test for their possible role as endophenotypes, and to search the genome for genetic factors that may be involved in the occurrence of these endophenotypic markers.

Methods: We applied a battery of recently established experimental paradigms in order to systematically investigate different core pathophysiological processes and neurocognitive and neurophysiological endophenotypes of schizophrenia and affective psychoses. These paradigms included different versions of circuit-specific working memory tasks (Gruber & van Cramon 2003), a combined task-switching, oddball and incongruency paradigm (Gruber et al., 2009), and the “desire-reason dilemma” paradigm (Diekhof & Gruber, 2010), which assesses functional interactions between the reward system and prefrontal control mechanisms. The functional integrity of all of these neural mechanisms was investigated in groups of patients with major psychoses and in their healthy first-degree relatives.

Results: Results from a cohort of more than 300 subjects will be presented. Patients with schizophrenia and patients with bipolar disorder, but not patients with unipolar depression revealed altered brain activation in different prefrontal and parietal brain areas during working memory. In specific decision-making tasks, all patient groups showed (in part diagnosis-specific) alterations in brain regions involved in reward processing and other motivational processes. In part, the same abnormalities in brain activation were also found in the healthy first-degree relatives, i.e. these pathophysiological changes may qualify as endophenotypic biomarkers for the disorder. Genome-wide association studies for these endophenotypic neuroimaging markers are currently underway.

Conclusion: The endophenotypic approach in functional neuroimaging may help to identify genes involved in the pathogenesis of psychiatric disorders and may provide important information for the development of valid animal models for further research.

Objective: To evaluate the hypothesis that [11C]yohimbine, a selective antagonist of the alpha 2a receptors in tracer dose, may be used to assess in vivo changes in synaptic noradrenaline (NA) during acute pharmacological challenges.

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Objective: We conducted functional MRI studies in healthy subjects, patients with schizophrenia and affective disorders and in their healthy first-degree relatives. This combination of investigations permits to identify pathophysiological abnormalities in brain circuits of psychiatric patients, to test for their possible role as endophenotypes, and to search the genome for genetic factors that may be involved in the occurrence of these endophenotypic markers.

Methods: We applied a battery of recently established experimental paradigms in order to systematically investigate different core pathophysiological processes and neurocognitive and neurophysiological endophenotypes of schizophrenia and affective psychoses. These paradigms included different versions of circuit-specific working memory tasks (Gruber & van Cramon 2003), a combined task-switching, oddball and incongruency paradigm (Gruber et al., 2009), and the “desire-reason dilemma” paradigm (Diekhof & Gruber, 2010), which assesses functional interactions between the reward system and prefrontal control mechanisms. The functional integrity of all of these neural mechanisms was investigated in groups of patients with major psychoses and in their healthy first-degree relatives.

Results: Results from a cohort of more than 300 subjects will be presented. Patients with schizophrenia and patients with bipolar disorder, but not patients with unipolar depression revealed altered brain activation in different prefrontal and parietal brain areas during working memory. In specific decision-making tasks, all patient groups showed (in part diagnosis-specific) alterations in brain regions involved in reward processing and other motivational processes. In part, the same abnormalities in brain activation were also found in the healthy first-degree relatives, i.e. these pathophysiological changes may qualify as endophenotypic biomarkers for the disorder. Genome-wide association studies for these endophenotypic neuroimaging markers are currently underway.

Conclusion: The endophenotypic approach in functional neuroimaging may help to identify genes involved in the pathogenesis of psychiatric disorders and may provide important information for the development of valid animal models for further research.
and each 5-minutes block beginning at the start of the ketamine infusion (t=3.2; \(p<0.001\) uncorrected voxel level).

Results: Functional connectivity analysis showed a consistent ketamine-induced increase in the precuneus (0–5 min: \(t=3.95\); 15–20 min: \(t=4.38\); 30–35 min: \(t=4.6\)) and the posterior cingulate cortex (PCC, 15–20 min: \(t=3.59\); 30–35 min: \(t=3.44\), see figure). For the later time points (15–20 min and 30–35 min) the cluster in the precuneus withstands correction for multiple comparisons (\(p<0.05\) FWE-corrected cluster level).

Conclusion: The application of a subanaesthetic dose of ketamine leads to a significant increase of the functional connectivity of the precuneus and the PCC, which represent key areas of the default-mode network. These results are consistent with findings in schizophrenic patients, which propose a hyperactivity of the DMN, pointing toward a possible implication of the NMDA-receptor on resting-state functional connectivity.

**P-16-010** An initial baseline for machine learning classifier performance on resting state fMRI data

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Objective: The classification of disease states has long been an important goal of fMRI research in biological psychiatry. Real world applications on other than severe cases, however, have been hindered by the low signal-to-noise ratio of fMRI data. Multivariate statistical methods can deal with this problem by taking into consideration the covariance structure in addition to the marginal distributions of a multivariate feature space. The goal of this study was to apply various machine learning classifiers to features extracted from resting-state fMRI data in order to classify subjects as male or female and thus establish a baseline for what to expect employing naive features in clinical samples.

Methods: Resting-state fMRI data of 84 healthy subjects (43 male) from the 1000 Functional Connectomes Project database (Biswal et al., 2010) was subjected to standard preprocessing (Weissenbacher et al., 2009), features for subsequent classification were extracted based on the correlation of all pairs of voxel time series. Gaussian Naive Bayes, k-Nearest-Neighbors, Support Vector Machine, and Random Forest classifiers were trained on the raw features and their principal components, classification accuracy was assessed using leave-one-out cross validation.

Results: Classification accuracies for the classifiers were shown to be highly dependent on sample size, with mean accuracies up to 60% (SVM results see figure). Estimation on 20 principal components yielded results comparable to classification on the whole dataset for most estimators.

Conclusion: On an empirical basis, we identified a classification accuracy of about 55 percent as a relatively stable result for our naively selected features, in contrast to published classification accuracies of up to 80 percent using small sample sizes (around 40 subjects). Our results, however, show that those are prone to high variability, warranting caution when interpreting reliability in the growing field of machine learning in fMRI data analysis (Pereira et al., 2009).

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**P-16-011** Metabotropic glutamate receptor 5 densities and free glutamate concentrations in occasional and dependent cocaine users

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Objective: The primary focus of previous addiction research was on the dopamine system, by which the rewarding and reinforcing effects of cocaine are mediated. However, over the past decade evidence from preclinical studies emerged showing that cocaine use also leads to long-lasting neuroadaptations in the corticostriatal glutamate system, in which the dopamine axon terminals are embedded (Kalivas, 2009). Disruption of the glutamate homeostasis seems to be particularly relevant for drug-seeking and relapse-related behaviors (McFarland et al., 2003; Reissner and Kalivas, 2010). The metabotropic glutamate receptor 5 (mGluR5) seems an interesting candidate to be

Figure: Sagittal views of differences in the functional connectivity of the default-mode network at different time-periods during (0-20 minutes) and after ketamine infusion (30-35 minutes) compared to baseline. x=0mm MNI-space

Classification Accuracy Dependent on Sample Size
investigated because mGluR5 null mutant mice did not self-administer cocaine and mGluR5 antagonists attenuated self-administration and reinstatement of cocaine use in rodents (Backstrom and Hytya, 2006; Chiamulera et al., 2001). Moreover, a human magnetic resonance spectroscopy (MRS) study with chronic cocaine users found lower glutamate levels in the ACC in comparison to controls (Yang et al., 2009). Interestingly, years of cocaine use correlated positively with glutamate levels possibly implying a compensatory neurobiological mechanism over time. Therefore, achieving a more in-depth understanding of cocaine-related glutamatergic alterations in humans may eventually lead to the development of novel drug treatment approaches.

**Methods:** Sixteen male cocaine users either with an occasional or chronic cocaine use pattern and 16 male controls will undergo [(11C)]-ABP688 positron emission tomography (PET) and 1H MRS. [(11C)]-ABP688 is a selective radioligand for the mGluR5, allowing to investigate potential group differences in mGluR5 densities in selected regions of interest such as the DLPFC, OFC, ACC, MPFC, and the striatum. Free in vivo glutamate concentrations of the perigenual ACC and the DLPFC will be acquired in MRS by means of a 2D PRESS sequence and quantified by using ProFit. In addition, participants will complete a comprehensive neuropsychological test battery to relate putative neurobiological alterations to cognitive impairment.

**Conclusion:** The aim of the current study was to compare the volumes of the hippocampus and amygdala in depression patients with melancholic depression, patients with psychotic depression and normal controls.

**Methods:** Twenty two patients with melancholic major depression, 17 with psychotic major depression and 18 normal controls were included in the study. Hippocampal (HV) and amygdala (AV) volumes were measured on magnetic resonance volumetric images.

**Results:** There were no volumetric differences between patients with melancholic and psychotic subtypes. We identified larger AVs in both patient groups compared to controls, while there were no differences in HVs across the 3 groups. AV bilaterally differed between early- and late-onset patient groups and between patients with and without sleep disorder. Larger amygdalae bilaterally were significantly associated with smaller tail of the left hippocampus in patients, but not in controls.
The histamine H3 receptor represents an appealing CNS target for the treatment of cognitive disorders. Importantly, the therapeutic benefit of this mechanism may be hampered by disruption of sleep, and adverse cognitive impairment. Importantly, the therapeutic benefit of this mechanism may be hampered by disruption of sleep, and adverse events related to sleep has been observed in human subjects at high (>80%) H3 receptor occupancy (H3RO) during treatment with H3 antagonists. AZD5213 is a novel highly selective H3 antagonist (in vitro inverse agonist) developed to achieve a pharmacokinetic profile permitting circadian fluctuations of H3RO. Efficacy has been demonstrated in rodent behavioural models of cognition, and in vivo microdialysis has shown release of histamine, acetylcholine, dopamine and noradrenaline in the rodent brain. In human subjects, AZD5213 was safe and well tolerated following repeated doses (1–14 mg/d) and demonstrated a short (5–6 h) half-life. AZD5213 was shown to dose and concentration dependent H3RO ranging from 16 to 90 % H3RO at peak while falling clearly below 80 % during night. Modeling predicted that for most subjects the dose range 0.5–6 mg given in the morning would achieve >90 % H3RO at peak while falling clearly below 80 % during night. This study confirms that AZD5213 rapidly equilibrates across the human blood-brain barrier. A dose range permitting high daytime and low nocturnal H3 occupancy has been defined. Such circadian fluctuation may be expected to reduce the risk of sleep disruption while maintaining daytime efficacy. AZD5213 may thus be an optimal candidate to evaluate the clinical benefit of selective H3 antagonism in cognitive disorders.

**Conclusion:** These preliminary findings implicate disorganization of white matter tracts involved in top-down cognitive control in PSP and have implications for diagnostic classification systems and future research.

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**Objective:** Bipolar Disorder (BD) is a chronic mood disorder with a prevalence estimated around 1–2 %. Bipolar patients may experience social and working residual impairment even during euthymia. Furthermore, specific cognitive deficits, particularly involving working memory (WM), may persist during euthymia as well. To evaluate the possibility of cognitive and functional differences between euthymic bipolar subjects vs. healthy controls during euthymia by means of a WM task at fMRI associated with neuropsychological evaluations.

**Methods:** A sample of 47 subjects aged between 20 and 55 years (12 with BD type I, 12 BD type II and 23 controls) underwent fMRI examination at 3 Tesla with tasks of working memory (n-back). All participants received a neuropsychological evaluation and Stroop Color-Word Interference test, Tower of London, Trail Making test, Wisconsin Card Sorting Test and Verbal Fluency Test. Comparison tests were performed using statistical software SPSS and SPM5.

**Results:** The performance of the control group was significantly higher than both at the n-back task and at the neuropsychological tests. The full-factorial analysis of fMRI data showed a hypoactivation in bipolar patients in particular hippocampus and thalamus, associated with increased involvement of areas not involved in the frontal-parietal networks classically associated with WM.

**Conclusion:** The results seem to confirm the existence of a residual dysfunction during euthymia phase in BD, suggesting two distinct patterns of activation in the two groups studied, both from a neuro-psychological point of view and from a neuroimaging perspective.
**P-16-018** Depressive symptoms and apathy are associated with psychomotor slowness and frontal activation

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**Objective:** Affective symptoms, such as depression and apathy, and cognitive dysfunction, such as psychomotor slowness, are known to have negative impacts on the quality of life (QOL) of patients with mental and physical diseases. However, the relationships among depressive symptoms, apathy, psychomotor slowness, and QOL in a non-clinical population are unclear. The aim of the present study was to assess these relationships and examine the underlying cortical mechanisms in a non-clinical population.

**Methods:** Fifty-two healthy male volunteers were assessed for depressive symptoms using the Zung Self-rating Depression Scale (SDS), for apathy measured using the Apathy Scale, and QOL using the Short-Form 36 item questionnaire (SF36). The volunteers also performed the Trail Making Test Part A (TMT-A) while undergoing assessment of hemoglobin concentration changes in the frontal cortical surface using 24-channel near-infrared spectroscopy (NIRS).

**Results:** The scores of the SDS and Apathy Scale showed significant negative correlations with the scores of most of subscales of the SF36. In addition, the SDS score had a significant positive correlation with the time to complete the TMT-A. Further, activation of several frontal cortical areas had a significant positive correlation with the scores of the SDS and Apathy Scale.

**Conclusion:** These results suggest that the degree of depressive symptoms and apathy are associated with a lower QOL in a non-clinical population, and that cortical hyperactivation during a psychomotor task measured by NIRS may identify objectively individuals with a high degree of depressive symptoms and apathy.

**P-16-019** PET imaging of serotonergic system in monkeys: Effects of maternal separation, and chronic fluoxetine treatment during development

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**Objective:** Major depressive disorder (MDD) is a serious disorder that often begins following stress during adolescence. Selective serotonin reuptake inhibitors (SSRIs) are a common treatment for both adolescent and adult MDD. While MDD's early onset and available efficacy data support use of SSRIs in adolescents, concerns about safety have arisen, based on associations with suicidal behavior in adolescents, coupled with minimal data on long-term effects on the developing brain. This study used rhesus monkeys as a model to study the long term effects of both early life stress and chronic antidepressant treatment on the central serotonergic system in young adult rhesus monkeys.

**Methods:** Thirty-two monkeys were randomly assigned to one of four groups (8 monkeys/group). They were peer-reared (PR) vs. mother-reared (MR), and with or without fluoxetine treatment. For PR, monkeys were separated from mothers at birth and nurse-reared until 6 months of age and thereafter housed with their peers. Chronic fluoxetine treatment began at 2-year of age for one year. One to two years post-washout, monkeys (average age of 5) were scanned with Positron Emission Tomography (PET) using three radioligands: 1) [11C]CUMI, an agonist; 2) [11C]RWAY, an antagonist, both for 5-HT1A receptor; and 3) [11C]DASB for serotonin transporter (SERT).

**Results:** Preliminary data from 24 monkeys (6 in each group) show 1. A significant global decrease in SERT binding in PR compared to MR monkeys, 2. SERT binding is reversed in PR monkeys that received fluoxetine treatment, and 3. 5-HT1A receptor binding is decreased in PR compared to MR monkeys only in cortex and unlike SERT, the binding was not reversed with fluoxetine treatment.

**Conclusion:** Our study demonstrates serotonergic alterations in PR monkeys, and chronic fluoxetine treatment may reverse deficits in SERT density that is persistent more than one year after medication discontinuation.

**P-16-021** Differential effect of risperidone versus haloperidol on brain activation in first-episode schizophrenia patients: A multicentre fMRI study

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**Objective:** Neurocognitive impairments in schizophrenia are common and clinically relevant. The majority of people diagnosed with...
schizophrenia will experience a significant decline in global, social and occupational function levels in the course of their illness. This disability is largely driven by cognitive impairment. Amongst the different cognitive domains, memory impairments in particular are regarded as possible intermediate phenotypes of schizophrenia. Whether haloperidol and risperidone, two neuroleptic drugs with differential receptor binding profiles show distinct impacts on functional networks mediating working memory is subject of the current study.

Methods: 36 first episode schizophrenia patients (DSM IV) were recruited as part of the German Research Network of schizophrenia. Patients received either risperidone (N=17, mean daily dose: 4.5±1.7) or haloperidol (N=19, mean daily dose: 2.9±1.5) in a double blind treatment regime. The task during fMRI data acquisition (1.5 Tesla scanner) consisted of an n-back paradigm with a randomized sequence of 0-back and 2-back conditions arranged in a block design. The data was analysed using a flexible factorial design (SPM8) including medication dose (in mg) and gender as a covariate.

Results: Functional analysis revealed greater activations in the risperidone group in a network comprising of superior parietal, orbitofrontal, middle frontal, thalamic, temporal and occipital areas; p<0.05 at voxel level, Monte-Carlo-corrected p<0.05, >147 contiguous voxels.

Conclusion: Risperidone treated patients showed stronger activations in a cortical network that has previously been associated with this kind of working memory task than patients treated with a comparably moderate dose of haloperidol. As the results were controlled for dose, and neither side effects nor co-treatment differed between the groups, the results are not likely to be affected by these confounding factors, but rather reflect the drugs different receptor binding profile. Risperidone binds much stronger to 5-HT2A and less strongly to D1- and D2-receptors, which might be responsible for the differences in BOLD between the two medication groups.

P-16-022 Spontaneous low-frequency oscillations during resting state and personality traits measured by the temperament and character inventory and NEO Five-Factor inventory in healthy volunteers

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Objective: Default mode network measured by resting state fMRI (R-fMRI) has received a great deal of attention, because of its critical role in ego function, such as attending to environmental stimuli, reviewing the past and planning the future. Using R-fMRI, we examined the relationships between the amplitude of low-frequency oscillations (LFO) and the personality traits assessed by two self-rating scales, Temperament and Character Inventory and NEO Five-Factor Inventory in healthy subjects.

Methods: Twenty-four healthy right-handed subjects participated in 5-min R-fMRI and completed the Temperament and Character Inventory and NEO Five-Factor Inventory.

Results: We observed that Neuroticism correlated negatively with regional activity of the middle frontal gyrus (MiFG) and precuneus; Extraversion correlated positively with regional activity of the superior frontal gyrus (SFG), striatum, MiFG, subcallosal and posterior cingulate cortex (PCC); Openness correlated positively with the parahippocampal gyrus, and negatively with the SFG; Conscientiousness correlated positively with regional activity of the MiFG and correlated negatively with the cerebellum. Additionally, we observed that Harm avoidance correlated positively with regional activity of the culmen, and negatively with regional activity of the MiFG and insula; Reward dependence correlated positively with regional activity of the anterior cingulate, medial frontal and superior temporal gyrus; Cooperativeness correlated positively with the PCC; Self-transcendence correlated positively with regional activity of the culmen, inferior frontal gyrus and thalamus, and correlated negatively with the middle temporal and occipital gyrus.

Conclusion: Our results revealed the neural substrates of personality traits in the amplitude of spontaneous LFO.

P-16-023 Effects of ketamine infusion on brain activation during an emotion discrimination task – a double-blind placebo-controlled pharmaco-fMRI study

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Objective: The application of low dose ketamine, a NMDA-receptor antagonist, is used to modify the functional connectivity in brain networks of healthy subjects as a model for schizophrenia associated with altered glutamatergic connectivity. Altered connectivity changes the processing of emotional and cognitive stimuli. Therefore we assessed ketamine-induced changes in brain activation using an emotion discrimination task (EDT).

Methods: 10 healthy volunteers underwent twice fMRI in a double-blind, placebo-controlled study. During a 5 min run, subjects performed EDT, before and after either ketamine (mean dose 15.12±1.76 mg) or placebo (0.9% saline solution) intravenous maintenance infusion. FMRI was carried out at 3T with a single-shot gradient-recalled EPI sequence (TR=1800 ms, TE=38 ms, 23 slices, matrix=128×128×voxel). After spatial normalization to MNI-space, individual activations were computed by contrasting EDT vs. ODT (object discrimination task) in SPM8. Effects of ketamine vs. placebo were assessed by paired-samples t-test and random effects analysis.

Results: According to previous fMRI-studies, task-specific activation before infusion was found in several regions, including the amygdalae, fusiforme and dorsolateral prefrontal cortices (t>4.3, p<0.001 uncorr.), when contrasting EDT vs. ODT. Direct comparison between ketamine vs. placebo showed an increased activation in the retrosplenial cortex (RSC) and precuneus (p<0.01 voxel level, p<0.05 FWE corr. cluster level). Subsequent analysis shows that differences of ketamine vs. placebo emerge mainly from a reduced deactivation during EDT in the RSC (t=-2.2) and to a lesser extent in the precuneus (t=-2.6).

Conclusion: While performing EDT, results revealed a reduced deactivation in the RSC and precuneus, both representing essential regions of the default-mode network (DMN) that is associated with self-related processing. This ketamine-induced activity maintenance in the DMN during goal-oriented tasks might be caused by alterations
of NMDA receptor-modulated networks, suggesting an insufficient regulation of DMR in schizophrenia.

Objective: Aggression is a multifarious type of (re-)action. Whereas impulsivity could be well related to serotoninergic deficiency, also dopaminergic mechanisms were postulated in the modulation of aggression. This investigation was performed to enlighten the influence of striatal dopaminergic synthesis capacity on the vulnerability for aggressive, defensive, or resilient behaviour during a standardized aggressive provocation task (PSAP).

Methods: 18 healthy male subjects (24.7±4.0 years) underwent a single [18F]FDOPA-PET scan (124 min.; 10 min. transmission scan; arterial blood sampling; metabolite detection) without any pharmacologic challenge except carbidopa pre-treatment. Directly before the scan, the subjects underwent the Point Subtraction Aggression Paradigm (PSAP). In short, this is an evaluated monetary reward game against a putative adversary which habitually tries to cheat. The proband can react by punishment (money subtraction), by pressing a defensive button, or by continuing his money-making behaviour (resilience). The PET-dynamics were analyzed according to the "inlet/outlet-model" of Kumakura et al. (2005) to obtain the total uptake of [18F]FDOPA (K), the total distribution volume (VD) and klos in the striatum.

Results: The subjects showed mean K values of 0.025±0.006, VD-values of 4.7±1.3, and klos-values of 0.0059±0.0022 (NC: K=0.030±0.007, VD: 3.3±0.9, and klos-values of 0.0078±0.0037). Correlation analyses to the PSAP-parameters revealed that the striatal (especially left putamen) K and klos parameters were negatively correlated with combined defensive/aggressive behaviour (leftPut-K: r=-0.65, p=0.003) and positive correlated with the resilient money-making behaviour (bilPut-K: r=0.52, p=0.028).

Conclusion: Apparently, lower presynaptic dopamine synthesis capacity/turnover distract healthy subjects from reward-oriented behaviour during aggressive provocation and let them shift to inter-actional behaviour. The negative relations were dominated by defensive strategies. This investigation suggests that the influence of dopamine on aggression is not directly linked with harmful-behaviour but with the distractibility from goal/reward-directed behaviour.

Conclusion: Treatment with atomoxetine resulted in significantly improved executive function compared with placebo in adults with ADHD; the observed improvement was maintained for at least 25 weeks.

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Objective: To validate Conners’ Adult Attention-Deficit/Hyperactivity Disorder Rating Scale Investigator Rated Screening Version (CAARS-Inv-SV) in European patients.

Methods: We used data from adult patients with ADHD participating in the initial 12-week open-label treatment phase of a long-term clinical trial to examine maintenance of response to atomoxetine 40–100 mg/day. We recruited patients from European countries (E-patients) and from countries outside of Europe (OE-patients). Primary efficacy measures: CAARS-Inv-SV and Clinical Global Impression-ADHD-Severity (CGI-ADHD-S). Internal consistency of CAARS-Inv-SV total and subscales were assessed by Cronbach’s alpha (α). Predictive validity of CAARS-Inv-SV total and subscale baseline scores for 12-week scores were tested with an analysis of covariance model. Convergent validity was determined by Pearson’s correlation coefficients between the CAARS-Inv-SV total and subscale scores and CGI-ADHD-S scores at baseline and at 12 weeks.

Results: A total of 2017 patients (1217 E-patients [57.7% male; mean age 33.0 years] and 800 OE-patients [60.3% male; mean age 33.4 years]) were included in the analyses. In both patient populations, CAARS-Inv-SV showed good internal consistency (E-patients: Cronbach’s α=0.930; OE-patients: Cronbach’s α=0.930) and convergent validity (Pearson’s correlation coefficients: 0.65 to 0.82, P<0.001) with the CGI-ADHD-S scale over 12-weeks of treatment. Baseline scores on the CAARS-Inv-SV total, inattentive, and hyperactive/impulsive subscales showed significant predictive validity (P<0.001) for 12-week outcome scores.

Conclusion: The CAARS-Inv-SV was validated in adult patients with ADHD in a pan-European population. No substantial differences in scale validity were observed between patients from within and outside of Europe. Based on these results, use of the CAARS-Inv-SV is
P-17-003 Microdialysis and behavioural comparison of lisdexamfetamine dimesylate and methylphenidate in freely-moving rats

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Objective: The simultaneous collection of dual-probe microdialysis samples and locomotor activity data in freely moving rats administered lisdexamfetamine dimesylate (LDX; Vyvanse®), Shire US Inc), a d-amphetamine (d-AMF) prodrug, or immediate-release methylphenidate (MPH).

Methods: The effects of a range of comparable oral doses of LDX (d-AMF base = 0.5, 1.5, 4.5 mg/kg) and MPH (3, 10, 30 mg/kg) on extracellular levels of norepinephrine (NA), dopamine (DA) and 5-HT in the prefrontal cortex (PFC) and striatum (STR), and locomotor activity, were determined using the Culex Bambino.

Results: In the PFC, LDX dose-dependently and significantly (p< 0.05) increased efflux of NA (≥529% of baseline), DA (≥296%), and, at the highest dose, 5-HT (≥284%). MPH increased DA efflux (≥202%) at the low dose and both DA (≥217%; ≥343%) and NA (≥261%; ≥289%) at mid and high doses; it had no effect on 5-HT. In the STR, LDX dose-dependently increased extracellular DA (≥364%) and, at the high dose, 5-HT (≥359%). MPH (3.0 mg/kg) did not increase DA or 5-HT in STR but DA increases were produced at 10 mg/kg (≥131%) and 30 mg/kg (≥243%). MPH (30 mg/kg) only increased 5-HT efflux at one time-point. The actions of LDX and MPH in PFC and STR reached a plateau at 45–60 min, but locomotor effects were larger and more sustained. LDX did not significantly enhance locomotor activity at 0.5 mg/kg or 1.5 mg/kg except at two time-points. A small sustained increase (≥3.6/15 min) was seen at 4.5 mg/kg. All doses of MPH significantly increased locomotor activity (≥4.7/15 min).

Conclusion: LDX had larger and more sustained enhancing effects on NA and DA neurotransmission in PFC and STR than IR-MPH. That substantial increases in STR DA can be achieved without causing unacceptable locomotor activation predict that LDX will have a greater separation between efficacy and stimulant adverse events than MPH.

Policy of full disclosure: Studies funded by Shire Biosciences, Basingstoke, UK.

P-17-004 Lisdexamfetamine dimesylate and d-amphetamine – important differences for the relationships between extracellular striatal dopamine, locomotor activity and plasma drug concentrations in freely-moving rats revealed by hysteresis analysis

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Objective: Lisdexamfetamine dimesylate (LDX; Vyvanse®), Shire US Inc) is a prodrug of d-amphetamine (d-AMF) that is approved for the treatment of ADHD.

Methods: The Culex Bambino automatically collects intracerebral microdialysates, intravenous blood samples and simultaneously measures locomotor behaviour in freely moving rats. The effects of immediate release (IR) d-AMF SO4 (d-AMF base = 1.5 mg/kg ip) and LDX (d-AMF base = 1.5 and 5.0 mg/kg ip) on extracellular dopamine levels ([DA]) in the striatum, locomotor activity and plasma d-AMF concentrations (d-AMF) were compared over 8 hr.

Results: LDX dose-dependently increased striatal [DA] <300 min. The effect of LDX (1.5 mg/kg) on [DA] was gradual and sustained with maximum increase of ≥154% @ 75 min. IR-AMF (1.5 mg/kg) evoked a more rapid and substantial increase [DA] (≥129% @ 30 min). LDX (1.5 mg/kg) produced a small increase in locomotor activity, maximal between 90–180 min returning to pre-drug levels by 195 min. IR-AMF (1.5 mg/kg) evoked much more locomotor activity with an earlier peak (30 min) and shorter duration of effect. Three hysteresis analyses were performed. The most interesting and important difference came from the relationship between the changes in [DA] over time versus locomotor activity. The hysteresis was antclockwise for LDX, but clockwise for IR-AMF (P<0.05). Thus, with LDX the rats were less prone to activation as extracellular [DA] was rising, but reduced activation was maintained for longer when [DA] declined; the opposite was found for IR-AMF.

Conclusion: The findings are clinically important because subcortical DA is implicated in efficacy and side-effects of ADHD drugs. The sustained increase in [DA] and reduced locomotor activation predict that LDX will have an enlarged “therapeutic window” compared with IR-AMF. Moreover, the maintenance of LDX’s pharmacodynamic effect when CNS [DA] was declining indicates the unusual PK of LDX optimises the utilisation of its active metabolite, d-AMF.

Policy of full disclosure: Studies funded by Shire Biosciences, Basingstoke, UK.

P-17-005 Efficacy and safety of atomoxetine in Asian adults with ADHD: A multinational 10-week randomized, double-blind placebo-controlled Asian study

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Objective: This study aims to study efficacy and to assess the safety profile of atomoxetine compared with placebo in Asian adult patients with ADHD.

Methods: This study was conducted in Asian countries including Japan, Korea and Taiwan with approval of the ethical reviews boards. The Conners’ Adult ADHD Diagnostic Interview for DSM-IV (CAADDI) was used for Adult ADHD diagnosis. After obtaining informed consent, patients were randomly assigned to treatment with atomoxetine or placebo for 10 weeks. Atomoxetine was initiated at 40 mg once daily and then titrated up to a maximum of 120 mg once daily. The efficacy of atomoxetine versus placebo was evaluated using the mean change from baseline to endpoint in CAARS Inv: SV total score. Safety was assessed by adverse events (AEs), vital-signs, and ECGs.

Results: A total of 388 patients (atomoxetine, n=193; placebo, n=195) were included in the efficacy and safety analyses. The mean age (mean±SD) was 32.3±8.0 years; 52.3% of the patients were female. The study population consisted of patients from Japan (63.7%), South Korea (18.6%), and Taiwan (17.5%). The mean changes of CAARS Inv: SV total score were −14.3 (atomoxetine) and −8.8 (placebo) (p<0.001; effect size, 0.55). Statistically significant reductions in CAARS Inv:SV total scores following atomoxetine administration versus placebo were observed from week 2 to week 10, with a least-mean difference of 6.16 (p<0.001) at week 10. Treatment-emergent adverse events were reported more frequently in the atomoxetine group (80.8%) than the placebo group (53.8%) (p<0.001). Most AEs were mild or moderate in severity. Ten atomoxetine treated patients and 3 placebo patients discontinued due to AEs.

Conclusion: This is the first placebo-controlled clinical research for adults with ADHD in Asia. Atomoxetine was shown to be superior to placebo in reducing the symptoms of ADHD, and was well tolerated in adult Asian patients with ADHD.

Policy of full disclosure: Yūko Hirata, Yasuaki Takita and Michihiko Takahashi are employees of Eli Lily Japan KK. Taro Goto, Paula T Trzepacz and Alber t J Allen are employees of Eli Lilly and Company. Hironobu Ichikawa is an advisor of Eli Lilly Japan and has ever been invited as a speaker of Lilly-sponsored lecture meeting. Dong-Ho Song is an advisor for Eli Lilly Korea and has ever been invited as a chairperson/speaker of Lilly-sponsored lecture meeting.
Objective: The efficacy and safety of atomoxetine in adult ADHD patients were investigated in a double-blind placebo-controlled Asian study. This study compared Health—related QOL and Executive functions between atomoxetine-treated and placebo-treated patients in Asia.

Methods: This study was conducted in Japan, Korea and Taiwan with approval of the ethical reviews boards. The Corners’ Adult ADHD Diagnostic Interview for DSM-IV (CAADID) was used for Adult ADHD diagnosis. After obtaining informed consent, patients were randomized treatment with atomoxetine or placebo for 10 weeks. Atomoxetine was initiated at 40 mg/day and then titrated up to a maximum of 120 mg/day. Health—related QOL was measured by Adult Attention-Deficit/Hyperactivity Disorder Quality of Life (AAQoL). Executive functions were assessed by Behavior Rating Inventory of Executive Function—Adult Version (BRIEF-A): Self Report and Informant.

Results: A total of 388 patients (atomoxetine, n=193; placebo, n=195) were included in the analyses. The mean age was 32.3 (SD = 8.0) years; 52.3% of the patients were female. The study population consisted of patients from Japan (63.7%), South Korea (18.8%), and Taiwan (17.5%). The mean changes of AAQoL were significantly greater in total score (p < 0.001) and its components of life outlook (p = 0.049), life productivity (p < 0.001) and relationships (p = 0.007) in the atomoxetine group than the placebo group. Atomoxetine showed statistically significant reductions in global executive composite (p < 0.001), behavioral regulation index (p < 0.001) and metacognition index (p < 0.001) of the BRIEF-A self report, including all 9 components. Though the group differences in BRIEF-A informant components were not statistically significant, tendency for improvement in atomoxetine group were observed in behavioral regulation index, emotional control and task monitor.

Conclusion: This is the first placebo-control clinical research for adults with ADHD in Asia. Atomoxetine was effective in improving the disease—specific functional impairments measured by AAQoL and executive functions.

Policy of full disclosure: Yuko Hirata, Yasushi Takita and Michihiro Takahashi are employees of Eli Lilly Japan KK. Taro Goto, Paula T Trzepacz and Albert J Allen are employees of Eli Lilly and Company. Hironobu Ichikawa is an advisor of Eli Lilly Japan and has ever been invited as a speaker of Lilly—sponsored lecture meeting. Dong—Ho Song is an advisor for Eli Lilly Korea and has ever been invited as a chairperson/speaker of Lilly—sponsored lecture meeting. Susan Shur—Fen Gau is an advisor for Eli Lilly Taiwan and has ever been invited as a chairperson/speaker of Lilly—sponsored lecture meeting.
to clarify pathophysiological alterations in neurotransmission and brain regions related to their behavioral abnormalities.

Methods: Juvenile (4–5 weeks old) Male SHR and Wistar Kyoto rats (WKY) were used. Spontaneous activity of animals were evaluated with the open-field test. Fos protein expression in various regions of the brain was immunohistochemically stained using ABC-DAAB methods. In addition, the effects of a selective D1 antagonist SCH-23390 on open-field behaviors and brain Fos expression in SHR were also examined.

Results: In the open-field test, juvenile SHR exhibited a significant increase in ambulation and rearing activity as compared with WKY. Brain mapping analysis of Fos-immunoreactivity (IR) revealed that SHR showed a marked increase in Fos expression in the core part (ACc) of the nucleus accumbens (NAc). Small to moderate increases were also observed in the shell part of the NAc and some regions of the cerebral cortex (e.g., parietal association cortex). However, Fos-IR levels in other brain regions including the limbic area, striatum and diencephalon were unaltered. In addition, treatment of SHR with SCH-23390 (0.2 mg/kg; i.p.) significantly reduced behavioral hyperactivity in SHR. Elevation of Fos expression in the ACc and cortices in SHR was also reversed by SCH-23390.

Conclusion: The present study strongly suggests that D1 receptor-mediated transmission in the ACc is specifically elevated in SHR, which could be responsible for behavioral hyperactivity.

P-17-010 Identification and management of adult attention deficit disorder: Case discussions and brief literature review

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Objective: Introduction: Not all children with ADHD remit in adolescence and many continue to manifest a host of behavioral and lifestyle problems, and are often treated as ‘lazy’ or ‘disorganized’ by family members. Adult ADD needs more clinical and research attention. Objective: To describe the case histories and management of three patients diagnosed as Adult ADHD and present a brief review of relevant literature.

Methods: The case details of three adult male patients (Mr A, 25 yrs; Mr B 30 years and Mr C 34 years) presenting to the out-patient psychiatric clinic of V.I.M.H.A.N.S., New Delhi are being presented. All three patients reported long standing histories of difficulties experienced in organizing work or home affairs, poor time management/inability to keep appointments, at times not even making it on time for examinations/interviews, tendency to delay/procrastinate important things, frequent inattention towards the work at hand affecting the academic/job performance, multiple changes of job, considered to be ‘chronically lazy’ and ‘inattentive’ by family members. All three patients had childhood histories of ADHD.

Results: After a careful history and assessments, and ruling out any other psychiatric/medical comorbidity, a diagnosis of Adult ADHD was considered. They were initiated on stimulants and were carefully monitored. All the three patients responded well to Atomoxetine.

Conclusion: The diagnosis of adult ADD should be considered in all patients presenting with chronic histories of inattention. The childhood history of ADHD should be enquired from family members and if positive, these patients can be considered for an adequate trial of stimulant-based pharmacotherapy.

P-17-011 Conversion of lisdexamfetamine dimesylate to d-amfetamine: Low variability in exposure to d-amfetamine after administration of lisdexamfetamine dimesylate to children with ADHD

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Objective: Lisdexamfetamine dimesylate (LDX, Vyvanse®) is a long-acting prodrug stimulant that requires hydrolytic cleavage to generate active d-amfetamine. Preclinical studies indicate that LDX is rapidly absorbed via active transport, and is a likely substrate for PepT1 in the small intestine. Here, we describe the formation of d-amfetamine from LDX in human tissues maintained in vitro, and the low variability in d-amfetamine exposure in children with ADHD treated with LDX.

Methods: Studies on LDX hydrolysis were performed in homogenized tissues and fractions of blood obtained from human donors. Tissues were incubated (37 °C) with 1 μg/mL LDX, and samples were collected for <4 hrs. Variability in systemic exposure of d-amfetamine following administration of LDX 30 mg, 50 mg and 70 mg was examined in a single-dose, randomized, crossover study in boys and girls (6–12 years) with ADHD severe enough to require a treatment change.

Results: Half-lives for the disappearance of LDX were 1.6 h, 2.3 h and 9.7 h in whole blood, kidney and liver, respectively; LDX was stable in homogenates of upper and lower intestines, pancreas and plasma. When incubated with red blood cells (RBC), the half-life for the disappearance of LDX was 1.0 h; and there was still substantial conversion at 10–15% of normal haematocrit. In children with ADHD the diastolic activity of d-amfetamine increased proportionally with increasing LDX dose (mean [standard deviation] ng·h/mL: 30 mg, 84.4 [116.7]: 50 mg, 151.0 [241.6]: 70 mg, 215.7 [383.3]). The variability (percent coefficient of variation) in d-amfetamine AUC0–∞ was below 20% for all three doses of LDX (30 mg: 13.8%; 50 mg: 16.0%; 70 mg: 17.8%).

Conclusion: LDX was converted to d-amfetamine primarily in RBC. In children with ADHD, exposure to d-amfetamine increased in proportion to dose, and variability in exposure was low, within the therapeutic dose range (30–70 mg).

Policy of full disclosure: Studies conducted by Shire Pharmaceuticals Limited.

P-17-012 Does methylphenidate have an impact on ocular motor system? A controlled study on children with attention-deficit/hyperactivity disorder

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Objective: Attention-Deficit/Hyperactivity disorder (ADHD) is characterized by behavioral symptoms of inattention and may include hyperactivity and impulsivity. The impulsivity and inattention suggest deficits in the voluntary control of behavior. Eye movements depend on structures implicated in attention and in motor control, both areas critical of dysfunction in ADHD. In the present study, objective was to evaluate the effect of methylphenidate (MHP) on ocular motor system in ADHD children.

Methods: Subjects were aged 7–12 years, with ADHD on and off MPH (N = 9), and control subjects (N = 9). Saccade latencies, mean velocity, precision, accuracy and percentage of anticipatory errors were determined in visually-guided-saccades (automatic and voluntary attentional tasks) and antisaccades tasks.

Results: Significant differences existed between ADHD on MPH and ADHD off MPH, in latencies (p < 0.02), precision (p < 0.04), accuracy (p < 0.05) and percentage of anticipatory errors (p < 0.05). Compared to controls, ADHD on MPH had normalized performances, in automatic task, while they still impaired in voluntary attentional tasks.

Conclusion: MPH modified motor planning and response inhibition in ADHD children. Benefits depend on 1) the type of tasks (automatic and voluntary attention) and 2) the analyzed variables (motor control). These results suggest that eye movements could be a good predictor response to MPH.

P-17-013 Prevalence of adult attention deficit hyperactivity disorder in anxiety disorders sample

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Objective: Adult Attention Deficit Hyperactivity Disorder (ADHD) is a life-long, chronic disorder, affecting 8.1% of the US population.

Studies conducted by Shire Pharmaceuticals Limited.

Policy of full disclosure: Studies conducted by Shire Pharmaceuticals Limited.
ADHD is highly comorbid with other psychiatric disorders, however little is known about the prevalence of ADHD in anxiety disorder clinical samples.

Methods: Consecutive adult patients (N=264) at an anxiety disorders clinic in Hamilton Canada, completed the Adult ADHD self-report scale and were assessed with a Structured Clinical Interview for DSM-IV, and the ADHD module of the Mini International Neuropsychiatric Interview (MINI).

Results: The rate of lifetime ADHD was 37.3% (48.5% male, 51.5% female, p<0.05). Adult ADHD was significantly associated with lifetime comorbid diagnoses of impulse control disorder and bipolar disorder as well as a higher number of comorbid disorders. Symptom severity measure scores on the Padua Inventory, Yale-Brown Obsessive Compulsive Scale, Sheehan Disability Scale (SDS), Anxiety Sensitivity Index (ASI), the QUIIDS depression rating scale, the Penn State Worry Questionnaire and the Davidson Trauma Scale were significantly higher in those with ADHD. Individuals with ADHD, plus generalized anxiety disorder, and ADHD plus panic disorder with agoraphobia had higher scores on a variety of symptom severity measures than those without ADHD. Increased ADHD severity was associated with a greater number of lifetime comorbidity diagnoses, and higher symptom severity scores. Males were more likely than females to have received ADHD treatment in the past; 76% with adult ADHD had never received the diagnosis and 17.2% had received prior ADHD treatment. Of the patients who had received previous ADHD diagnoses, 25% were diagnosed in childhood.

Conclusion: The prevalence of lifetime ADHD was higher in our anxiety disorders clinic sample than that found in the general population. The presence of comorbid ADHD appears to have a significant impact on the severity and impact of comorbid anxiety disorders.


P-17-015 Decreased density of muscarinic acetylcholine receptors in fibroblast from boys with attention deficit/hyperactivity disorder (ADHD): An in vitro study

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Objective: The reduced density of muscarinic acetylcholine receptors (mACHRs) in fibroblast from boys with ADHD has been reported in previous studies. However, the density of mACHRs in fibroblast from boys with a hereditary ADHD has not been investigated.

Methods: Fibroblast cell homogenates from 11 boys with ADHD, fulfilling the DSM-IV diagnostic criteria and from 9 matching controls were used in the study. The maximal binding capacity (Bmax) and the equilibrium dissociation constant (KD) of mACHRs were determined by radioligand binding assay, using the mAChR antagonist 3H-QNB. Due to non-normally distribution of the calculated data, three outliers were identified by the MADE method (two in the ADHD group, both with a non-hereditary ADHD and one in the comparison group), and were therefore excluded from the statistical analyses (Student’s unpaired t-test).

Results: A significantly (p=0.01), lower Bmax for the binding of the muscarinic antagonist 3H-QNB was observed in the fibroblasts from the ADHD children (n=9) with a hereditary family history compared to controls (n=8), while the KD did not differ between the two groups (p=0.40).

Conclusion: The present results indicate a reduced density of mACHR in fibroblasts from children with a hereditary ADHD, which might be a marker of the disorder. However, further studies are needed to confirm these observations.

P-18. Neurophysiology

P-18-001 Simultaneous, but not separate activation of beta-1- and beta-2-adrenoceptors in the nucleus accumbens increases accumuald dopamine efflux in freely moving rats

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Objective: Dopaminergic neurons, which arise in both the ventral tegmental area and the substantia nigra pars compacta, terminate among others in the nucleus accumbens (NAc). The NAc receives a noradrenergic input from the locus coeruleus and the ventral medial area. The NAc contains beta-adrenoceptors. There exists a close beta-adrenoceptor mediated noradrenaline (NA) – dopamine (DA) interaction within the NAc. We have already reported that endogenous NA in the NAc activates accumbal beta-adrenoceptors that, in turn, enhance accumbal DA release (Eur J Pharmacol, 2008, 601, 94-98). In the present study, the effects of selective agonists of the beta-adrenoceptor subtypes on the NA and DA efflux in the NAc of freely moving rats were investigated, using in vivo microdialysis.

Methods: Male Sprague-Dawley rats were used. NA and DA levels in accumbal dialysates taken every 20 min were measured by HPLC-ECD system. Drugs were locally applied through the microdialysis probe.
Results: Neither beta-1– (dobutamine: 60 and 120 fmol) nor beta-2–adrenoceptor agonist (salbutamol: 0.36 and 3.6 pmol) altered the basal NA and DA efflux in the NAc. Co-administration of 60 fmol of dobutamine with salbutamol (0.36 or 3.6 pmol) also increased DA efflux till approximately 120% without affecting NA levels. The non-selective beta–adrenoceptor antagonist I-propanolol (1.2 nmol) which failed to alter the basal NA and DA levels, suppressed the DA efflux, induced by co-administration of dobutamine (120 fmol) and salbutamol (3.6 pmol).

Conclusion: The present study provides in vivo neurochemical evidence that simultaneous, but not separate activation of accumbal beta-1– and beta-2–adrenoceptors which are suggested to be located on the dopaminergic nerve endings in the NAc, stimulates accumbal DA release.

P-18-002 The role of the arcuate nucleus in the regulation of cytochrome P450 in the liver

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Objective: The monoamine neurons of the arcuate nucleus (ARC) produce and release growth hormone-releasing hormone. Growth hormone released in the anterior pituitary regulates the expression of cytochrome P450 (CYP). In particular, CYP2C11 – one of the main male rat isofoms. In our previous study we showed that the intra- cerebral ventricular injection of the noradrenergic neurotrans CYP450 leads to a decrease in the expression of CYP2C11 and CYP3A in the liver. The aim of present study was to estimate the role of noradrenergic innervation of the ARC in the regulation of cytochrome P450 expression in the liver.

Methods: The experiment was carried out on male Wistar rats. DSP-4 (N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine) was injected locally into the ARC. One week after the injection, the brains (and livers) were rapidly removed, dissected into selected structures and stored at −80 °C. The levels of noradrenaline, dopamine and serotonin in the part of the hypothalamus containing ARC were determined (HPLC). Liver microsomes were prepared and the activity of liver cytochrome P450 was measured as a rate of testosterone hydroxylation (HPLC).

Results: A substantial decrease in the noradrenaline level was observed after DSP-4 injection into the ARC. The levels of other neurotransmitters were unchanged. The activity of the CYP2C11 in the liver of the lesioned rats was significantly lower compared to the controls.

Conclusion: In conclusion, our study showed that destruction of the noradrenaline terminals innervating ARC results in the decrease of the activity of CYP2C11 in the liver. The finding seems to be of physiological and pharmacological importance since CYP2C11 constitutes the major part of male liver cytochrome P450 and is responsible for the metabolism of testosterone and some drugs such as lidocaine or propyrene. (Grant no. N405 304363 from the Ministry of Science and Higher Education (Warsaw, Poland) and statutory funds of the Institute of Pharmacology PAS).

P-18-003 First and second generation antipsychotic differences in 50 and 100 ms superior temporal gyrus paired-click gating

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Objective: Introduction: Auditory gating deficit continues to be a widely studied schizophrenia endophenotype. Degree of gating is typically measured via a paired-click paradigm that generates two evoked potentials (S1 and S2) at Cz. Individuals with schizophrenia often exhibit a diminished S1 response and higher S2/S1 50 ms (P50) and 100 ms (N100) ratio scores than controls. Previous studies suggest that atypical antipsychotics, particularly clozapine, may be associated with improved 50 ms Cz (PSO) ratio scores. Whether such effects are detectable at the primary neuronal generators of the 50 and 100 ms auditory response (superior temporal gyrus, STG) remains unstudied.

Methods: Methods/Hypotheses: Magnetoencephalography (MEG) source localization provided measures of left and right STG paired-click auditory S1 and S2 activity. As previous work demonstrates the importance of prefrontal (PFC) dopamine in enhancing brain signal-to-noise measures such as auditory responses, it was hypothesized that (1) compared to first generation antipsychotics, second generation antipsychotics are associated with smaller ratio scores due to a smaller degree of dopaminergic blockade, and (2) ‘normalization’ of gating is greater at 100 ms (M100) than 50 ms (M50), due to greater involvement of other cortices such as PFC modulating STG activity.

Results: In a sample of 74 healthy controls and 79 medicated schizophrenia patients (first to second generation ratio of 1:3), second generation antipsychotics were associated with improved gating, with S1 amplitude and ratio scores between healthy controls and patients on first generation Furthermore, these effects were most pronounced at left STG and for M100. No differences were detected among the second generation antipsychotics, although a trend of a more attenuated left S2 M100 response was seen with quetiapine and olanzapine.

Conclusion: Present findings support the hypothesis that auditory gating in schizophrenia is influenced by a left-dominant PFC-driven dopaminergic signaling pathway, a network sensitive to differences across antipsychotics in the degree of dopaminergic blockade.

P-18-004 Prepulse inhibition deficits in unmedicated patients with Parkinson’s disease

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Objective: Most patients with degenerative neurological diseases involving the basal ganglia, such as Parkinson’s disease (PD), present with functional abnormalities of brainstem reflexes. One method of interest for the assessment of brainstem functions is prepulse inhibition (PPI) of the startle reflex. PPI occurs because processing of the prepulse transiently inhibits brainstem interneurons involved in the generation of the reflex blink. In normal subjects, the response to the second stimulus is smaller than the response to the first stimulus, whereas there is evidence suggesting diminished PPI in PD patients. We aimed to determine whether PPI in PD is impaired at all intervals or whether only some specific PPI levels are impaired.

Methods: We used a sample composed of 49 unmedicated patients with PD and a control group of 37 healthy subjects. We used a commercial human startle response monitoring system (CIBERTEC, S.A.) to generate and deliver the startle stimuli, which were presented to subjects binaurally through headphones. The startle measures used were: prepulse inhibition percentages at 30, 60 and 120 milliseconds (% PPI-30, % PPI-60 and % PPI-120, respectively), and habituation percentage of the startle response. The SPSS statistical package version 15 was used for the statistical analysis.

Results: ANOVA only demonstrated a significant effect of group x intervals interactions at 120 ms (F(1,84) = 14.35, p < 0.001). Bonferroni post-hoc analysis determined that PD patients exhibited lower PPI at 120 ms (p < 0.001), whereas no differences were obtained regarding PPI at 30 and 60 ms and habituation.

Conclusion: Our data suggest that within unmedicated patients with PD, PPI is diminished at some levels compared to controls subjects. Therefore, this examination with PPI can provide relevant information on functional abnormalities in PD. Furthermore, studies with medicated patients with PD will be of interest, in order to determine whether these deficits still persist after being medicated.
**P-18-005** Alpha-1, but not alpha-2-adrenoceptor in the nucleus accumbens exerts an inhibitory control upon the accumbal noradrenaline and dopamine efflux in freely moving rats

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**Objective:** It is known that there exists a close alpha-adrenoceptor-mediated noradrenaline (NA)-dopamine (DA) interaction within the nucleus accumbens (NAc). We have shown that the alpha-adrenoceptor antagonist phentolamine and the alpha-adrenoceptor agonist phenylephrine increased and decreased accumbal NA efflux, respectively (J Neural Transm, 2007, 114, 1135–1142). Both alpha-adrenergic compounds increased accumbal DA efflux (Neuroscience, 2000, 99, 55–64). However, phentolamine and phenylephrine have a limited selectivity in terms of affecting alpha-1- and alpha-2-adrenoceptors. Therefore, by using selective alpha-1- and alpha-2-adrenoceptor ligands, we studied the role of alpha-adrenoceptor subtypes in the regulation of accumbal NA and DA efflux of freely moving rats.

**Methods:** Male Sprague-Dawley rats were used. NA and DA levels in the accumbal perfusate samples taken every 20 min were measured by HPLC-ECD system. Drugs were administered intracerebrally through the microdialysis probe.

**Results:** Alpha-1-adrenoceptor antagonist prazosin (6 nmol) increased the NA efflux by 207% and decreased the DA efflux by 43%, respectively. Alpha-1-adrenoceptor agonist methoxamine (24 pmol) that fails to alter the NA efflux reduced the DA efflux by 85%, and an ineffective dose of prazosin (6 pmol) counteracted these effects on DA efflux. Neither the alpha-2-adrenoceptor antagonist RO17-4955 (6 nmol) nor the alpha-2-adrenoceptor agonists UK14304 and clonidine (300 pmol) altered NA and DA efflux.

**Conclusion:** The present study shows that accumbal NA efflux is under tonic inhibitory control of alpha-1-adrenoceptor that are suggested to be presynaptically located on accumbal noradrenergic nerve endings. This study also indicates that the accumbal alpha-1-adrenoceptor that are suggested to be located on dopaminergic terminals, play an inhibitory role on the regulation of DA efflux. The presynaptic alpha-2-adrenoceptors play a major role in the regulation of NA and DA efflux in the NAc.

**Poster Sessions, Wednesday, 6 June 2012**
Results: Responders (n = 11) to ketamine in compare to non-responders (n = 18) showed significant difference in cordonate at the end of ketamine infusion (Spearman test, p = 0.039). The decrease of cor-
dance next day after ketamine infusion positively correlated with antidepressant response fourth day after infusion (two-tailed Fisher’s Exact test, df = 1, p < 0.0076; NPI 0.91 (95 % CI 0.64–0.99); PPV 0.63 (95 % CI 0.44–0.68)).

Conclusion: Our study confirmed the capacity of early prefrontal theta cordonate changes to anticipate the ketamine induced anti-
pressant response in patients with unipolar depressive disorder. More evidence is needed for utilizing predictive value of prefrontal
theta cordonate in clinical practice. The results also support the hy-
pothesis about common antidepressant mechanisms underlying both standard antidepressants and novel glutamatergic agents.

Policy of full disclosure: Supported by Ministry of Health of the Czech Republic (IGA MZCR NS/10579-3). The study was assigned
the number 2009-010625-39 in the European Clinical Trials Database (Eudra CT).

P-18-009 Does serotonin depletion augment or counteract the aggression-provoking effect of testosterone in mice?

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Objective: While sex hormones increase aggression in most mamm-
als, the neurotransmitter serotonin has been reported to exert the oppo-
site effect. Since testosterone influences various indices of sero-
tonergic transmission, one possibility would be that it exerts its pro-
aggressive influence by reducing a tonic anti-aggressive serotoninergic influence. Alternatively, however, the hormone and the transmitter may influence aggression-regulating areas by parallel, independent
paths. Here, we sought to shed light on these possibilities by assessing if testosterone is capable of enhancing aggression also in the absence of serotonin, assuming that, in the case testosterone enhances ag-
gression by reducing serotoninergic output, serotonin depletion would be at least as effective as testosterone in enhancing aggression, and that no pro-aggressive effect of testosterone above that induced by serotonin depletion would be found.

Methods: Male C57Bl/6 mice were gonadectomised, implanted with slow release testosterone or blank pellets and housed indivi-
dually after 3 weeks of recovery. During which territorial behaviour was established, baseline aggression was assayed using the resident intruder paradigm. After this, mice were treated with the serotonin synthesis inhibitor par-
chlorophenylalanine (pCPA) or saline for 3 days and re-tested 24 hours after the final dose of pCPA.

Results: While both groups of testosterone-treated animals displayed enhanced aggression as compared to hormone-depleted ani-
imals, serotonin depletion did not enhance aggression in mice lacking testosterone, and did hence also not diminish the difference between testosterone-treated and hormone-depleted animals. On the other hand, serotonin depletion did enhance aggression further in testos-
terone-treated mice (after omission of animals failing to display any aggressive behaviour in spite of hormonal replacement). The present study confirms that heavy cannabis users

P-18-011 The role of the dorsal noradrenergic pathway of the brain (the locus coeruleus) in the regulation of liver cytochrome P450 expression

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Objective: Cytochrome P450 (CYP) expression is regulated by endo-
genous hormones and cytokines which remain under control of the central nervous system. Our previous study indicated that in-
tracerebroventricular injection of the noradrenergic neurotoxin DSP-4 decreased noradrenaline concentration in the brain and the activity, level and mRNA of liver CYP2C11 and CYP3A. The aim of the present study was to investigate the role of the brain dorsal noradrenergic
pathway (the locus coeruleus) in the expression of liver cytochrome P450.

Methods: The experiment was carried out on male Wistar rats. The anesthetized animals were injected with 6-hydroxydopamine into the locus coeruleus. One week after the neurotoxin injection, selected brain structures (the cerebellum, hypothalamus, striatum, hippocampus, frontal cortex, rest of the cortex, anterior and posterior brain stem) and a liver tissue were isolated. The levels of neurotransmitters (noradrenaline, dopamine, serotonin) in those brain structures and the activities of CYP isoforms in liver microsomes (CYP1A: caffeine 8-hydroxylation and 3-N-demethylation; CYP2A, CYP2B, CYP2C11, CYP3A: testosterone hydroxylation) were deter-
mied by HPLC. CYP protein levels in liver microsomes were esti-
mated by the Western blot analysis.

Results: Local injection of 6-hydroxydopamine into the locus coe-
ruleus selectively decreased noradrenaline level in the brain structures
tested (except for the hippocampus and cortex). However, in contrast to the intracerebroventricular administration of DSP-4, the expression of isoforms CYP2C11 and CYP3A was enhanced.

Conclusion: Since locus coeruleus fibers innervate the paraven-
tricular subnucleus (PeV) of the paraventricular nucleus (PVN) of the hypothalamus, it is concluded that damage to the noradrenergic in-
nervation of the PeV (containing a growth hormone release- inhibiting factor) may be responsible for the enhanced expression of isoforms CYP2C11 and CYP3A, which is positively regulated by the growth hormone. (Grant no. N N405 304/06 from the Ministry of Science and Higher Education (Warsaw, Poland) and statutory funds from the Institute of Pharmacology, PAS).

P-18-012 Pharmaceutical choices in involuntarily admitted patients of the psychiatric hospital of Attica

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Objective: Since most mentally ill patients who are involuntary ad-
dmitted do not accept any kind of pharmaceutical therapies, mostly
P-19. Suicide

**P-19-001 Depression and history of suicide attempts are risk factors for pregnancy among adolescent girls**

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**Objective:** To examine if depression and history of suicide attempts are risk factors for pregnancy among adolescent girls.

**Methods:** A matched case-control study with cases and controls identified within a community-based demographic and health survey was conducted in La Paz Bolivia, from January 2010 to November 2011. A questionnaire was applied to 645 adolescent girls (9–19 years of age). Depressive symptoms were measured by the Center for Epidemiological Studies Depression Scale (CES-D), with score >16 indicative of elevated depressive symptoms. Conditional logistic regression was used to adjust for potential confounders.

**Results:** Respondents included 99 cases and 546 controls. Through multivariate analysis, depression [odds ratio (OR) 2.16, 95% confidence interval (CI) 1.24–3.77], the history of a prior suicide attempt (OR 2.16, 95% CI 1.24–3.77), the occurrence of an episode of depression (OR 2.16, 95% CI 1.24–3.77), and being less than 6 years in school at the time of the interview (OR 2.16, 95% CI 1.24–3.77) were associated with increased risk of adolescent pregnancies. As expected, another factors statistically associated in the multivariate analysis were: physical and sexual abuse during childhood-adolescence (OR 2.13, 95% CI 1.35–3.38,OR 2.07, 95% CI 1.05–4.49 respectively); being use of contraception (OR 3.51, 95% CI 1.92–9.65); history of anxiety disorders (OR 1.69, 95% CI 0.80–3.53); being less than 6 years in school at the time of the interview (OR 2.71, 95% CI 0.82–8.93); and living in a very poor household (OR 2.71, 95% CI 0.82–8.93).

**Conclusion:** These findings suggest that depression (including suicidality) may be a key mechanism accounting for pregnancy among adolescents. The study found that in addition to depression and lifetime and 12 month suicide attempts, having suffered from physical and sexual abuse during childhood-adolescence, being use of contraception, a reported history of anxiety disorders, lower education and living in a very poor household were associated with adolescent pregnancy in La Paz.

**P-19-002 Association between IL-8 and anxiety in suicidal patients**

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**Objective:** IL-8 (CXCL8) is a chemokine that controls migration of neutrophils. Emerging evidence suggests that IL-8 is also involved in diverse physiological functions in the CNS. However, the role of IL-8 in psychiatric disorders remains to be defined. The aim of this study was to assess if IL-8 is altered in patient with suicidal behavior.

**Methods:** We measured CSF and plasma levels of IL-8, as well as the genotype frequency of a single nucleotide polymorphism (−251A/T, rs4073) in the promoter region of the IL-8 gene, in suicide attempters compared to healthy controls. A total of 250 patients and 579 controls from several cohorts were included in the study. Plasma and CSF levels of IL-8 were quantified using ultra-sensitive electrochemiluminescence-based immunoassay. Psychiatric symptoms were rated with the Comprehensive Psychiatric Rating Scale with subscales for anxiety and depression.

**Results:** We found negative correlation between plasma IL-8 levels and anxiety scores in suicide attempters. In the CSF, low IL-8 was associated with more severe symptoms of anxiety in females and depression in males. Female suicide attempters had a significantly lower prevalence of the IL-8−251A allele. Moreover, the −251A allele was coupled to higher plasma IL-8 and lower anxiety.

**Conclusion:** Taken together these findings implicate IL-8 in the pathobiological mechanisms underlying symptoms of anxiety and depression.

**P-19-003 The suicidality in Thai population: A national survey**

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**Objective:** To study the rate of suicidality and factors related to the Thai people.

**Methods:** Nationally representative face to face household survey based on a stratified clustered sampling of people aging 15 to 59 (n = 17,140). The data were conducted between June and August 2008 using Mini International Neuropsychiatric Interview (M.I.N.I.) module C. Suicidality and general information questionnaire by trained psychiatric professionals. The data analysis was determined by means adjusted weight of rate generalized to Thai population and analyzed with descriptive statistical methods by accounting percentage of mean, proportions, standard errors, population estimation and probability inference from the data.

**Results:** The overall national rate of suicidality accounted for 7.3%, the severity risk of suicide was found mild 6.0%, moderate 0.6% and severe 0.7%. The highest risk of suicide was found in the north (8.8%, severe degree 1.3%) females (8.6%), age of 35 to 44 (8.1%), separated, divorced or widowed (11.8%), being unemployed (13.8%), mood disorders with psychotic features (87.9%), current manic episode (64.3%).

**Conclusion:** For effective surveillance and prevention of suicide in Thailand’s population, the focus should be on the population of Northern provinces, females, those in productive age, being unemployed and those concurrently having mental disorders particularly, mood disorders.

**P-19-004 The role of anxiety and its correlates in suicide re-attempters**

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**Objective:** Among the large population of suicide attempters, frequent re-attempters present specific features. They are significant consumers of health care resources. An increasing severity of the attempts could end to be lethal. They have also been associated with
Anxiety traits and diagnoses but the relationship of anxiety and frequent suicide attempts remains unclear.

Methods: We examine a large sample of suicide attempters that were assessed at a specialized unit of the Montpellier University Hospital. Only subjects with one-time lifetime suicide attempt (n = 477; one-time attempters) and subjects with more than two lifetime suicide attempts (n = 411; frequent attempters) were included in the analyses. These two populations were compared with regards to demographic, diagnostic and suicidal features, including characteristics of the first suicide attempt (Suicide Intent Scale, Scale of Suicide Ideation, age at first attempt). Trait anxiety scores of the State-Trait Anxiety Inventory (STAI) were also examined in a subsample of patients.

Results: Frequent attempters were more often females with family history of suicide behavior. Several lifetime diagnoses were associated with frequent attempters: affective disorders, eating disorders, alcohol and substance use disorders. Lifetime diagnoses of anxiety disorders differed significantly between one-time attempters and frequent attempters (p < 0.0006). Frequent attempters were also younger at their first attempt and presented higher suicide ideation scores. However, no difference was found in trait anxiety scores according to the STAI between subjects with and without lifetime anxiety diagnoses or one-time attempters and frequent attempters.

Conclusion: Anxiety diagnoses may be independently associated with frequent attempters when compared to one-time attempters. However, the negative finding of an association between anxiety traits, as measured by the STAI, and frequent suicide attempters limits the possibility of determining a cut-off level of anxiety to distinguish frequent attempters from one-time attempters. The lack of association between anxiety traits and diagnoses in suicide attempters warrants further investigation.

Epidemiological overview on pattern of suicide in the district of Tirana in Albania, over the period 2001–2010

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Objective: Suicide risk in patients with schizophrenia is 20 to 50 times higher than the general population. Recent data show increased association between schizophrenia and self-destruction or/and violence against others. Purpose of this study is to investigate pharmacological choice in patients with severe mental illness exhibiting suicidal and violent behaviour issues during their examination at the emergency department of Psychiatric Hospital of Attica.

Methods: The participants (423 patients) were selected randomly from the inpatients of the acute treatment departments of the Psychiatric Hospital of Attica. The statistical program SPSS has been used for the data analysis.

Results: 423 patients participate in the study. The mean age was 45.9 years and 60.8% were men. 63.7% were involuntary hospitalized and the mean age of the first episode was 28.4 years. The main diagnosis was schizophrenic disorders 72.1%, with the rest having bipolar disorders 16.8%, depression 11.1% and drug abuse 18.7%. The main reasons of admission were disease relapse 46.1%, discontinuation of medication 27% and aggression 24.3%. The presenting symptoms at the emergency department were: aggression against others 30.8%, self-destructive behavior 17.5%, verbal aggression 14.5%, aggression against objects 5.5%. At the admission 25.6% were administered with more than one antipsychotic drug and the second medication used was benzodiazepine at 53.7%, antidepressant at 19.1% and mood stabilizer at 16.8%.

Conclusion: Suicide is the most common cause of premature death among psychiatric patients suffering from both depression or schizophrenia. Several factors have been historically associated with suicidal behaviour such as alcohol or drug abuse. These have been repeatedly indentified as the most important factors for attempted or successful suicide and demand immediate care most efficiently with combination treatment.

Analysis of polymorphism in the gene for alpha-1 subunit of a voltage-dependent calcium channel in suicide victims

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Objective: Suicide is complex, multifactorial phenomenon, and is an outcome of interplay of environmental, genetic, and epigenetic factors. Slovenia belongs to the group of countries with the highest suicide rate in the world; in the year 2011 ranked 7th with suicide rate of 30.9 suicide victims per 100,000. In the present study we investigated association between suicide and gene for alpha-1 subunit of a voltage-dependent calcium channel (CACNA1C). Gene for CACNA1C is localised on chromosome12, and has 55 known exons, whereas 19 follow alternative splicing, consequently leading to numerous different combinations. Efficiencies of alternative splicing, having effects on alterations of neural transmission, have been associated with suicide. In gene for CACNA1C more than 200 single nucleotide polymorphisms (SNPs) have been identified, but very few have been studied. The most often investigated SNP was rs1006737 in the 3rd intron. In meta-analysis this SNP has been implicated in suicide in depressed, bipolar, and schizophrenic patients.

Methods: We analyzed polymorphism rs1006737 with quantitative real-time PCR using LNA probes in 599 subjects (384 suicide victims, 215 controls) of Slovenian nationality. We determined the impact of polymorphism on suicide, by comparing the distribution of genotypes and alleles between the groups of suicide victims and controls. For detailed analysis additional subgroups were formed (e.g. male, female, violent and non-violent suicide, alcoholics).

Results: Genetic analysis of polymorphism in suicide victims did not show a direct association with suicide in any of the studied groups.
Poster Sessions, Wednesday, 6 June 2012

P-19-009 CNR1 gene polymorphism and psychological functioning in persons who have attempted suicide

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Objective: An analysis of the psychological functioning of patients after their suicide attempts when compared to the comparative group and a description of the link between the occurrence of the polymorphism CNR1 – 1359 G/A (SNP rs1049353) and suicide attempts made by patients of psychiatric units. The work also aims at providing the answer to the question about whether there is a link between genotype 1359 G/A and a higher risk of suicide attempts.

Methods: 78 patients have made psychological tests. 1359G/A CNR1 polymorphism test was made in all patients by RFLP method. Allel frequencies were compared between control subjects and patient after suicide attempt. We analysed association between 1359G/A CNR1 polymorphism and suicide attempt.

Results: Allel frequencies did not differ significantly between two groups of subjects. There is significant difference between Individuals attempting suicide and the control group in their psychological functioning. There is no evidence for association between SNP rs1049353 and suicide attempt.

Conclusion: The genetic research and analysis of psychological tests reveal that a 1359 G/A polymorphism does not lead to so drastic a change in the functioning of the endocannabinoid system that this change would have any effect whatsoever on the functioning of other systems of neurotransmitters in the central nervous system and thus on leading to an increased incidence of suicide attempts in persons with this particular polymorphism.

P-20. Anxiolytics

P-20-001 Some psychotrophic effects of kolanut (colza nitida) extract on adult wistar rats

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Objective: Kola nut (Cola nitida) is a widely consumed snack in the western part of Africa, and observed effects on consumers indicate it possesses some pharmacological properties. Caffeine is the most active ingredient in the fruit and the potential of its interaction with prescribed medication underscores the necessity for investigations of its pharmacological properties.

Methods: This study investigated the effects of aqueous extract of Kola Nut (C. nitida) on novelty-induced behaviours, weight and food consumption patterns of adult wistar rats. Twenty rats (mean weight of 150.6 g) were divided randomly into two groups (Test and Control) of ten rats each. Each group was subjected to the same environment of experiments. The test group was fed with the aqueous extract of kola nut in addition to normal feed, while the control group had normal feed plus clean water.

Results: Test rats on kola nuts extract exhibited novelty-induced rearing (NIR), novelty-induced grooming (NG) and open field locomotion (OFL) at the first two days of oral administration in rats (P<0.05) but prolonged ingestion of the extract caused decreased effects (P<0.05). They also exhibited anxiolytic behaviour as measured by elevated plus maze on the first day (P<0.05) and anxiogenic behaviour after prolonged feeding with the kola nuts extract (P<0.05). The test group compared to the control group had significant weight loss (P<0.05) and progressive decrease in food consumption even when feeding with the kola nut extract was discontinued.

Conclusion: Kola nuts extract possesses anxiogenic, anxiolytic and anorectic properties. These properties could be exploited in designing weight reducing therapies since no toxicity has been associated with human consumption.

P-20-002 Amygdala response to SSRI s in social anxiety disorder

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Objective: Selective serotonin reuptake inhibitors (SSRIs) are commonly accepted as the first line pharmacological therapy for anxiety disorders and depression. However, there is a high percentage of patients that fail to achieve satisfactory response with SSRI treatments. The neural mechanisms underlying effective and ineffective outcome with SSRIs are not well characterized. The amygdala has dense serotonergic innervation, and studies have suggested the amygdala to be a crucial brain target for SSRI treatment. This study aimed at investigating differences in amygdala responsiveness between responders and nonresponders to SSRI treatments in patients with social anxiety disorder (SAD).

Methods: Stress-related regional cerebral blood flow (rCBF) was measured in SAD patients (n=35) with [15O]-water positron emission tomography (PET) during public speaking before and after 6-8 weeks of treatment with citalopram or paroxetine. Response rate was determined by the Clinical Global Impression-Improvement scale.

Results: Within-group comparisons revealed reduced rCBF response bilaterally in the amygdala in responders (n=20) as well as in nonresponders (n=15). Between-group contrasts revealed a greater amygdala attenuation in responders (>nonresponders) in the left basolateral/basomedial (x=16, y=6, z=14, Z=1.66, P[uncorr]=0.024) and right ventrolateral subregions (x=26, y=4, z=26, Z=2.12, P[uncorr]=0.009). However, greater rCBF attenuation in nonresponders (>responders) was observed in the left lateral amygdala (x=28, y=6, z=14, Z=2.38, P[uncorr]=0.005).

Conclusion: Lowered amygdala responsivity does not seem to be exclusively related to clinical phenomenology, but it may reflect a general impairment in the amygdala functions. In accordance with animal literature, our data suggest that amygdala subregions are functionally heterogeneous with regards to anxiolysis.

Policy of full disclosure: This work was supported by GlaxoSmithKline and the Swedish Research Council.

P-20-003 Rapid anti-anxiety effects in women of picogram quantities of a 19-carbon steroid

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Objective: Picogram (pg) quantities of androstadienone (ADO), a naturally occurring non-hormonal steroid in male skin, induces in vitro, robust inward currents in isolated patch recorded human nasal chemosensory neurons (Monti-Bloch, 1995). When administered intranasally to healthy women, ADO rapidly decreases tension, nervousness, and other negative feeling states (Grosser et al., 2000). Similar observations subsequently, have been shown by others (Jacob et al., 2001). Because of these findings, we studied the effects of androstadienol (ADOL), an odorless 19-carbon steroid and analog of ADO, administered intranasally to women with generalized anxiety disorder (GAD).

Methods: Nineteen women with GAD and a Hamilton Anxiety Scale (HAM-A)>18, selected after placebo run-in, were randomized for double blind treatment with 200 pg ADOL (N=11) or placebo (N=8) administered in a one second aerosol pulse directly to nasal chemoreceptors. HAM-A, Covi Anxiety Scale (COVI), and clinical electrophysiological measures (respiratory and cardiac frequency, electromyography, skin conductance, electroencephalogram, body temperature) were administered at randomization and 30 and 60 min later.

Results: Thirty min after administration of ADOL, there was a significant reduction in the HAM-A (p<0.03) and COVI (p<0.02). Seven of the 11 subjects administered ADOL exhibited decreases in the HAM-A of 50% or more whereas two of the eight controls had similar reductions. After 60 min, all significant improvements had disappeared. Electrophysiological readings were concordant with the reduction in anxiety.
Conclusion: 1. Nasal chemoceptors appear to be a portal of entry for substances affecting feeling states. 2. The rapid and temporary effect in GAD suggests that ADOL may be useful in rapid-onset and short-lived psychiatric conditions. FDA approved clinical trials of ADOL in social anxiety disorder are currently in progress.

Policy of full disclosure: Supported by funding from Pfizer Pharmaceuticals.

P-20-004 The influence of an α5GABAA selective agonist XLi356 on rats’ performance in Morris water maze
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Objective: The impairing effects of diazepam in Morris water maze (MWM) could be partially antagonized with co-administration of an α5 subunit selective agonist XLi356 (Savic et al., 2009). In order to further assess the role of the α5GABAA receptors population in mediating amnesic effects in rats, the present study examined effects of an α5GABAA selective agonist XLi356 on the MWM performance.

Methods: Male Wistar rats were given vehicle or 5, 10 and 20 mg/kg of XLi356 intraperitoneal 20 minutes before the testing. A single-day water maze task had three swimming blocks, each consisting of 4 trials, lasting a maximum time of 60 s each. Afterwards, a probe trial was given and a number of standard parameters was calculated. Additionally, rats were tested in spontaneous locomotor activity (SLA) and elevated plus maze (EPM) tests, where the sedative and anxiolytic effects were assessed.

Results: Results were analyzed using one-way ANOVA with post hoc Student-Newman-Keuls test where applicable. XLi356 significantly increased latency to platform (F(3,44) = 3.129; p = 0.026); post hoc test revealed that the dose of 20 mg/kg was significantly different from vehicle. The same dose of XLi356 significantly increased cumulative distance from the platform zone (p = 0.028) and the time spent in the periphery ring (p = 0.009), while the path efficiency was on the control level. On the other hand, XLi356 did not show behavioral activity in SLA and EPM tests at either of three doses tested.

Conclusion: The present results suggest that ligands with appropriate agonist activity at GABAA receptors containing α5 subunits may improve memory acquisition in Morris water maze task, without discernible effects on general behavior. Thus the activity of the benzodiazepine type drugs at α5GABAA receptors should be decreased if the amnesic effects are to avoid.

P-20-005 The investigation of 2-mercaptobenzimidazole derivatives interaction with sigma-1 receptors in mice
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Objective: At present sigma-1 (σ1) receptor is considered to be prospective target for neuroprotective and anxiolytic drugs. In 1Zakusov Institute of Pharmacology1 RAMS neuroprotector and anxiolytic afobazole (5-ethoxy-2-[2-(morpholino)-ethylthio] benzimidazole dihydrochloride) was developed. In vitro afobazole revealed ligand properties towards MT1, MT3, Ω1 receptors and MAOA with IC50 = 2.7 ± 10⁻³ M, 9.9 × 10⁻⁴ M, 7.1 × 10⁻⁴ M, 6.2 × 10⁻⁴ M correspondingly (Sereidenin et al., 2009). The main metabolite of afobazole (2-[2-(3-oxomorpholine-4-yl)-ethylthio]-5-ethoxy benzimidazole dihydrochloride) interacted only with MT3 receptors with Ki = 9.7 × 10⁻³ M. The aim of the research is to study the interaction of afobazole and its main metabolite with σ1 receptors versus prototype σ1 ligands of different pharmacological groups on mice ex vivo.

Methods: Binding experiments were carried out in 2 fraction obtained from brain of male CD-1 mice according Entrena et al. with slight modifications (Entrena et al., 2006).The radioactive ligand used in the assays was [Ring-1,3-3H] (+)-Pentazocine in final concentration of 1 nM. The cold ligands of different pharmacological groups were used with a concentration range of 10⁻¹–10⁻⁴ M.

Results: In ex vivo experiments the displacement curves of [Ring-1,3-3H] (+)-Pentazocine by afobazole versus ligands of different pharmacological groups were obtained. IC50 obtained for afobazole was 2.67±0.2 M. The value is close to compounds, considered as endogenous ligands DHEA and progesterone. IC50 for afobazole main metabolite was in the millimolar range. The results of research on male CD-1 mice confirmed the previously established ligand properties of afobazole and its main metabolite in regard to σ1 receptors in vitro experiments.

Conclusion: Binding experiment with afobazole versus prototype σ1 ligands on CD-1 mice was carried out. Due to the results obtained from the binding experiments afobazole can be regarded as a novel σ1 ligand.

P-20-006 Non-selective and α5 subunit-selective negative modulators of GABAA receptors in a single-day Morris water maze task in rats
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Objective: It is well known that benzodiazepine binding site ligands influence learning and memory and that the α5 subunit is significantly involved in cognition enhancement mediated by the negative modulation of GABAa receptors function. PWZ-029, a moderately selective α5GABAa receptor inverse agonist, improved learning in passive but not in active avoidance test, without effects on anxiety or muscle tone. The aim of this study was to investigate effects of PWZ-029 and DMCM, a non-selective inverse agonist, on learning ability and short-term memory in Morris water-maze (MWM) test.

Methods: MWM test was conducted 20 minutes after intraperitoneal administration of treatments (solvent, 5, 15 or 30 mg/kg PWZ-029 or 2 mg/kg DMCM) to male Wistar rats. The single-day MWM task consisted of 3 consecutive blocks of 4 trials lasting maximally 60 s each and a probe trial. During spatial learning the platform was hidden in the middle of the NE quadrant.

Results: Two-way ANOVA with one repeated measure (block) and animals nested in treatment has shown that latency to find the platform, path efficiency and total distance travelled were on the control level for DMCM and all doses of PWZ-029. Factors block and treatment were significant only for latency to first entry to the NE quadrant [block effect: F(2,36) = 10.50, p < 0.001, treatment effect: F(4,3) = 5.40, p < 0.05]. Tukey’s post-hoc test revealed that animals treated with DMCM and 5 mg/kg of PWZ-029 had longer latency to first entry to the target quadrant than those treated with solvent (p = 0.001, p < 0.001, respectively). Probe trial performance did not differ significantly between treatments.

Conclusion: These results suggest that neither non-selective nor α5 subunit-selective negative modulation of GABAa receptors is sufficient to enhance learning and short-term memory in the single-day MWM spatial task.

P-20-007 Riluzole produces distinct anxiolytic-like effects in rat innate anxiety models
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Objective: Growing evidence suggests that sodium channel blockers, such as riluzole and lamotrigine, are effective as non-benzodiazepine treatments of anxiety disorders. In the present study, we first investigated the anxiolytic-like effect of riluzole using innate anxiety models in rats.

Methods: Male Wistar rats were used for experiments. We used three different anxiety models, such as the elevated plus-maze, the light/dark and the open-field tests. A benzodiazepine, diazepam, was used as a positive control anxiolytic drug. To clarify the involvement of sodium channels in the anxiolytic-like effects of riluzole, we examined the effect of co-administration of the sodium channel activator, veratrine.

Results: In the elevated plus-maze test, riluzole (3 mg/kg) significantly increased the time spent in, and entries into, the open arm after 60 min administration. This finding was supported by results obtained from the light/dark and the open-field tests. The magnitude of
the anxiolytic-like effects of riluzole in each of the behavioral models was similar to those produced by diazepam (1 mg/kg). Interestingly, the anxiolytic-like action of riluzole was diminished by the co-administration of veratrine (0.1 mg/kg) in the elevated plus-maze, the light/dark and the open-field tests. In contrast, veratrine had no significant effect on the anxiolytic effects of diazepam in these tests.

Conclusion: In this study, riluzole produced robust anxiolytic-like effects in rats. In addition, it is also suggested that the anxiolytic mechanism of riluzole is clearly distinct from that of diazepam. The voltage-activated sodium channels may play some important roles in these anxiolytic-like effects of riluzole. We propose that riluzole would be considered as a candidate compound for the development of anxiolytics with novel class of actions.

P-21. Pharmacoeconomics

P-21-001 Antidepressant treatment optimization with BrainChip test: Effectiveness and costs
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Objective: BrainChip is a genetic biomarker test that determines CYP450 isoenzyme polymorphisms, making possible response prediction to pharmacological treatment of patients suffering from major depression disorder (MDD). The objective of this study was to assess the efficiency and the budget impact of BrainChip test addition after failure to a first line antidepressant treatment in Spain.

Methods: A Markov model was developed per each treatment after simulating regimen therapy changes derived from BrainChip test addition. Clinical parameters were collected from literature reviews, and health resource use and costs were calculated to the Spanish context. Budget impact results were analyzed during 3 years after BrainChip addition: the efficiency was studied after 1, 3, 5, 7, and 10 years. Both analysis were builtunder the National Health System (NHS) perspective and was considered a 3% discount for effects and costs (euro 2011).

Results: BrainChip improves patient remission around 9.5%–11.7% and patient response 5.5%–10.2%, reaching after 10 years a total response rate of 72%. Patients with MDD and BrainChip improve their quality of life between 0.04 and 0.25 in terms of quality adjusted life years. BrainChip cost will be compensated after 2 years, being always a cost-effectiveness alternative in a short term and dominant from the third year.24,308 out of 64,713 patients could receive an alternative therapy based on the results of BrainChip information. BrainChip can reach after 3 years cumulative savings of more than 13.6 million euros (6.8% of budget) taking into account direct costs, and 194.4 million euros in terms of total costs (direct and indirect).

Conclusion: BrainChip incorporation allows less risk on pharmacological prescription and health care cost reductions in MDD for the NHS, being a dominant option.

Policy of full disclosure: This study was funded by BRAINcoBiopharma, the manufacturer of BrainChip. Dr. Blanca-Tamayo M receive consulting fees from BRAINcoBiopharma, Crespo C. and Villacampa A worked in an independent consultant company and they got funds from BRAINcoBiopharma. Lobo S is an employee of BRAINcoBiopharma.

P-21-002 Is pharmaceutical industry influence distorting psychiatric practice?
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Objective: To examine the impact of pharmaceutical industry on psychiatric practice.

Methods: Interrogation of relevant information and data available in the public domain to construct the evidence base for evidence-based evaluation of the ways in which pharmaceutical industry related interests influence psychiatric practice.

Results: Pharmaceutical companies are amongst the most profitable in the corporate world and the margins are rising even as the pill for every ill culture penetrates the emerging economies. The oft-repeated argument that these high profit margins are justified by the high costs of research and development (R & D) of new drugs does not bear scrutiny. These companies spend thrice as much on marketing and advertisements, increasingly supplemented with aggressive direct to patient approaches, as on R & D. This in itself could perhaps be condoned as mildly laissez faire free-market capitalism, but what cannot be glossed over is the lack of transparency in the relationship between the industry and the medical profession. Doctoring research evidence by suppressing negative findings (“failed studies”), substituting the integrity of peer-reviewed medical journals through questionable tactics like ghost writing and passing off hired guns as independent experts are some of the shady tactics which threaten to distort clinical practice at the cost of good patient care. Disease-mongering is an even more worrying phenomenon and the extensive financial linkages of the experts drafting diagnostic systems like the DSM-V with the pharmaceutical industry have resulted in lowered thresholds of caseness and the manufacture of new disorders on an industrial scale. The implications, medical as well as economic, of these pernicious trends are wide and far-reaching.

Conclusion: The proposed presentation aims to examine the evidence in this regard, contextualizing the evidence within practices in the developed and developing world, evaluate possible remedial strategies, and suggest the way forwards.

P-21-003 Healthcare costs before and after diagnosis of depression in patients with unexplained pain: A retrospective cohort study using the United Kingdom general practice research database
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Objective: To assess the impact of pain severity and time to diagnosis of depression on healthcare costs for primary care patients with pre-existing unexplained pain who subsequently received a diagnosis of depression.

Methods: In this retrospective cohort study, 4000 adults (aged ≥18 years) with unexplained pain (defined as painful physical symptoms [PPS] without any probable organic cause) and a subsequent diagnosis of depression, identified from the UK General Practice Research Database using diagnostic codes, were analysed. Patients were categorised into four groups based on pain severity (milder or more severe based on pain-relief prescriptions with or without opioid use) and time to diagnosis of depression (<1 year or >1 year, respectively, from PPS index date). Health care costs were calculated (2009 values) and included GP consultations, secondary care referrals and prescriptions for pain-relief medication for the 12 months before depression diagnosis and in the subsequent two years. Multivariate models were adjusted for age, gender and co-morbid conditions.

Results: Total annual healthcare costs before and after diagnosis of depression for the four groups of patients were higher for the two groups with more severe pain (£819–£988 vs. £565–£628; p < 0.001 for all pair-wise comparisons) and highest for the group with more severe pain and longer time to depression diagnosis in the years subsequent to diagnosis (p < 0.05). Total GP costs were highest in the group with more severe pain and longer time to depression diagnosis both before and after depression diagnosis (p < 0.05). In the second year following depression diagnosis, this group also had the highest secondary referral costs (p < 0.01). The highest drug costs were in the two groups with more severe pain (p < 0.001), although costs within each group were similar before and after depression diagnosis.

Conclusion: Co-existing pain and late depression diagnosis contribute to higher costs for the UK healthcare system.

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P-21-004 Factors determining efficacy of specialized psychiatric help under conditions of primary care unit

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Objective: Using clinical diagnostic criteria of course and outcome of mental disorders co-morbid with somatic pathology to distinguish basic treatment programs and to assess their efficacy.

Methods: Clinical-diagnostic, clinical-follow-up “scale of efficacy of therapy of patients with borderline states”, SF-36, correlation and factor analyses. Material: 680 patients with mental disorders co-morbid with somatic pathology needing systematic therapy and dynamic observation by a psychiatrist.

Results: We have developed six rehabilitative programs with their gradual realization for patients with neurotic and somatoform disorders, organic mental and personality disorders, affective mood disorders, alcohol dependence, for elderly. Basic therapeutic stages: initial, basic therapy and maintenance therapy. Basic and important method of therapy at all stages of treatment was medication. Most effective and used preparations were tranquilizers (sonoral, radedorm, nozepam, phenazepam, grandaxin, sibazon, relandan); neuroleptics (sonopax, chlorprothixen, haloperidol, egnolin); antidepressants (amitriptiline, fluoxetin, azafen, pirazidol, anafranil). Conducted by us investigations during 25 years allowed distinguishing basic and obligatory principles of therapy providing its quality and efficacy, gradual character, complexity (treatment of somatic and mental pathology), sufficiency (necessary volume of therapy with minimum side-effects), individual-differentiated approach (along with other factors, account for financial possibilities), accessibility (not only territorial but also psychological), continuity (collaboration of psychiatrist and physicians at all stages of therapy), cooperativeness (possibility of concomitant curing by doctors of various specialties). According to data of follow-up and assessment of efficacy of treatment programs, recovery has been achieved in 46.2% of cases, stable remission in 15.6%, improving in 27.9%, deterioration in 1.4%, and 3.0% of patients in hospitals. Temporary disability decreased in patients with somatoform disorders as many as 1.8 times and number of not grounded seeking for help and examinations per 1 patient during the year as many as 2.3 times.

Conclusion: Integrative approach to medical help rendering as well as all-sided differentiated and grounded medication were enough effective according not only on clinical but also economic indices.

P-21-005 Investigations of the accessible drugs used for central nervous system in Bangladesh: An explorative survey among medical-staffs and patients

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Objective: Drugs are usually distinguished from endogenous biochemicals by being introduced from outside the organism. Drugs acting on the central nervous system (CNS) influence the lives of everyone almost every-day. Drugs affecting the CNS are important therapeutically because they may relieve pains, fevers, suppress disorders of movement, induce sleep, reduce the desire to eat, inhibit motion sickness, and schizophrenia etc. Generally CNS patients are not found in the willing for operation. In that cases the CNS products can also be proved as a key factor for the earning of foreign currency through its export.

P-21-006 The brain-derived neurotrophic factor (BDNF) polymorphism Val66Met is associated with neither serum BDNF level nor response to paroxetine and sertraline in depressed Japanese patients

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Objective: We investigated the relationship between the brain-derived neurotrophic factor (BDNF) polymorphism (Val66Met) and the clinical response of patients with major depressive disorder to selective serotonin reuptake inhibitors (SSRIs; here, paroxetine and sertraline). In addition, serum BDNF levels in these patients were considered together with the clinical response.

Methods: A total of 132 patients who met the DSM-IV criteria for major depressive disorder were enrolled in the study. Of these patients, 54 were male and 78 were female (age range, 20–74 years; mean ± S.D., 51 ± 15). The patients’ clinical improvement was evaluated using the 17-item of Hamilton Rating Scale for Depression (HAM-D-17) at before (T0), and at 8 weeks after, the administration of SSRI treatment (T8). Patients with at least a 50% decrease in the HAMD-17 score were classified as responders.

Results: No correlation was observed between BDNF Val66Met polymorphism and response to SSRIs or between BDNF Val66Met polymorphism and serum BDNF levels at T0. An inverse correlation was found between serum BDNF levels and HAMD-17 scores at T0.

Conclusion: These results suggest that the BDNF Val66Met polymorphism is independent of both the response to SSRI treatment and serum BDNF levels. The finding in the present study reconfirms that serum BDNF level is a state biomarker for depression.

P-21-007 A cost-consequence analysis of long-acting injectable risperidone in schizophrenia: A one-year mirror image study with national claim-based database in Taiwan

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Objective: The development of long-acting, injectable, second-generation antipsychotics (SGA) has provided a new treatment paradigm to improve treatment outcome of schizophrenia. Recent studies have demonstrated that risperidone long-acting injection (RLAI) treatment was associated with significant reductions in relapses and hospital service utilization. This study was designed to assess the change of service utilization and costs for schizophrenia before and after treating patients with RLAI in Taiwanese national database.

Methods: This 1-year mirror image study was conducted with national claimed-data. Comparison was made for service sectors and cost components (outpatient, inpatient, emergency, medication and non-medication costs).

Results: Service uses reduced in the post-RLAI period, with significant reductions of inpatient service costs. However, overall psychiatric service costs went up by 26%, with increases of 190% on total non-medication costs.

Conclusion: With significant reductions of inpatient service uses, overall psychiatric service costs were compromised by costs incurred from increased outpatient service and RLAI medication costs.

P-21-008 Improving somatic health for outpatients with severe mental illness; the development of an intervention

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Objective: Patients with severe mental illness (SMI) suffer from more somatic illness than the general population. Possible causes are side effects of neuropsychiatric medication, genetic vulnerability, and...
insufficient health care and lifestyle. This co-morbidity is potentially reversible and augments the costs for health care and diminishes quality of life. Screening on symptoms and risks of somatic diseases and coordination of care are proposed to improve SMI-patients' somatic health status.

Methods: A clinical facility was started to improve the somatic health status of patients in an outpatient centre in southern Netherlands. This outpatient centre was added to the specialized care for severe and enduring SMI. The intervention consisted of the inventionisation of side-effects and the detection of gaps in health care provision for 72 patients. This was based on interviewing the patients, laboratory screening, collecting information from their general practitioner and pharmacy. A list was compiled of possible diagnosis and health risks, and a plan of action was made for the treatment. Healthcare consumption, quality of life and general functioning were assessed to analyze cost-effectiveness. Evaluations were performed with the psychiatric care team on the process.

Results: Mean annual cost of GP’s and medical specialist’s consultations were €492. There existed a negative relation between EQ5D VAS and the number of self reported chronic diseases.

Conclusion: The authors conclude that the procedure is well feasible, but should be set up in close collaboration with all health care professionals of these patients to make tailor made solutions possible.

P-22. Brain Stimulation/Deep Brain Stimulation

P-22-001 Psychiatric side effects of bilateral monopolar high frequency stimulation or stimulation at the ventro-medial part of the subthalamic nucleus in patients with parkinson’s disease

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Objective: To investigated the relationship between contact location within the subthalamic nucleus (STN) or stimulation parameters during programming and the occurrence of psychiatric side effect in patients with parkinsonian’s disease (PD).

Methods: Fifty consecutive patients with PD with bilateral STN DBS were enrolled in a 6-months follow up study. Patients’ spontaneous utterances or behaviors were systematically identified during DBS parameter optimization. The location of each of the stimulating electrode contacts within the STN was verified post-operatively. stimulation parameters (polarity, voltage, pulse width, and frequency) were recorded at each follow up visit.

Results: Within 6 months of follow-up period, there were 29 instances (in 15 patients) of emotional or behavioral induction [EBI (+)] at time of adjustment of stimulation parameters to obtain better control of tremors. The majority (86%: 13/15 patients) of experienced EBI occurred during stimulation of ventro-medial contact. The frequency of EBI (+) instances was significantly higher (Fisher’s Exact p-value = 0.042) in subjects who received bilateral monopolar stimulation compared to subjects who received non-monopolar stimulation on at least one side. The presence of EBI was associated with lack of improvement in depressive symptoms and quality of life.

Conclusion: We found significant association between bilateral monopolar stimulation or stimulation at the ventro-medial contact and the EBI (+) status. The neurobiological underpinnings of this relationship remain to be investigated.

P-22-002 Regulation of dopaminergic brain functions by exercise or music

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Objective: Our previous studies suggested that the convulsions in epileptic mice rectify the decrease in dopamine synthesis in the brain through the calcium/calmodulin-dependent system and subsequently improve abnormal physiology. These studies led to the hypothesis that neurologic disorders that involve dopamine dysfunction require intense movement to improve the principal disorder. On the other hand, we suggested that music also enhances this pathway. In this study, the effect of daily activities such as exercise and music on brain functions was investigated.

Methods: Spontaneously hypertensive rats (SHR) were used to confirm this hypothesis. A decrease in calcium-dependent dopamine synthesis results in hypertension in SHR.

Results: Exercise or exposure to music increased serum calcium levels, and the calcium was transported to the brain and in turn enhanced dopamine synthesis. The subsequent increase in dopamine rectified hypertension and various other disorders.

Conclusion: Our animal experiments indicate that exercise and music rectify dopaminergic functions and related disorders. We suggest that the activities of daily life such as participating in exercise and listening to music might regulate and/or affect various brain functions through dopaminergic neurotransmission. These daily life experiences therefore might lead to the amelioration of symptoms of various diseases, such as hypertension, Parkinson’s disease, dementia with Lewy bodies, epilepsy, and attention-deficit/hyperactivity disorder. Also, it is possible that abnormal movements in neurologic disorders, such as tremor in Parkinson’s disease, wandering around and fuge in senile dementia, and movement in attention-deficit/hyperactivity disorder, in addition to convulsions in epilepsy, play a role in improving the principal disorder.

References

P-22-003 In vivo alpha2 adrenoceptor binding demonstrates a prolonged effect of electroconvulsive therapy on noradrenergic function in Gottingen minipigs

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Objective: Major depression is one of the leading causes of disability, affecting 121 million individuals worldwide. Approximately one third of depressed patients are unresponsive to antidepressant drugs. Brain stimulation therapies, such as electroconvulsive therapy (ECT) are potential alternatives for drug refractory patients. The noradrenergic (NA) hypothesis of depression posits a deficiency in cortico-limbic NA circuitry. It is supported by the increased presence of NA receptors in the cortex of depressed suicide victims and the effective antidepressant actions of NA reuptake inhibitors. Our objective is to investigate the longitudinal effect of ECT, a highly effective non-pharmacological antidepressant, on NA neurotransmission.

Methods: Here we use positron emission tomography and the alpha 2 adrenoceptor antagonist tracer [11C]yohimbine to study the effect of ECT on NA receptor binding in cortical (frontal, temporal and occipital cortices) and limbic (hippocampus and amygdala) regions in Gottingen minipigs. Seven female adult minipigs were anesthetized with isoflurane and scanned prior to the onset of a clinical course of ECT (baseline), and at 24–48 hours and 8–10 days after the end of ECT (10 ECT sessions in anesthetized animals over a 3.5 week period).

Results: The volume of distribution of yohimbine binding to alpha 2 adrenoceptors was decreased after ECT treatment in all the cortical and limbic regions considered by 15–22% at 24–48 hours after ECT, and by 12–16% 8–10 days post-ECT. Binding data from 3 animals that were scanned at 6–8 weeks after the end of the ECT treatment showed either return to baseline, increased compared to baseline or continued decrease, reminiscent of the wide variability in length of efficacy of the antidepressant effect of ECT observed in the clinic.

Conclusion: The decrease in alpha2 adrenoceptor binding after ECT treatment may suggest increased NA release and/or receptor downregulation. Potential increased NA neurotransmission in the
The brain stimulation by pulsed low-intensity electromagnetic fields (PLEF) in acute ischemic stroke (AIS) patients with psycho-vegetative disorders, within 24 hours of symptom onset

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Objective: To study the possibility of the usage the PLEF brain stimulation within the first 24 hours of acute ischemic stroke onset. To research the psycho-vegetative and neuro-hemodynamics indices changes, under transcranial PLEF effect in AIS patients.

Methods: The randomized, double-blind, placebo-controlled study of PLEF brain stimulation had been done in 60 AIS patients. The main group (30 patients) had received the drug therapy and the PLEF treatment, which had begun within the first 24 hours of acute ischemic stroke onset. PLEF (2 mT/cm, 30 Hz) brain stimulation was carried out through optical-vegetative system. It was applied 3 minutes per day, 12 days. The 1-st control (15 patients) applied electric field-placebo (device not included) and drugs. In the 2nd control (15 patients) were used only drugs. In all groups of patients used comparable drug therapy.

Results: In the main group after the treatment course it was showed the positive dynamics of clinical symptoms: reducing of psycho-somatic changes, improved locomotion. The increase percentage slow waves (electroencephalography data) correlated with decrease sadness. It had been estimated the control glycine blood level, reduction of cortisol, what correlated with decrease anxiety. In the main group had been indicated the improve cerebral blood circulation by doppler sonography computed tomography, IMR data. It was a indicated a more pronounced dynamics of clinical and laboratory indices effectiveness of the treatment in the main group compared to controls.

Conclusion: It had been stated the improving psycho-somatic, neuro-hemodynamic indices by the early pulsed low-intensity electromagnetic fields brain stimulation in the examined patients.

The role of transcranial magnetic stimulation in cognitive processes and treatment psychiatric disorders

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Objective: Transcranial magnetic stimulation (TMS) is a neuro-stimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain. This field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, even beyond the duration of the train of stimulation. This has behavioral consequences and therapeutic potential. Due to its easy use and relatively fair side effects, nowadays transcranial magnetic stimulation is widely used in neurosciences and medicine.

Methods: The method of research in this paper is review of literature in that researches that applied TMS for treatment and investigation goals. 104 paper relative to the subject were studied and results gathered here.

Results: TMS through induce the electric field is a useful instrument to visualize regional activities in response to stimulation, the mechanism of effect of TMS is induce depolarization of neurons that in turn activate other neurons and produces behavioral and cognitive outcomes, depends on the stimulated area and its function. For example some of the observable TMS-induced effects are induce phosphenes in stimulation occipital cortex or interrupt working memory and speech processes due to stimulate frontal lobe or improving verbal memory in major depressive disorders through modulating effects on dopaminergic system. TMS has effects on neurochemical and synaptic processes in neurons. depression, mania, schizophrenia, pain disorder, hallucination, catatonia, post traumatic stress disorders, obsessive-compulsive disorder, Parkinson’s disease, and epilepsy were improved by TMS procedure.

Conclusion: Current published studies and meta-analyses have evaluated the efficacy of TMS as given in treatment paradigms that are almost certainly suboptimal (e.g. of two weeks' duration) TMS is a safe and tolerable intervention. These findings raise the possibility of using TMS as a therapeutic device in psychiatric disorders and neuroscience researches.
stimulation inhibits DA neural activity, resembling phasic “dips” associated with reward prediction errors. What is unclear is how phasic suppression of DA neural firing may modulate choice in cost/ benefit decision scenarios. Accordingly, the present study examined the effects of temporally-discrete stimulation of the LHb on probabilistic decision-making.

**Methods:** Rats were trained on a discounting task entailing choice between a small/certain (1-pellet) and a large/uncertain reward (4-pellets). The odds of obtaining the larger reward decreased systematically over a session (50-12.5%). Following extended training, electrical stimulation of the LHb (20-80 pulses, 100 Hz, 200 μA) was delivered following or prior to certain outcomes/actions (ie; immediately after a large/risky “win”, after smaller/certain reward delivery, prior to a choice, during the inter-trial interval).

**Results:** Phasic manipulation of LHb activity influenced probabilistic choice. Specifically, stimulation of the LHb only after risky “wins” decreased choice of the large/uncertain option. Conversely, stimulation only after receipt of the small/certain reward had the opposite effect, increasing risky choice. Similar effects were observed on non-stimulation probe trials, when the large or small reward was never delivered, which decreased/increased risky choice, respectively. Importantly, LHb stimulation did not affect preference for larger vs. smaller reward when both were delivered with 100% certainty. Ongoing experiments are investigating the effects of LHb inactivation on risky choice.

**Conclusion:** These results suggest that phasic activation of the LHb (and presumably, inhibition of DA neurons) provides an important “reward emission” signal that can bias decision making in situations involving reward uncertainty.

**P-23. Miscellaneous**

**P-23-001 The neurosteroid dehydroepiandrosterone sulfate suppresses neuroinflammation produced by human and feline immunodeficiency viruses**


**Objective:** Neurosteroids, cholesterol-derived molecules synthesized within the brain, can exert trophic and protective actions. Infection by human (HIV) and feline (FIV) immunodeficiency viruses causes neuroinflammation and neurodegeneration. The objective of the study reported here was to investigate interactions between neurosteroids and lentivirus infection outcomes.

**Methods:** Human brain tissue was obtained from a brain bank in the Division of Neurology at the University of Alberta. In the FIV studies, cats were infected with FIV-Ch29 at day 1 postnatal. Behavioural tests included gait analysis, a modified T maze (to test spatial memory, cognitive learning capacity and performance speed) and an emotion test.

**Results:** Analyses of postmortem brain tissue from HIV-infected and infected persons disclosed a reduction in expression of 5α-reductase, P450bcc and 3βHSD, enzymes involved in the synthesis of neurosteroids, in neurons of HIV-infected samples. Neurons exposed to supernatants from HIV-infected macrophages exhibited suppression of 5α-reductase and 3β-HSD expression (p <0.05) without re-duced cellular viability. We then focused on dehydroepiandrosterone sulfate (DHEA-S) and found that HIV-infected macrophages treated with this neurosteroid showed suppression of inflammatory gene (IL-1β, IL-6, TNFα) expression (p <0.05). Treatment of HIV-infected cats with DHEA-S resulted in a reduction of inflammatory gene transcripts (IL-1β, NF-kB, CCL2, G-CSF) in brain (p <0.05), and blood CD4+ T-cell levels were increased in DHEA-S-treated FIV-infected animals (p <0.05). DHEA-S treatment also markedly reduced neurobehavioral deficits and neuronal loss among HIV-infected animals (p <0.05).

**Conclusion:** Thus, reduced neuronal neurosteroid-related enzyme expression accompanied lentivirus infections but treatment with DHEA-S limited inflammation and neurobehavioral deficits. Neurosteroid-derived therapies might be effective in the treatment of virus- or inflammation-mediated neurodegeneration. (Funded by CIHR, AHFMRI, the Canada Research Chairs program and the University of Alberta).

**P-23-002 Cerebral ischemia in mice: Neuroprotection by progesterone and curcumin**

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**Objective:** Ischemic damage to brain leads to morbidities like seizures, motor functional loss, memory impairment and others. The study was designed to evaluate the effects of progesterone and curcumin on sub-acute phase changes induced by partial global cerebral ischemia in male, Swiss strain mice.

**Methods:** Animals were randomized into four groups (6 animals per group): Sham- operated and Saline-, Progesterone- and Curcumin – treated surgically operated groups. Cerebral ischemia was produced by bilateral common carotid artery occlusion with aneurysmal clips for 10 min followed by reperfusion in anesthetized animals. On post-ischemic day 15, the animals were subjected to: Behavioral studies on elevated plus maze, rotarod, hole- board and kainic acid (20 mg/kg intraperitoneal) – induced seizure susceptibility tests; Biochemical studies for estimation of whole brain tissue malondialdehyde (MDA), catalase, super oxide dismutase (SOD), glutathione peroxidase (GPO) and TNF-α: Histopathological study of brain. The protocol was approved by Institutional Animal Ethics Committee.

**Results:** Compared to the Sham- operated group, the Saline-treated surgically operated group showed significant decrease in the exploratory behavior in hole-board, retention time on rotarod and entry into the open arm of the plus maze while there was significant increase in the closed-arm entry in plus maze and seizure susceptibility to kainic acid; brain levels for MDA and TNF-α were increased while that for SOD, catalase and GPO were reduced significantly following ischemia; ischemia caused significant increase in the histo-pathological score. Intrapetional administration of progesterone (15 mg/kg) and curcumin (300 mg/kg), once-a-day, for post-ischemic 14 days, showed significant reversal of the data for all the parameters compared to the Saline- treated surgically operated group of animals.

**Conclusion:** The study showed the antioxidant and neuroprotective effects of progesterone, a neurosteroid and curcumin, a phytophenolic compound against cerebral ischemic injury during the sub-acute phase in the mice model.

**P-23-003 Alterations in gene expression of FG2 in HIV and major depressive disorder**

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**Objective:** Altered expression of neurotrophic factors has been implicated in both the pathology of human immunodeficiency virus (HIV) infection and major depressive disorder (MDD) in the brain and may be linked to the higher incidence of MDD in the HIV+ population.

**Methods:** This current investigation assessed gene expression changes of fibroblast growth factor 2 (FG2), microtubule-associate protein 2 (MAP2), growth arrest and DNA damage-inducible protein 45 beta (GADD45β), somatostatin (SST), and serum/glucocorticoid regulated kinase 1 (SGK1), previously implicated in neurodegenerative and mood disorders, in the frontal cortex of a novel brain cohort from patients with documented HIV, MDD, or HIV with MDD (HIV/ MDD) by qRT-PCR. We further assessed the contributing effects of HIV and cortisol, known to be elevated in MDD, in primary human neuronal-glial in vitro cultures exposed to 6000 pg/ml HIV (Bal) and/or 500 nM cortisol after 6 and 24 hours.

**Results:** Post-mortem FG2 was increased in both HIV and HIV/ MDD compared to controls (p <0.01) but was significantly lower in HIV/MDD compared to HIV alone (p <0.01). Additionally, MAP2 was significantly decreased in HIV and HIV/MDD (p <0.05) and was significantly correlated with FG2 in the post-mortem HIV group (p =0.02). Increased GADD45β and decreased SST were detected in...
post-mortem HIV and HIV+MDM groups (p < 0.05). With the exception of SST, expression changes correlated with directional changes in vitro.

**Conclusion:** Whilst we did not detect significant changes specific to MDD or cortisol alone, upregulated FG2 in the brains of HIV patients may reflect a neuroprotective mechanism which is diminished in patients with comorbid MDD and associated reduction in MAP2. Our overall findings indicate that HIV is associated with compensatory gene expression changes of several neurotrophic and mood-related genes in the brain.

**Results:** Group-rate analysis found that no tests except PAL showed significant impairments at baseline to Week 4. In event-rate analysis, 13(45%) patients had no cognitive deficit or superior performances whereas 16(55%) patients still had cognitive deficits from baseline with 0.68 ± 0.69 of the mean number of cognitive deficit variables at Week 4. Pearson’s correlation analysis found no correlations between the number of microinfarctions and the cognitive sum z-score at both Week 1 and Week 4 (r = −.18, p = 0.35; r = 0.06, p = 0.79). No correlation was also found between the number of microinfarctions and any individual test score.

**Conclusion:** Neuropsychometric evaluation of patients undergoing coil embolization for UIAs demonstrates recovery or improvements after one month in general. However, we failed to prove any relationships between cognitive changes and microinfarct lesions.

**Results:** Olig1-immunoreactive oligodendrocytes are elevated in the white matter of the anterior cingulate gyrus in patients with major depression

**Objective:** Alterations in oligodendrocyte cell density, thickness of myelin sheaths and expression of myelin-associated genes have been described in patients with affective disorders and schizophrenia. This may indicate impaired myelination, leading to disturbed connectivity of brain regions which are relevant for the pathogenesis of affective disorders and schizophrenia. In this context, the transcription factor Olig 1 is of particular interest, because it is expressed by oligodendrocytes and choline in myelin-repair.

**Methods:** In this postmortem study, the cell density of Olig1-immunoreactive oligodendrocytes was analyzed in the pregenual anterior cingulate (pACC, Brodmann Area 24/32) and dorsolateral prefrontal (DLPFC, Brodmann Area 9) cortices, including a separate analysis of the adjacent white matter in 8 patients with major depression, 8 patients with bipolar depression, 13 patients with schizophrenia and 12 matched control subjects. Statistical analyses were performed with analysis of variance (ANOVA) followed by post-hoc Tukey-HSD Tests.

**Results:** A significantly increased density of Olig1-immunoreactive oligodendrocytes was observed in patients with major depression compared with controls, particularly in the white matter of the pACC. These findings could indicate a regenerative attempt in order to reestablish connectivity between the pACC and other brain regions, such as the limbic system or the medio-dorsal thalamic nucleus in subjects with major depression. Impairment of pACC- connectivity with these brain regions has been shown by various MRI-studies (Liu S. et al., 2011, Anand et al., 2009).

**Conclusion:** This study reveals an increased expression of Olig1 in patients with major depression compared to healthy controls, particularly in the white matter of the pACC. These findings could indicate a regenerative attempt in order to reestablish connectivity between the pACC and other brain regions, such as the limbic system or the medio-dorsal thalamic nucleus in subjects with major depression. Impairment of pACC- connectivity with these brain regions has been shown by various MRI-studies (Liu S. et al., 2011, Anand et al., 2009).

**Results:** Perceptual disturbance in schizophrenia is related to differential EGRF mRNA expression in cortical layers in post mortem brain

**Objective:** There is emerging evidence for dysregulation of the Epidermal Growth Factor (EGF) system in schizophrenia (SCZ). Previously we have shown that the antipsychotic drug clozapine transactivates the EGF receptor (EGFR) which may relate to its effectiveness in treatment resistant SCZ. We hypothesised therefore that EGRF changes in schizophrenia may be related to the clinical characteristics of the disorder and examined EGFR mRNA expression in the DLPFC (Dorsolateral Pre Frontal Cortex) (BA46) of post mortem tissue from people with SCZ and healthy controls.
Methods: Messenger RNA expression was measured using in-situ hybridization in a cohort of 37 patients with SCZ and 37 controls matched for age, sex, post-mortem interval and pH. All samples were obtained from the NSW Tissue Resource Centre (University of Sydney). Relevant parametric statistical analyses with post hoc tests and correlation coefficients were computed.

Results: In schizophrenia, people without auditory hallucinations (AH) had significantly higher EGFR mRNA expression in layer VIa compared to those with AH (AH negative 0.071±0.008 pg/μg mean±sem vs. AH positive 0.054±0.002 pg/μg; p=0.043, t=2.11, df=35) and this trended to significance in layer VI (AH negative 0.009±0.01 pg/μg vs. AH positive 0.052±0.002 pg/μg; p=0.057, t=1.97, df=35). In schizophrenia with visual hallucinations (VH) EGFR mRNA expression was significantly higher in layers II (VH negative 0.063±0.008 pg/μg vs. VH negative 0.044±0.002 pg/μg; p=0.006, t=2.96, df=35) and III (VH positive 0.067±0.007 pg/μg vs. VH negative 0.050±0.002 pg/μg; p=0.01, t=2.65, df=35). There were no main effect differences between schizophrenia and control groups and no other differences within the schizophrenia group with regards other symptoms or clinical parameters.

Conclusion: EGFR mRNA dysregulation may be implicated in the pathology of perceptual disturbances within schizophrenia, and this varies between auditory and visual perceptual modalities.

**P-23-009** Therapeutic management of borderline personality disorder in emergencies

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Objective: To describe demographic and clinical factors of BPD patients that visit PES and their association with psychotropic drugs and hospitalization indication.

Methods: Socio-demographic, clinical, severity and treatment variables are collected from visits attended at PES during a 4 years period. Logistic regression model is used to analyze which factors are related to pharmacotherapy and hospitalization.

Results: A sample of 11,578 patients was obtained. 1032 (8.9%) received BPD diagnosis and were mostly women (n=653) with a mean age of 31±9. Psychiatric and substance abuse history were more common in BPD group (p<0.001). They showed more severe symptoms, frequently related to behavior disorders (27%) or anxiety (21.5%). Anxiety was the condition more frequently related to benzodiazepines prescription for BPD patients (OR 3.77, IC 95% 2.52-5.66). Female gender (OR 0.52, IC 95% 0.35-0.76), substance abuse (OR 0.58, IC 95% 0.38-0.88), improper self-care (OR 0.61, IC 95% 0.42-0.88) and lack of family support (OR 0.49, IC 95% 0.27-0.87) decrease likelihood of receiving benzodiazepines. Psychotic symptoms (OR 6.68, IC 95% 1.64-28.90) and danger to others (OR 2.07, IC 95% 1.39-3.06) increase probability to prescribe antipsychotics. BPD patients were less hospitalized (p<0.001). High risk of suicide (OR 10.33, IC 95% 6.38-16.71), opposition to treatment (OR 4.50, IC 95% 1.89-10.69) or danger to others (OR 2.55, IC 95% 1.59-4.11) were variables related to hospitalization.

Conclusion: Although clinical presentation was more severe in BPD patients, hospitalization was less indicated. The use of psychotropic drugs was more common in BPD patients with an atypical socio-medical profile.

**P-23-010** Personality traits of different professional groups and their impact on coping with stress and job satisfaction

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Objective: Temperament is the most stable dimension of personality. According to the recently validated questionnaire TEMPS-A, there are five distinguishable types of temperament, including depressive temperament, cyclothymic, hiperthymic, irritable, and anxiety temperament. All of the above except for the hiperthymic temperament predispose to psychiatric disorders. With the help of this test one may also predict propensity for addiction. The aim of this study was to evaluate the temperament of different social groups. The study looked at seven different groups. The survey examined ways of coping with stress and the level of job satisfaction.

Methods: The examined group included 77 people, including 30 men and 47 women aged from 21 to 60 years. Mental illness was ruled out in all participants, all of them agreed to participate in the study. We used the TEMPS-A questionnaire to assess temperament, while Minnesota’s questionnaire was used to assess the level of job satisfaction and the COPE questionnaire was used to assess the style of coping. The results were analyzed using Statistica 9.0.

Results: Among the interviewees there was 35 people (45.5%) with no specific temperament, 19 (24.6%) with mixed temperament and 23 (29.9%) people with a determined temperament. Among those of determined temperament, hiperthymics dominated (65%). We observed significant differences in the various study groups and found that there is a correlation between temperament and the level of job satisfaction, but found no clear correlation between the type of temperament and the strategies used to cope with stress.

Conclusion: It may be imortant to evaluate the personality traits of people working in different professions in order to achieve a better job satisfaction. The problem of coping with stress seems to be a more complex phenomenon and needs further investigation.
Methods: 22 cross sectional and longitudinal studies were reviewed.

Results: Older subjects most frequently presented with avoidant and dependent PDs followed by schizoid PDs. Borderline personality disorder became less impulsive but relationship instability persists. Extraversion, Agreeableness, Conscientiousness, and Intellect declined significantly in old age. Neuroticism declined up to the age 70. Extraversion, Agreeableness, Conscientiousness, and Intellect declined significantly in old age. Neuroticism declined up to the age of 70.

Conclusion: Some personality disorders are being diagnosed more frequently because of the bias created by some DSM criteria for PD diagnosis. It seems that a dimensional approach might eliminate this bias, thus allowing for a better diagnosis and management of personality disorders in the elderly.

P-23-012 Childhood trauma, telomere length and hiv-associated neurocognitive impairments in women
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Objective: The neuropathogenesis of the human immunodeficiency virus (HIV) may manifest as various neurocognitive impairments (NCI). HIV-positive individuals also have significantly shorter telomere length (TL) in peripheral blood mononuclear cells (PBMCs) and CD8+ T cells compared to HIV-negative individuals. Additionally, reduced TL has been found to be associated with chronic psychological stress. This study focused on the effects of chronic stress associated with childhood trauma and HIV status on telomere length and investigated whether leukocyte TL (TLt) in particular represents a risk factor for NCI.

Methods: 83 HIV-positive and 45 HIV-negative women were assessed for childhood trauma and were subjected to detailed neurocognitive testing. Blood from each participant was used to extract DNA. Relative TLt were determined by performing real time quantitative PCR reactions as described by Cawthon et al. (2002).

Results: As expected, relative TLt in the HIV-positive individuals was significantly shorter than that of HIV-negative individuals. Notably, in HIV-positive participants a significant positive correlation was evident between relative TLt and learning performance. Within the HIV-positive group, there also was a significant difference between trauma groups, with a negative correlation between relative TLt and verbal fluency within the trauma group.

Conclusion: Our results suggest that reduced TLt negatively influences the learning process in HIV-positive individuals, indicating that TLt could act as a susceptibility factor in increasing neurocognitive decline in HIV-infected individuals.

P-23-013 The dopamine D2 receptor (DRD2) – 141C Ins/Del polymorphism affects the personality traits of healthy Japanese participants
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Objective: Dopamine neurotransmitter systems have been associated with emotional and novelty-seeking personality traits. We investigated the possible relationship between the personality traits measured by the Temperament and Character Inventory (TCI) and the Taq1 A and –141C Ins/Del polymorphisms in the dopamine D2 receptor gene (DRD2).

Methods: The sample consisted of 1084 healthy Japanese medical students and medical staff (age = 29.0±9.7 years), each of whom completed the TCI. Their genomic DNA was isolated from whole blood and genotyped using the TaqMan allelle-specific assay method. The associations between gene polymorphisms and the scores for TCI were statistically analyzed by one-way analysis of covariance (ANCOVA) adjusting age. Males and females were analyzed separately. Epstatis was assessed using two-way ANCOVA between the DRD2 and ANKK1 genes.

Results: Men with the Ins/Ins genotype of the –141C Ins/Del polymorphism had significantly higher self-directedness scores than those with the Ins/Ins genotype (p = 0.021). None of the TCI scores differed among women with regard to the three genotype groups of the –141C Ins/Del polymorphism. The DRD2/ANKK1 Taq1 A polymorphism did not affect any TCI factor for either men or women. An epistatic analysis did not reveal main effects of the two genes with regard to TCI scores, but an ANKK1 × DRD2 interaction significantly predicted TCI scores.

Conclusion: These findings suggest the possibility that the –141C Ins/Del polymorphism and the DRD2/ANKK1 Taq1 A polymorphism are not strongly linked to personality traits directly, but influences them under the interaction between the DRD2 and ANKK1 genes.

P-23-014 Exercising autonomy
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Objective: The concept of autonomy occupies a central role in both the legal and ethical frameworks governing clinical practice. In the latter half of the twentieth century this new ethical principle has emerged, resulting in many changing in patient centered models of care, shared decision making processes and stricter requirements for consent processes. One important change is from long term inpatient, to daycare patient to outpatient, the balance between individual and public interests.

Methods: Participants were patients with diagnosis of severe mental disorders treated in psychiatric clinic in Constantza by a psychiatrist at list six months, with good compliance to treatment, with good therapeutic alliance and good improvement on CGI scale. During a period of four years clinical, demographic and routinely collected outcome data was obtained from clinical case notes for people who were patients with diagnosis of severe mental disorders. They received letters from psychiatrists to their family doctors, and they were asked to change the visit of their family doctor to the psychiatrist. Outcome and engagement data were collected on 79 service-users who were included in the study.

Results: Data was collected over three distinct time periods, first contact until transfer, time under the care of family doctor, and time under the care of psychiatrist or in-patient, during a period of four years. Findings suggested that some factors were associated with less admittance and less bed days, for example treatment compliance determined by perception of usefulness of treatment, quality of therapeutic interactions and openness.

Conclusion: Clinical and demographic variables associated with good outcome were single service users, longer than three years and those who did not use substances and who were well engaged in change. Better engaged clients might more easily accept the need for early or even voluntarily admission, which in turn has been shown to reduce length of hospitalization. The engagement once developed is fairly stable over several years and collaboration with treatment increases over time.

P-23-015 The effects of modafinil on ‘cold’ cognition, creativity, and motivation in healthy volunteers
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Objective: The aim of this study was to investigate the effects of modafinil on cognition, motivation and creativity in healthy volunteers.

Methods: A double-blind placebo-controlled parallel design study evaluated the effects of 200 mg of modafinil (n = 32) or placebo (n = 32) in non-sleep deprived healthy volunteers. Reliable tests of divergent and convergent thinking were used to measure creativity. The difficult versions of the CANTAB tasks were used to measure executive function. Finally, subjective effects were measured using a novel motivational salience task.

Results: For the CANTAB tasks, significant improvements with modafinil were seen on a load dependent manner (p < 0.05). On a test...
The effects of modafinil on ‘cold’ cognition, creativity, and motivation in healthy volunteers

Ahmad O. Mohamed, Ulrich Müller, Christopher L. Cook, James D. Rowen, Timothy Ritnan, Trevor W. Robbins, and Barbara J. Sahakian

Background

Modafinil, a novel wake-promoting agent licensed for the treatment of narcolepsy, has been shown to significantly improve performance on ‘cold’ cognitive tasks such as working memory, cognitive flexibility, and planning in healthy volunteers and in patients with neuropsychiatric disorders (McKenna and Sahakian, 2010). It has also recently been reported to increase performance on tasks such as the Remote Associates Task (RAT; Rotello et al., 2010), which as a result of its higher modafinil yields within effects on cognition and whether it affects other brain cognitive processes (such as motivation) and creativity. These points of this study were to investigate the effects of modafinil on motivation and creativity in healthy volunteers. However, there were no prior studies examining modafinil effects on RAT; Rotello et al., 2010) and convergent thinking (Gendlin 1974) were used to measure creativity. The different versions of the CANTAB on Tract (Breen et al. 2001) were used to measure salience.

Methods

A double-blind placebo-controlled parallel design study evaluated the effects of 200 mg of modafinil (n=25) or placebo (n=25) on cognitive and measured healthy volunteers. Reliable tests of divergent (Clare & Hennon, 2000) and convergent thinking (Rotello et al., 2010) were used to measure creativity. Performance on the different versions of the CANTAB on Tract (Breen et al. 2001) were used to measure salience and motivation. Finally, the effects of modafinil on a novel measure of subjective motivation, valence, and pleasure were investigated. Differences between group scores were analysed using ANOVA.

Results

Performance on the RAT improved significantly in the modafinil group in comparison to placebo (p<0.05). Performance on the CANTAB on Tract (Breen et al. 2001) was greater for the modafinil group relative to the placebo group (p<0.05). The total ratings were significantly greater in the modafinil group relative to the placebo group (p<0.05).

Conclusion

This is the first study investigating the effects of modafinil on objective measures of creativity. We demonstrated improvements in creativity by modafinil but only in subjects who had low trait creativity at baseline. Similarly, Farah et al. (2003) reported improvements in forms of creativity when subjects were in adolescent but not in those individuals who had baseline levels of creativity. We also confirmed improvements on tasks of ‘cold’ cognition. It was independently reported that when CANTAB on Tract (Breen et al. 2001) was more difficult, performance improved under modafinil. This improvement was seen in a placebo study with a version of this task due to ceiling effects (Turner et al., 2003). The delayed version of CANTAB on Tract (Breen et al. 2001) was more difficult, and performance improved under modafinil. This improvement was seen in a placebo study with a version of this task due to ceiling effects (Turner et al., 2003). The delayed version of CANTAB on Tract (Breen et al. 2001) was also improved, performance improved under modafinil. This improvement was seen in a placebo study with a version of this task due to ceiling effects (Turner et al., 2003).

Pharmacotherapy in pregnancy and breastfeeding: Clinical database

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Objective: Decision on drug treatment of mental disorders in pregnancy and lactation is based on available information on teratogenic effects, neonatal toxicity, withdrawal symptoms, or long-term neurobehavioural effects of drugs on fetus and infant is based mostly on anecdotal case vignettes, case series, drug registries, and epidemiological studies.

Methods: In the Prague Psychiatric Center, a specialized outpatient clinic for treatment of mental disorders in pregnancy and lactation was established in 2005. The Clinic provides treatment, counseling, and consultation services. We present an overview of our clinical experience and summarize treatment recommendations.

Results: Our clinical database currently includes 148 patients (54% diagnosed with anxiety disorders, 24% psychotic, 9% depressive, 7% bipolar, 5% personality disorders, and 1% behavioral syndromes. Approximately 20% pregnant patients were without drug treatment. Clinical complications were observed in 14% cases. Experience with administration of psychotropic drugs and the most frequent adverse outcomes are reviewed, including the use of alternative non-pharmacological interventions (psychotherapy, ECT, rTMS).

Conclusion: In general, monotherapy is recommended, changes in prescription should be avoided. Preferred are drugs with low number of metabolites, higher protein binding affinity and low potential for drug-drug interactions. Our results support the notion that the cautious use of psychotropic drugs in pregnancy and breastfeeding may be associated with a low number of drug-induced complications. Supported by the research project MZ0PCP2005.
Comparison of pharmaceutical treatment in patients hospitalized in different acute departments of psychiatric hospital of Attica

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Objective: Despite the constant recommendations for avoiding anti-psychotic polypharmacy and the absence of a convincing reasoning in such pharmaceutical treatment, the combination of antipsychotic drugs remain a common and widespread practice. The aim of this audit is calculating the prevalence of polypharmacy in hospitalized patients, and finding out if there are any differences concerning medication options among the 9 acute departments of Psychiatric Hospital of Attica.

Methods: Participants (423 inpatients) were selected randomly among the 9 acute departments of Psychiatric Hospital of Attica. The statistical program SPSS was used in the analysis.

Results: Participants (423 inpatients) had the following characteristics: Age of 45.9 years on average (SD = 13.1), 60.8% males, 63.7% involuntary hospitalized, onset of disease 28.4 years (SD = 12.1), with a diagnosis of schizophrenia disorder in 72.1%, bipolar disorder in 16.8%, and depression in 11.1%. Use of illegal substances in 18.7% with cause of hospitalization: destructive or self-destructive behaviour in 24.3%, disease recurrence in 46.1%, and discontinuation of drug treatment in 27%. During their hospital admission, their aggression decreased to 22.9% with verbal aggression estimated to be the main type (14.4%). 41.9% of patient treatment involved more than one antipsychotic. Despite the similar profiles of patients hospitalized in different acute departments of the Psychiatric Hospital of Attica, we revealed great differences concerning the treatment options and the use of multiple concomitant formulations.

Conclusion: There is a concern about the balance between the risks and the benefits of polypharmacy in psychiatry. The combination of several drugs should be the last option for treatment of resistant psychiatric disorders. In future, prospective observational studies on this issue should be conducted among the different acute departments of the Psychiatric Hospital of Attica in order to decide about the best practices for the treatment of mentally ill patients.

Medication used in aggression in a sample of involuntarily hospitalized patients at the psychiatric hospital of Attica

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Objective: Violent behavior and psychiatric disorder such as schizophrenia seem to be strongly associated with the involuntary hospitalization in the mind of people outside the mental health system. The aim of the present research is to study the choice of pharmaceutical drugs in patients who were involuntarily hospitalized in the psychiatric hospital of Attica and have exhibited aggression or/and violent behavior while either arriving to the emergency department of the hospital or throughout their hospitalization.

Methods: Data collection was made by randomly selected 532 patients who were involuntarily hospitalized in the psychiatric hospital of Attica from 01/08/08 to 03/09/10. The statistical program SPSS was used for the data analysis.

Results: Our sample consists of 532 patients, mean age 43.64 yrs (SD = 13.7), 64.3% male, 63.3% of which diagnosed with the schizophrenia spectrum disorders, 10.8% with bipolar disorder, 5.1% with depression and 24.1% with other diagnoses. Our research showed that 92.7% of the patients were escorted by the police, while 11.1% was escorted by an ambulance, and 6.2% by relatives. That wasn’t justified by the absence of any kind of aggression in 46.4% of them, as 12.6% were in need to be placed under protective restraint. In 32.7% of them, typical antipsychotics were administered, in 59.4% of them atypical antipsychotics were used and in 5.1% of the patients a combination of both typical and atypical antipsychotics. There was a need to administer intramuscular antipsychotics in 34.4% of our sample.

Conclusion: In patients who are hospitalized involuntarily, have no capacity to decide for their self and show increased aggression, the need for intramuscular antipsychotic drug treatment and protective restraint is decreased after their involuntary admission in the hospital.
Exploding head syndrome – case study and therapeutic approaches

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Objective: Exploding head syndrome (EHS) is a relatively rare type of paroxysm characterised by a sense of an explosive loud banging noise in the head usually in the twilight stage of sleep. The sudden awakening due to this loud noise shortly after falling asleep is occasionally accompanied by the sensation of a flash light. Ablupt electroencephalographic and electromyographic changes during polysomnography indicate suddenly increasing alertness in stage N1 or stage N2 sleep at the time of the attacks. Although EHS attacks are usually quite painless, however, they may precede migraines in certain cases.

Methods: The authors present the case of a 47-year-old female patient suffering for EHS attacks for 4 years. The painless attacks were characterised by auditory sensations as if noisy lorries would quickly pass by. In roughly one third of the cases sparking flash light was simultaneously perceived. After a sudden awakening palpitation and excessive sweating was often reported by the patient. However, migraine or other type of headache has never been related to the attacks.

Results: EHS patients are mostly reported to require getting reassured about the benign nature of the rush. Beyond that, treatment with clomipramine is suggested by some authors. Thus, in our case 75 mg clomipramine has been administered as a first therapeutic approach. Due to disturbing adverse effects (blurred vision, drowsiness, and constipation), however, clomipramine medication had to be ceased and topiramate therapy (50 mg in the evening) has been gradually launched. From the third week of the treatment on, no EHS attacks could have been observed any more.

Conclusion: The aetiology of EHS is still unclear. A detailed analysis of polysomnographic data could probably help in understanding the underlying pathophysiology. The plausible link to migraine may encourage clinicians to choose new therapeutic strategies, administering for example topiramate or some other second- or third-generation antiepileptic drugs.

Elevated levels of serum plasminogen activator inhibitor-1 are associated with very severe sleep disturbances in individuals with a history of elevated depressive symptoms

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Objective: Plasminogen activator inhibitor type 1 (PAI-1) is an acute-phase reactant and an inhibitor of intravascular fibrinolysis. Its increased levels lead to pathological intravascular fibrin deposition (Aso, 2007). Elevated PAI-1 levels have been reported to associate with disturbed sleeping disorder, but not with self-reported sleep quality (Matthews et al., 2010). Furthermore, depressive symptoms also modulate PAI-1 levels (Lahlu-Laforet et al., 2006). We sought to examine the association between sleep disturbance and the serum levels of PAI-1 in a population-based sample with a history of elevated depressive symptoms.

Methods: A total of 136 general population study participants, who reported elevated depressive symptoms (Beck Depression Inventory (BDI) >9; Beck et al., 1961) at least once during the earlier study phases (1998, 1999, or 2001), participated the clinical part of the study in 2005. They rated their sleep disturbances as none or mild and occasionally as moderate to very severe (n=46), and recorded data on socioeconomic status and lifestyle. They were also examined to diagnose metabolic syndrome. Circulating PAI-1 levels were analysed with a human serum adipokine LincoPlex kit using a Bio-Plex Suspension Array System.

Results: Individuals with moderate to very severe sleep disturbance had elevated levels of PAI-1, and each 1 standard deviation increase in the level of PAI-1 was associated with an almost doubled likelihood of belonging to the disturbed sleep group (OR 1.91, 95% CI 1.22–2.98, p = 0.004) in a logistic regression model adjusted for age, gender, BDI scores and metabolic syndrome. No differences between the sleep disturbance groups were observed with regard to socioeconomic or lifestyle variables.

Conclusion: Elevated circulating levels of PAI-1 were independently associated with disturbed sleep, which may lead to increased vulnerability to adverse vascular events in this group.
REM sleep behavior disorder in psychiatry-a case control study

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Objective: REM sleep behavior disorder (RBD) is a sleep disorder characterized by loss of normal REM-related muscle atonia with enactment of violent dreams and sleep-related injury. In recent years, RBD variants have been reported in young population, women and psychiatric population. While early case reports suggested that RBD symptoms in psychiatric patients were secondary to antidepressant treatment, we found that the lifetime prevalence of RBD symptoms in psychiatric out-patients was 5.8% and the risk of developing RBD symptoms among those taking selective serotonin reuptake inhibitor (SSRI) was only 1 out of 20.

Methods: This is a case-control study, aimed at establishing the clinical and polysomnographic features of RBD in psychiatric populations. Two age-, sex-matched control groups were selected: 1) one from psychiatric clinic (also psychiatric diagnosis matched) and 2) healthy controls. All case and control subjects undergo standard measurements, including self-reported questionnaires, structural clinical interviews, overnight polysomnography, neuro-cognitive tests and neurological examinations.

Results: 40 subjects were recruited for each arm. (Total number of subjects: 120). Results showed that patients with RBD reported more core features of RBD, including nightmares, dream enactment and resultant sleep-related injury. They also scored higher marks in anxiety scale (p < 0.05) when comparing with the controls. For the PSG features, the cases had a higher REM-related muscle activities and loss of REM related muscle atonia (p < 0.05). Despite there was no significant difference over the use and dosage of antidepressants between the cases and psychiatric control group, the cases still had a significant higher degree of loss of REM atonia. (p < 0.01).

Conclusion: This study suggested that RBD exists in psychiatric populations and antidepressant per se could not fully account for the clinical and polysomnographic features.

Alcohol use among Indigenous group in Gombak, Malaysia

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Objective: To investigate the pattern of alcohol use and psychiatric morbidity among the indigenous people in Malaysia and their psycho-social correlates.

Methods: The cross sectional study conducted among 18 years and above of 201 Orang Asli settlement in Tekala river village of Gombak district, Malaysia in year 2010. We interviewed every third house after house mapping procedures based on previous studies using systematic sampling. The study was approved by the ethic committee board of the University hospital. The alcohol use were measured using ASSIST-BI and psychiatric comorbidity using MINI Ver 5.0.

Results: The study population consist of 201 respondents from 76 house. The respondent mean age is 37.3 years, almost three quarters are married, more than half are females and 84.1% are employed at the time of study. We found the lifetime and current prevalence of alcohol use are 14.4% and 13.4% respectively. The number of respondents fulfilled at least one psychiatric diagnosis is 40.9%. There was significant negative correlation between Islamic religion and alcohol use even after adjusted with gender and marital status. However, there was no significance correlation found between psychiatric morbidity and alcohol use in this study.

Conclusion: The prevalence of alcohol use among orang asli Gombak is higher as compared to the general population group in Malaysia. Islamic religion seems to have protective factors against alcohol use. There is a need for further study to prove the causal relationship of Islamic religion and alcohol use in this population.

Mass psychogenic illness-temporal spread and containment- a south east Asian story

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Objective: Mass hysteria, also known as mass psychogenic illness (MPI), has been reported for hundreds of years in different socio-cultural settings. MPI has been characterized by a group of symptoms that usually mimic an organic disease, but without any identified cause, and occurs in those who share a common belief that those symptoms constitute a definite illness.

Methods: Few months back in a wedding party in Jharkhand, India, a lady had a sudden death and among the guests it spread that the death was caused due to henna or mehendi poisoning. Henna is used to colour the hands of the bride and other women during wed- ding in India. This news spread more through mobile and sms service than through mass media and a particular brand of henna was discussed as the cause. For the next 2 weeks more than 500 young women were admitted in various hospitals and nursing homes across Jharkhand and West Bengal with conversion symptoms similar to poisoning.

Results: Recently in October 2010, there was an epidemic of Koro in West Bengal which spread to Assam, Mumbai and Delhi which is an area of more than 1500 km of epidemic like spread in temporal fashion. The name Koro means shrinking penis. Other local languages in South-East Asia also have similar names for the condition. The classic syndrome in South-East Asia is culture-bound and is characterized by the belief that the penis is shrinking; it will disappear into the abdomen and it will cause death. These beliefs are accompanied by an intense fear and by preventive manoeuvres such as tying, clamping or grasping the penis.

Conclusion: This poster addresses the issues on factors affecting the origin and spread of Mass Psychogenic Illness and its containment.

Caffeine counteracts impairments in task-oriented psychomotor performance induced by chlorpheniramine: A double-blind placebo-controlled crossover study


Objective: The combined effects of chlorpheniramine and caffeine on task-oriented psychomotor function have not been systematically evaluated. This study aimed to evaluate the effects of chlorpheniramine on psychomotor performance and the counteracting effects of caffeine on those sedative antihistamine actions.

Methods: Sixteen healthy young men participated in this study. Using a double-blind placebo-controlled crossover design, each subject was administered one of the following conditions in a random order with a 1-week interval: ‘placebo-placebo’, ‘chlorpheniramine-placebo’, ‘placebo-caffeine’, or ‘chlorpheniramine-caffeine’. Before and after the treatments, psychomotor functions were assessed using a battery of tests. Additionally, subjective responses were assessed using a visual analogue scale (VAS).

Results: Psychomotor performance changed over time in different ways according to the combination of study medications. In the ‘chlorpheniramine-placebo’ condition, reaction times of the compensatory tracking task were significantly impaired compared with the other three conditions. In addition, the number of omission errors of the continuous performance test were significantly greater compared with the ‘placebo-caffeine’ condition. However, the response pattern of the ‘chlorpheniramine-caffeine’ condition was not significantly different from that of the ‘placebo-placebo’ condition. Changes of VAS for sleepiness were significantly greater in the ‘chlorpheniramine-placebo’ condition compared with the other three conditions.

Conclusion: Chlorpheniramine significantly increases subjective sleepiness and objectively impairs psychomotor reactions to a
stimulus. However, caffeine counteracts these sedative effects and psychomotor impairments.

**P-23-028**

Plants used in popular medicine for treatment of atherosclerosis: The experience of Dhaka city in Bangladesh

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**Objective:** Today a person is very much preoccupied. Modern lifestyle has contributed to serious increases in killer diseases like atherosclerosis. Currently, most medications or therapies for treatment of atherosclerosis have serious side-effects, which sometimes can be more life-threatening than the diseases itself. It is important, therefore, to turn to plant sources for discovery of novel yet safe compounds, which has less or no side-effects to treat atherosclerosis. We accordingly conducted a survey of several areas within Dhaka city of Bangladesh to learn more about plants used by the traditional medicinal practitioners to treat atherosclerosis.

**Methods:** Interviews were conducted with the help of a semi-structured questionnaire and plant specimens as pointed by the traditional medicinal practitioners were collected, deposited, and identified at the Bangladesh National Herbarium.


**Conclusion:** Since the Dhaka city patients appeared to be generally satisfied with the treatment offered through these plants, it is important to conduct proper scientific studies towards discovery of compounds of interest in these plants, which can be used as safe and effective medicines.

**P-23-029**

Manic episode after malaria prophylaxis with mefloquine: Case report

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**Objective:** Mefloquine (Lariam) is the drug of choice as malaria prophylaxis for travel to countries with chloroquine-resistant malaria. Mefloquine (Lariam) is the drug of choice as malaria prophylaxis for travel to countries with chloroquine-resistant malaria. Objective : Mefloquine (Lariam) is the drug of choice as malaria prophylaxis. It requires to investigate the risk factors such personal or familial history of psychiatric disorders.

**Methods:** Analysis of two cases and literature review.

**Results:** The first patient was evaluated in the emergency department during the first 24 hours of intoxication and the second one was evaluated two months later, in both cases we applied the Millonlental State Examination (MMSE), Hamilton Rating Scale for Anxiety and the Hamilton Rating Scale for Depression as well as a narrative description taken from several interviews. These patients had no previous psychiatric history. The first case showed a severe cognitive impairment in Millonlental test scoring 18/30, additional identification of depressive and anxiety symptoms was found on the scales. The second case was evaluated two months later and we found similar scores in the Millonlental (MMSE) and in the scales for anxiety and depression.

**Conclusion:** Scopolamine-induced deficits in cognitive and motor processes have been widely demonstrated in animals and humans, although the role of acetylcholine in working memory is not well understood. There is little information in the current literature about psychiatric symptoms related to criminal anticholinergic poisoning that can occur with scopolamine, antihistamines, tricyclic antidepressants, antiparkinsonian agents and other similar compounds. From the neuropsychiatric point of view, descriptions of changes are evident at the level of memory besides affective symptoms, therefore protocols for collaborative care that include an integrative approach are required for patients affected with delictive intoxication.

**P-23-030**

Criminal poisoning with scopolamine and psychiatric symptoms

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**Objective:** In Colombia and other Latin American countries, intoxications with delictive intentions are frequent in the emergency room of general and psychiatric hospitals and scopolamine is a substance frequently used. The present work aims to identify psychiatric symptoms secondary to criminal anticholinergic poisoning in exposed patients victims of theft.

**Methods:** Analysis of two cases and literature review.

**Results:** The first patient was evaluated in the emergency department during the first 24 hours of intoxication and the second one was evaluated two months later, in both cases we applied the Millonlental State Examination (MMSE), Hamilton Rating Scale for Anxiety and

**Conclusion:** Scopolamine-induced deficits in cognitive and motor processes have been widely demonstrated in animals and humans, although the role of acetylcholine in working memory is not well understood. There is little information in the current literature about psychiatric symptoms related to criminal anticholinergic poisoning that can occur with scopolamine, antihistamines, tricyclic antidepressants, antiparkinsonian agents and other similar compounds. From the neuropsychiatric point of view, descriptions of changes are evident at the level of memory besides affective symptoms, therefore protocols for collaborative care that include an integrative approach are required for patients affected with delictive intoxication.

**P-23-031**

The lithium archives project: The role of lithium in the protection of neurodegenerative and cardiovascular disease

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**Objective:** Since the 1950's Lithium has been used in the successful treatment of bipolar disorder. Advancements in neuroscience suggest that Lithium increases gray matter volume and therefore may also have neuro-protective properties. Lithium has also been shown to have a low incidence of suicide attempts when compared to other medications but little exists in the literature showing any relationship between lithium and cardiovascular disease. The Lithium Archives Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University and the Foundation for Depression and Manic Depression Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University and the Foundation for Depression and Manic Depression Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University and the Foundation for Depression and Manic Depression Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University and the Foundation for Depression and Manic Depression Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University and the Foundation for Depression and Manic Depression Project is based on systematic chart reviews of over 8,000 patients treated at the New York State Psychiatric Institute, Columbia University

**Methods:** The Lithium Archives Project is a retrospective, random electronic chart review conducted by a research scientist. Patient charts are examined for over 100 variables including neurological and cardiovascular diseases, eye disorders, medication history, side effects, demographics and patient histories. The current sample of over 800 charts was analyzed by a statistician using standard SPSS statistical software. Mean, standard deviation and significance of cerebrovascular disease, myocardial infarction, brain tumors, stroke, and seizures of patients treated with lithium and patients treated without lithium were compared and analyzed. Multivariate analysis was...
performed to analyze group (lithium/no lithium) and incidence of disease. The means of disease incidence in the lithium versus non-lithium groups were then charted.

**Results:** Analysis of the current data shows that group is a significant variable in the incidence of diseases analyzed (Pillai's Trace F = 2.926, df = 11.416, p = 0.004). The patients treated with lithium show less incidence of myocardial infarction (p = 0.014), seizures (p = 0.091), stroke (p = 0.014) and brain tumors (p = 0.072).

**Conclusion:** The current analysis indicates that in this patient population, lithium may have played a role in protection from developing both cardiovascular and neurodegenerative diseases.

**P-23-032 In utero exposure to lithium, fetal biometry and neonatal outcomes**

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**Objective:** To determine the effect of in-utero exposure to lithium on fetal biometry and neonatal outcomes.

**Methods:** Prospective observational study including 18 pregnant women on maintenance treatment with lithium alone (n = 13) or polytherapy (n = 5) during late pregnancy, which were treated at the Perinatal Psychiatry Program CLINIC between 2007 and 2011. We evaluated sociodemographic data, lithium plasma concentrations in maternal blood and umbilical cord, fetal biometry and neonatal outcomes.

**Results:** Women did not fulfill diabetes or obesity criteria pre-pregnancy and during pregnancy. Mean maternal serum (SD) 32.71 (4.02), 66% primiparaes, 95% Caucasian and 100% married or with partner. Tetuses exposed to lithium had a mean (SD) waist circumference of 51.8 vs. 48.89 cm), had increased head circumference (35.6 vs. 33.43). There were not differences in umbilical cord/maternal plasma lithium levels in both groups (0.95 vs. 0.98).

**Conclusion:** Lithium crosses the placental barrier almost completely. The fetuses that were exposed to lithium had a lower waist circumference and femur length, lower weight, gestational age and head circumference compared to polytherapy group. Foetal growth surveillance is recommended in pregnancy.

**P-23-033 The relationship between temperament and the efficacy of lamotrigine augmentation therapy for refractory depression**

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**Objective:** We showed that lamotrigine (LTG) augmentation was effective for the treatment of treatment-resistant mood disorder (TRMD). The combined model of the brief version of the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-aut questi onnaire (TE MPS-A), which assesses 5 affective tempera ments (depressive, cyclothymic, irritable, hypothyemic and anxious) and the Munich Personality Test (MPT), which examines other 2 personality traits (schizoid and melancholic), is suggested to be an useful pretreatment tool for the screening of baseline temperaments without a time-consuming interview process. This study investigated the relationship between therapeutic response to LTG augmentation treat ment and the patients’ temperament features assessed by TEMPS-A/MPT in TRMD.

**Methods:** The subjects were 39 depressive patients who had already shown insufficient response to at least 3 antidepressants or mood stabilizers despite enough therapeutic doses and durations. LTG was added to the ongoing antidepressants or mood stabilizers for 8 weeks. The daily dose of LTG was titrated by the clinician’s decision. Treatment response was assessed by MADRS before and after the 8-week treatment. Responders were defined as 50% or more symptom reduction from baseline, and complete remitters were defined as less than 4 of MADRS score for more than 2 weeks. The TEMPS-A/MPT was administered to the subjects.

**Results:** Twenty (51%) patients were responders, and 5 (13%) of them were complete remitters. 19 (49%) were non-responders. There were no significant differences in the 7 temperaments between responders and non-responders.

**Conclusion:** The present result suggests that therapeutic response to LTG augmentation in TRMD cannot be predicted by the patients’ temperaments by using the TEMPS-A/MPT.

**P-23-034 The effect of valproic acid on excessive dopamine release in the amygdala in response to conditioned fear stress: An in vivo microdialysis study in methamphetamine-sensitized rats**

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**Objective:** Emotional hypersensitivity in handling the event may play a role in patients with schizophrenia, therefore, it is meaningful to study dopamine dynamics in the amygdala. In our series of studies, we have found that dopamine release in amygdala was increased significantly higher in the methamphetamine (MAP)-sensitized rats than in un-sensitized ones under conditioned fear stress application. The hypersensitivity of dopamine release was considered to be a biochemical marker of vulnerability to psychosis. We also demonstrated this excessive dopamine release was inhibited by antipsychotics (Oshibuchi et al., 2009). Meanwhile, valproic acid (VPA) is used for augmentation therapy, in the treatment of schizophrenia and other emotional disorders. But there is no biochemical evidence of the difference of pharmacological effect on psychological stress. Therefore, in order to examine the differential effect between VPA and antipsychotic agents on fear response, the effect of VPA on the basal dopamine release and on dopamine response to the conditioned stress in amygdala in this model rats was measured.

**Methods:** Male Sprague-Dawley rats were used. Rats were administrated 2 mg/kg/day of MAP for 10 days to develop MAP-sensitization. The fear conditioning was conducted to develop psychological stress. Dopamine changes to conditioned fear stress in amygdala were measured by microdialysis and high-performance liquid chromatography (HPLC).

**Results:** As a result, VPA showed similar effect to antipsychotics on dopamine dynamics in amygdala.

**Conclusion:** Our results exhibit the partial mechanism of VPA in dopamine change in amygdala of emotional disorders.

**P-23-035 Prescription of mood stabilizers: Lithium vs. valproate – what clinicians expect for them**

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**Objective:** Although both lithium and valproate are used as classical mood stabilizer, the real world prescriptive comparison is not well known. Our study aimed to explore how common the use of lithium and valproate in psychiatric conditions of Japanese outpatients is to describe the difference of the characteristics of the patients. Because Japanese Society of Mood Disorders described the guideline for bipolar disorder in 2011, we surveyed the patients before 2011 to exclude the influence of the guideline.

**Methods:** We investigated prescriptions for lithium and for valproate given for psychiatric conditions to the first visit from 2005 till 2010 in Showa University Fujigaoka Hospital, Japan. Psychiatrist who sees new outpatients changed depending on the day of the week. DSM-IV and ICD-10 were used for diagnosis of psychiatric disorders.
Clinical records were assessed retrospectively. As valproate is also used as antiepileptic drug, subjects with diagnosis of epilepsy were excluded from the analysis.

Results: The numbers of the patients with prescription of lithium and valproate at the date of the first visit were 39 and 48, respectively. 2 patients were prescribed both lithium and valproate. There was no significant difference of age and sex between the groups. Patients with lithium prescription showed significantly more frequency of diagnosis of bipolar disorder (rate of bipolar disorder: lithium 71.8%; valproate 31.3%, p = 0.001). Among bipolar subjects, patients prescribed lithium were significantly younger compared with those prescribed valproate (50.0 ± 16.82 years old vs. 63.62 ± 12.63 years old, p = 0.020).

Conclusion: Lithium appears to be more expected as mood stabilizer for bipolar disorder rather than valproate in clinical practice.

P-23-036 The transcultural concept of epilepsy in beliefs
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Objective: The prevalence of epilepsy is 1.1%. But despite the high number of patients, epilepsy is still unknown and care is lacking.

Methods: Traditional beliefs reinforce the public on the idea that epilepsy is a disease caused by evil spirits. Besides the names we give this evil in language Moroccan dialect are revealing: jnoun, maskoun, krina, msalmin, ladam, riah. Unfortunately these beliefs are behind the delay in diagnosing the disease and hence the bad diagnosis.

Results: All these ideas are false and exacerbate the isolation of patients with epilepsy. Epilepsy affects people of all ages but especially children and adolescents, and because of the weight of prejudice and delay diagnosis, these patients outside the circuit of the public health system.

Conclusion: These difficulties autonomy may themselves be a source of pain or symptoms (emotional immaturity, self disorders, disturbances, aggressiveness) The loss of self-control during the crisis, affects self-confidence. Thus, the real trauma of the disease in addition to the psychological trauma that deserves to be considered.

P-23-037 Safety and efficacy of sustained release lamotrigine as monotherapy/add on therapy in the treatment of epilepsy
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Objective: Our aim was to determine the safety and efficacy of the LTG(SR) in Indian patients of epilepsy.

Methods: Total 20 patients were enrolled. All patients completed the full (12 weeks) duration of the study. Patients in the age range of 16–70 years with diagnosis of Epilepsy, as defined in ICES were selected. Patient-categories included were: Category-I: Newly diagnosed patients (n ≤ 2 seizures in last 3 months), Category-II: Patients who did not achieve adequate seizure control (>4 seizures in last six weeks) with other AED, Category-III: Patients who were on Lamotrigine Conventional release (IR) formulation, followed by exclusion criteria.

Results: LTG(SR) treatment reduced seizure frequency in all patient-categories. Statistically significant reduction in seizure frequency (per 4 weeks) was observed in Category-I: QOLIE-31 total score also significantly improved, in each patient-category. No serious adverse event (AE) was reported during the study.

Conclusion: It can be concluded that the LTG(SR) is safe and effective in the Indian patients of Epilepsy. It offers the advantage of a better tolerability profile as compared to conventional LTG. It also offers a safe switchability from conventional preparation at the same molar dose.

P-23-038 Involvement of the nicotinic acetylcholine system in the cognitive impairment induced by electroconvulsive seizures in rats
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Objective: Epilepsy is a chronic neurological condition characterized by recurrent seizures. The seizures are frequently comorbid with psychiatric disorders, including cognitive disorders. We recently reported that seven consecutive electroconvulsive shock (ECS)-induced seizures markedly impaired spontaneous alternation behavior in a Y-maze test, indicating impairments in short-term working memory. The involvement of the nicotinic acetylcholine system in these ECS-induced behavioral impairments remains incompletely understood.

Methods: Wistar rats were administered ECS (100 V, 50 mA, 0.2 sec, 60 Hz) once daily for 7 days. The Y-maze test was conducted 24 h after the last ECS administration. Phystostigmine, cholinesterase inhibitor, 0.5 and 1 mg/kg; anabuse, 0.7 nicotinic acetylcholine receptor agonist, 0.1 and 0.5 mg/kg; and ABT-418, 0.5 mg/kg, were administered i.p. to ECS-treated rats 30 min before the test. For immunohistochemical analysis, 0.4 nicotinic acetylcholine receptor-positive cells were quantified 24 h after the last administration of ECS.

Results: ECS induced spontaneous alternation behavior in the Y-maze test as reported previously. Increasing acetylcholine levels with phystostigmine (0.5 and 1 mg/kg) prevented this impairment, whereas α7 receptor activation by anabuse treatment had no significance effect. The impairment of spontaneous alternation behavior was significantly improved by the α4β2 nAChR agonist ABT-418 (0.5 mg/kg). In addition, the ECS administration caused a reduction in the number of α4 nicotinic acetylcholine receptor-positive cells in the prefrontal prelimbic cortex and the hippocampal areas CA1 and CA3, compared with the sham group.

Conclusion: These results suggest that impairment of the α4β2 nAChR underlies cognitive impairments induced by seizures, and that the positive effect of α4β2 nAChR activation on spontaneous alternation behavior may be mediated to the medial prefrontal cortex or hippocampus.

P-23-039 Assessment of comorbidity in post-neurosurgical patients with epilepsy
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Objective: The depressive comorbidity in epileptic patients is more frequent than in the general population and other chronic diseases. In this cross-sectional study, we investigated the prevalence and clinical features of interictal depressive symptomatology in a cohort of neurosurgical patients.

Methods: The study was carried out in 54 post-neurosurgical epilepsy patients (PNS), 53 with ‘no-postneurochirurgical’ epilepsy (NPNS) and 52 healthy control subjects. The majority of patients were receiving antiepileptic monotherapy, and had no prior history of mood disorders. Screening for depressive disorder (DD) was conducted by means of a self-assessment scale, the CES-D (Center for Epidemiologic Studies—Depression Scale), as validated in Italian, and already used in similar studies.

Results: In the group of PNS the total score for the individual CES-D scale value (mean ± SD) was 12.15 ± 9.42. The 45.40% of patients had a score >16, indicative of DD. The total score on the individual CES-D was 13.98 ± 8.90. The 54.55% of patients had a score >16, indicative of DD. In control subjects the total score on the individual CES-D was 9.11 ± 5.3, with scores indicative of DD in 17.30% of cases. A further stratification of patients with satisfactorily controlled frequency of seizures or less did not show any relationship with the presence of DD.

Conclusion: The results of the study showed no differences in the prevalence of comorbid interictal depression in neurosurgical patients, according to the type of epilepsy. However, the prevalence of...
depression ranged between 45.40% and 54.55% of cases and suggest the need for careful assessment of this comorbid condition in patients with epilepsy.

**P-23-045** Enhancement of morphine-induced antinociception by electroconvulsive shock

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Objective: Electroconvulsive therapy (ECT) is a widely used method for treating drug-resistant depression and schizophrenia, and reportedly has a positive effect on neuropathic pain. Interestingly, some studies have reported that an amount of opioid to relieve pain is reduced after a series of ECT. In the present study, we administered electroconvulsive shocks (ECS) to mice, since mice are supposed to have a similar response pattern to ECS as humans have to ECT, in order to clarify the effect of ECT on morphine-induced antinociception and to elucidate its mechanism.

Methods: Hot plate tests were performed to study morphine-induced antinociception in mice that were treated with ECS 24 hours before the administration of morphine.

Results: Results demonstrated that the dose-response curve for morphine-antinociception in ECS-treated mice was shifted left and the EC50 of morphine in ECS-pretreated mice was 30% decreased compared to it in mice which were not pretreated with ECS. Additionally, we administrated morphine twice with 24 hours interval to develop an acute tolerance to clarify the effect of ECS on the tolerance. Mice pretreated with ECS 21, 23, and 25 hours before the second administration of morphine did not develop acute morphine tolerance, while those pretreated with ECT 1 to 6 hours before did. Western blotting was performed with a specific antibody to detect mu-opioid receptors in the thalamus. The expression level of mu-opioid receptors was significantly higher in the thalamus of the morphine- and ECS-treated mice compared to that of the mice only treated with morphine.

Conclusion: These results indicate that ECS may facilitate the antinociceptive effects of morphine and counteract the development of a tolerance to morphine, possibly due to increased expression of mu-opioid receptors, suggesting that similar mechanisms may underlie the effect of ECT on opioid-induced analgesia in humans.

**P-23-044** Comparative characterization of ADX71653 and ADX71943, novel CNS- and peripherally-targeted GABAB receptor positive allosteric modulators

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Objective: There is evidence that the orthosteric GABAB agonist baclofen has anxiolytic- and analgesic-like profile, albeit showing a narrow therapeutic window, rapid onset of side-effects, with signs of tolerance, withdrawal and rebound. Here we compared efficacy and side-effect profiles of a CNS-targeted GABAB positive allosteric modulator (PAM) ADX71653 to that of a peripherally-targeted PAM ADX71943.

Methods: Efficacy of ADX71653 was evaluated in the mouse marble burying (MB) test of anxiety and circular avoidance test of motor function.

Results: ADX71653 reduced numbers of buried marbles (MED 3 mg/kg), indicative of its anxiolytic-like effect. However, it also reduced LMA, body temperature and impaired rotorod activity from 10 mg/kg. ADX71943 reduced the number of acetic acid-induced writhes (MED 3 mg/kg), indicative of antinociceptive-like efficacy. However, it failed to have an effect in MB when tested at up to 100 mg/kg. ADX71943 had no effect in the mouse LMA, rotorod and BT tests when tested at up to 100 mg/kg.

Conclusion: Thus, peripherally-targeted GABABR PAMs offer a wider therapeutic margin when evaluating indications with peripheral mechanisms, while being inactive in centrally-mediated conditions. However, centrally-targeted PAMs offer a narrow margin, similar to that seen with baclofen. Therefore, GABABR PAMs with a balanced central/peripheral profile may offer the potential for development of novel non-opioid alternative for chronic osteoarthritis (OA) pain and a non-muscarinic alternative for overactive bladder (OAB) with a wider therapeutic margin. Recently we develop a novel, orally-bioavailable GABABR PAM with a balanced central/peripheral profile which offers efficacy in models of anxiety, OAB and pain, with ameliorated side-effect liability. It is currently advancing toward the IND.

**P-23-042** Vitamin D in pediatric patients with chronic non-malignant pain

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Objective: Vitamin D deficiency (25(OH)D < 20 ng/mL) has been found to contribute to both medical and psychiatric conditions. The association with chronic pain has been noted in adult patients with chronic non-malignant pain (Turner 2008), with a 26% prevalence of hypovitaminosis D. Antiel et al. (2011) studied a group of adolescent patients with postural orthostatic tachycardia syndrome (POTS) and found that 22% of those patients met the criteria of Vitamin D deficiency with serum 25(OH)D < 20 ng/mL. To date there has been no report of the prevalence of Vitamin D deficiency in a population of adolescents with chronic non-malignant pain which is the purpose of this study.

Methods: This study reviewed the records of 333 adolescent and young adult (ages 11–21 years old) patients with chronic non-malignant pain who participated in a three week outpatient Pediatric Pain Rehabilitation Program. All patients administered the standard admission process, serum 25(OH)D level was measured in all patients at the start of the program. Supplementation of vitamin D is provided to those patients who are vitamin D deficient as part of the rehabilitation.

Results: In this group of pediatric patients with chronic non-malignant pain, we found a prevalence of 21.6% (72/333 patients) with vitamin D deficiency. Of those with vitamin D insufficiency/deficiency, mean serum 25(OH)D was 28 ng/mL. Female patients (n = 250) had a mean serum 25(OH)D level of 30.7 ng/mL, and male patients had a mean serum 25(OH)D level of 27.1 ng/mL. Female patients (n = 72) had a mean serum 25(OH)D level of 30.7 ng/mL, and male patients (n = 83) had a mean serum 25(OH)D level of 28 ng/mL. The remainder were Caucasian patients (n = 323) with a mean level of 26.2 ng/mL.

Conclusion: Supplementation of vitamin D may help improve pain and physical functioning in adolescent populations with chronic non-malignant pain.

**P-23-043** Sadness enhances the experience of pain and affects brain regions associated with pain

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Objective: Pain is a multidimensional experience. Human pain perception can be modulated by subjective emotional responses. We examined this association by using functional magnetic resonance imaging (fMRI) (15 healthy subjects) and magnetoencephalography (MEG) (19 healthy subjects).

Methods: Pain-inducing stimuli were presented during different emotional contexts, which were induced via the continuous presentation of sad, happy or neutral pictures of faces. Subjects also rated their subjective pain intensity.

Results: We found: 1) The intensity of subjective pain ratings increased in the sad emotional context, 2) pain-related activation in the anterior cingulate cortex (ACC) was more pronounced in the sad context, and we demonstrated amygdala to ACC connections during the experience of pain in the sad context, and 3) event-related de-synchronization (ERD) of lower beta bands in the right hemisphere after pain stimuli was larger in the sad emotional condition.

Conclusion: These results show that sadness can modulate neural responses to pain stimuli, and that it may be relevant to the experience of pain.
understanding the broader relationship between somatic complaints and negative emotion. We also consider that further research is needed to understand this relationship from the clinical viewpoint including the psychiatric treatment.

**P-23-044** Association between smoking and plasma brain-derived neurotrophic factor (BDNF) levels in healthy workers

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**Objective:** Brain-derived neurotrophic factor (BDNF) had been reported to play an important role in the development of nicotine dependence (ND). Chronic nicotine intake increased BDNF mRNA expression in rat hippocampus. In addition, human plasma BDNF level was found significantly increased after nicotine abstinence, but same result cannot be reconfirmed in another study using serum sample. In other words, the issue is controversial. In the present study, we investigate the association between smoker and non-smoker using health samples from industrial workers.

**Methods:** 85 never smokers and 220 current smokers from a major industrial company were enrolled in this study. Plasma was quickly separated in a centrifuge and stored at −80 degrees Celsius until it was used for assay. Plasma BDNF levels were assayed using ELISA methods following to the manufacturer’s instructions. All the statistics were performed using SPSS v16.0 Japanese version.

**Results:** The mean plasma BDNF concentration in smokers is 1636.31 (SD = 1250.33) pg/mL and, it is 1601.17 (SD = 1699.06) pg/mL in never smoker. We found a significant difference in the Log-transformed BDNF concentration between smokers and never smokers (p = 0.035). After adjusting age, the smoking behavior still increase the plasma BDNF concentration (p = 0.029).

**Conclusion:** Our results suggested that the plasma BDNF concentration in smoker is higher than that in non-smoker which is in line with a research in male schizophrenia patients. However, it was inconsistent with other human researches which revealed the lower BDNF concentration in smokers. The inconsistency between our and other human studies might due to different settings of participants background. Unfortunately, we still had some limitations in this study, such as BMI, excise and disease information of the workers. Association between smoking and the plasma BDNF level remains controversial. Further studies are needed to draw a firm conclusion.

**P-23-045** Smoking cessation in patients with chronic schizophrenia

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**Objective:** To examine whether smoking cessation is associated with psychotic symptom severity and antipsychotics side effects in smoking patients with chronic schizophrenia.

**Methods:** A total of 100 smoking patients with chronic schizophrenia were recruited at a Taiwan chronic mental hospital for the 8-week smoking secession program using nicotine patch replacement therapy (NRT). Medication adjustment was allowed during the NRT. Psychotic symptom severity and antipsychotic side effects at baseline and after the NRT. Psychotic symptom severity and antipsychotic side effects were measured by the Positive and Negative Syndrome Scale (PANSS) and the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale, respectively.

**Results:** After adjusting for age and hospitalization day, the clinical psychotic symptoms significantly improved after the NRT (PANSS score at baseline and after the NRT: 63.77±1.72; 60.85±1.55), especially in general and positive subdivisions. The antipsychotic side effects, however, were not significantly different (UKU Side Effect Rating Scale at baseline and after the NRT: 5.46±0.38; 5.09±0.39); items including fatigue, rigidity, and constipation significantly improved after the NRT, while blurred vision and drooling significantly worsened (p-value <0.05).

**Conclusion:** Smoking cessation is beneficial for smoking patients with chronic schizophrenia in reduction of clinical psychotic symptoms and certain side effects of antipsychotics.

**Poster Sessions, Wednesday, 6 June 2012**

**P-23-046** Genome-wide association study identified susceptibility loci associated with nicotine dependence in a Japanese population


**Objective:** Many genetic and environmental factors can be involved in the etiology of nicotine dependence. To date, several candidate genetic variations have been identified to be associated with smoking behaviors and vulnerability to nicotine dependence. These were found mostly by investigating single nucleotide polymorphisms (SNPs) on each gene related to phenotypes of concern or by genome-wide association studies (GWAS), which treat genetic markers in the whole genome, conducted for subjects with European ancestry. However, genetic factors have not been reportedly investigated for Japanese population utilizing whole-genome genotyping arrays. We comprehensively explored genetic contributors to nicotine dependence by GWAS in Japanese.

**Methods:** Subjects: 300 patients who visited Iwata City Hospital. A number of participants involved in this study had various smoking habits and filled in a questionnaire leaflet containing various questions. Whole-genome genotyping was performed with iScan System (illumina K.K.) and the BeadChip HumanCytoSNP-12.

**Results:** In association study between over 200,000 marker SNPs and scores of the Fagerstrom Test for Nicotine Dependence (FTND), a test that yields a continuous measure of nicotine dependence, the Tobacco Dependence Screener (TDS), consisting of 10 questions, and the numbers of cigarettes smoked per day (CPD), none of the SNPs were found to reach the genome-wide significant level and the P-values were no less than 10–6 in all analyses. However, several potent SNPs were found in loci that have not been highlighted, as well as in loci that include known candidate genes resulted from previous GWAS. Among them was CSMID, CUB and Sushi multiple domains 1, which appeared in top ranks of our GWAS results for all the three phenotypes examined.

**Conclusion:** Although future studies with larger sample size is required, these results will serve to discover genetic factors contributing to nicotine dependence and smoking behavior specific to Japanese population in addition to those common to other populations.

**P-23-047** Effects of smoking cessation on reward processing

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**Objective:** Research on nicotine addiction indicates greater ventral striatal activity in smokers compared to non-smokers in response to smoking-associated cues but blunted reactivity to non-drug rewards (David et al., Biol Psychiatry 2005, 58: 488–494; Martin-Soelch et al., Eur J Neurosci 2003, 18: 680–688). However, it is still unclear how reward processing changes after smoking cessation. The aim of the present study was to examine effects of long term smoking abstinence on neural correlates of reward anticipation and cue reactivity.

**Methods:** Thirty-three smokers and 30 non-smokers performed two paradigms on a 1.5 T scanner: Monetary and Social Incentive Delay task (Knutson et al., Neuroimage 2000, 12 : 20–27; Sprekelmeyer et al., SCAN 2009, 4 : 188–195). The second paradigm examined cue reactivity by presenting blocks of smoking-related, neutral or sexually arousing pictures. All smokers took part in a smoking cessation course. Fifteen smokers who succeeded in staying abstinent for three months underwent a second fMRI scan with the same paradigms.

**Results:** During both monetary and social reward anticipation paradigms smokers showed weaker striatal activity compared to non-smokers. However, in response to smoking-associated pictures stronger neural responses were found in the caudate nucleus. For both reward
P-23-048 The amnesic effects of benzodiazepines: A science or media concern?

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Objective: This study highlights the history and logic of the discovery and study of the amnesic effect of benzodiazepines, and how information about it is relayed in different sources, from research journals to the medical and lay media. Benzodiazepines are the most-prescribed drugs worldwide, thanks to their effects on anxiety and insomnia, but in some circumstances trigger amnesic episodes. Almost 20 years elapsed (at least in France) between when these effects were discovered and when general practitioners and users were told about them.

Methods: The written media are important for disseminating information about drugs. Unlike information relating to other fields of research, however, information about drugs has many different written sources (research and medical journals, rules and regulations, written sources of research, however, information about drugs has many different written sources (research and medical journals, rules and regulations, magazines and lay media). This study explored how information about them was relayed in the written media, and why it took so long to reach those who prescribe or use them.

Results: The amnesic properties of benzodiazepines were discovered by anesthesiologists, who considered them useful, and the relevant information was first confined to anaesthesiology journals. The molecules were later used by fundamental cognitive researchers to investigate memory processes and again considered useful tools. Gradually, however, medical and lay journals began to describe benzodiazepine-induced amnesic episodes, for the most part drug-induced aggressive disinhibition behaviour accompanied by amnesia. Since then, benzodiazepines have become unpopular with other segments of the population, namely the general practitioners who prescribe them, and users who take them to alleviate anxiety or insomnia.

Conclusion: This study demonstrates why physicians remained in the dark for such a long time, and how a beneficial effect became an undesirable effect, partly due to media coverage of a trial.

P-23-050 Conduction abnormalities and associated factors in Korean patients with eating disorders

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Objective: QT interval prolongation and dispersion known as the indicators of an increased risk for ventricular arrhythmias and sudden death, have been reported to be prolonged in patients with anorexia nervosa. The aims of this study were to compare conduction abnormalities in Korean patients with anorexia nervosa and bulimia nervosa, and to examine its relation with clinical and laboratory factors.

Methods: We retrospectively examined 45 women with anorexia nervosa and 75 women with bulimia nervosa who were assessed 12-lead electrocardiogram as a baseline assessment. Conduction abnormalities were measured as QT interval and corrected QT interval, QT dispersion of the difference between the longest and shortest QT intervals, and abnormal U wave.

Results: QT interval was significantly longer in patients with anorexia nervosa compared with patients with bulimia nervosa. There were no differences in QTc, QTd and abnormal U wave between patients with anorexia nervosa and patients with bulimia nervosa. QTd was significantly correlated with the lowest ever lifetime body mass index (kg/m²) as well as the serum amylase level in patients with anorexia nervosa.

Conclusion: These results suggest some conduction abnormalities reported in patients with anorexia nervosa are also found in patients with bulimia nervosa. It appears severity of weight loss and purging behavior could affect on the cardiac arrhythmia in patients with eating disorders. Appropriate attention should be paid to cardiac involvement in patients with eating disorders.

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P-23-051 Adverse effects of zolpidem and lorazepam in three-week treatment of primary insomnia

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Objective: Objective of this work was to establish differences in adverse effects of zolpidem and lorazepam during the three-week treatment of primary insomnia.

Methods: Forthly one patients with primary insomnia were included in double-blind randomized research, out of which 21 were treated with 10 mg/d of zolpidem and 20 mg/d of lorazepam during three weeks. Examinees received the medication each night during the first week, 5 times a week during the second week, and during the third week they received one of the investigated drugs 3 times a week. The most common adverse effects were recorded in patients at the beginning, then after the first, the second and the third week of treatment by using the list of adverse effects (AECL), and their intensity was estimated with visual analogue scale (VAS).

Results: Our results show that the examinees on zolpidem had total statistically significantly less adverse effects than examinees on
lorazepam (U = 82; p = 0.001), and that they also had less total intensity of adverse effects (U = 58.5; p < 0.002) and intensity by individual adverse event (U = 45; p < 0.008). In both groups of examinees there is statistically significant difference in time, that is, both examinees on zolpidem and lorazepam had decrease of adverse events and by number (F = 29,905; p < 0.001; F = 24,968; p < 0.001) and by intensity (F = 27,335; p < 0.001; F = 28,423; p < 0.001), during the course of treatment.

Conclusion: Based on results obtained, we can conclude that from the point of adverse events, zolpidem is safer drug than lorazepam, as well as that during the time there is a decrease of number and intensity of adverse events in both drugs.
Circadian rhythm dysfunction and severity of depression

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Circadian rhythms control many biological, physiological, and behavioral parameters such as variations in the daily pattern of mood, body temperature, and secretion of various hormones. Animal as well as human data support the assumption that dysfunction of the circadian system may underlie the pathophysiology of depression as well as other psychiatric diseases. Disruption of circadian rhythms affect mood, day-time functioning, concentration, energy, sleep-wake cycle, and cognition, and predispose individuals to a wide range of mood disorders including depression, mania, and impulsivity. Recent data established the correlation of circadian misalignment and depression symptom severity, indicating that the clinical expression of some core symptoms of depression reveal circadian rhythm deregulation and pointing out therefore the importance of a chronobiological approach to depression treatment. Among the established strategies such as sleep deprivation, circadian phase advance, entrainment by light therapy, and social rhythms, the development of drugs that target the circadian system appears to be the most promising approach. The novel antidepressant agomelatine acts as an agonist of MT1/MT2 receptors, as well as an antagonist of 5-HT2C receptors, and has been shown to resynchronize altered circadian rhythms in both animal models and humans. Agomelatine was shown to increase the flattened amplitude and to phase advance the circadian timing of several psychological parameters in healthy volunteers and depressives and to resynchronize the impaired circadian system in depressed patients. In particular, agomelatine rapidly improves daytime functioning, quality of sleep, and as a critical measure of circadian functioning the circadian rest-activity cycle. Its antidepressant efficacy has been demonstrated in a great number of clinical trials versus placebo and comparator drugs. Its robust antidepressant efficacy in severe depression, versus placebo and comparators, suggests that agomelatine can reduce unmet therapeutic needs in the treatment of depressed patients, thanks to the resynchronization of disturbed circadian rhythms in these patients.

Synergistic mechanisms involved in the antidepressant effects of agomelatine

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Major depression is considered as a complex disorder resulting from interactions between genetic, physiological, psychological, and environmental factors. The clinical manifestations of depression include affective, cognitive, somatic, and behavioral symptoms. Despite their variety, current antidepressants still have limitations in terms of efficacy, onset of action, and tolerability. In particular, none of them can alleviate all the symptoms of depression. Since the core symptoms of depression reveal disturbance of circadian rhythms in their clinical expression, an antidepressant with resynchronizing effects would be of value. The new antidepressant agomelatine is an agonist of melatonergic MT1/MT2 receptors as well as an antagonist of serotonergic 5-HT2C receptors. Both properties contribute to agomelatine's antidepressant activity, which has been proven in several animal models of depression and in patients with major depressive disorder. Moreover, agomelatine was shown to resynchronize disturbed circadian rhythms in several animal models and in patients. Given the action of agomelatine through these receptors, it was important to investigate how agomelatine really works: through a modulatory or a synergistic interaction between MT1/MT2 and 5-HT2C receptors. Recent data on the cellular processes involved in the mechanisms of antidepressants have demonstrated that agomelatine increases the expression of brain-derived neurotrophic factor in the prefrontal cortex and hippocampus, as well as the expression of activity-regulated cytoskeleton-associated protein (arc) in the prefrontal cortex. Moreover, chronic agomelatine therapy increases neurogenesis in the hippocampus, via enhancement of neuronal cell survival, and attenuates stress-induced glutamate release in the cortex. 5-HT2C antagonists or melatonin alone fail to reproduce these effects. These data suggest therefore that agomelatine acts through a synergistic action on MT1/MT2 and 5-HT2C receptors. This novel pharmacological profile translates into a distinctive antidepressant efficacy demonstrated in depressed patients.

Agomelatine in real life: practical experience with agomelatine

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Agomelatine is an innovative antidepressant, an MT1, MT2 receptor agonist and a 5-HT2C antagonist, which is being investigated in noninterventional studies to assess its efficacy and tolerability in daily practice. The French D-CHANGE trial assessed in daily practice the efficacy of agomelatine in depressed patients who were either not treated before for this episode (naïve population) or previously treated with another antidepressant (switch population). In this
6-week prospective study, more than 2700 depressed patients received agomelatine (25–50 mg) once daily at bedtime. In order to detect early clinical markers predictive of clinical response after 6 weeks, assessments were performed at day 0, week 2, and week 6: severity of symptoms using the Quick Inventory of Depressive Symptomatology by Clinicians (QIDS-C) and the Clinical Global Improvement Severity (CGI-S) scale, the level of mood with a VAS, sleep complaints with the Leeds Sleep Evaluation Questionnaire (LSEQ), social functioning (SDS), and emotional state (MATHYS). The balance between sensitivity and specificity for each parameter was assessed using ROC curves. The early improvement at week 2 with agomelatine, perceived by both clinicians (QIDS and CGI-E) and patients (VAS), was the criterion most predictive of response later (week 6). The severity of symptoms was similarly reduced after just 2 weeks in the total population and both subpopulations, confirming the clinical benefit of agomelatine in the native and switch populations. All noninterventional trials conducted in real daily practice conditions, ie, representing the heterogeneous depressed population with severe symptoms and symptoms of anxiety, confirmed the antidepressant efficacy and good tolerability profile of agomelatine. Taken together, the converging data observed in both randomized clinical trials and prospective trials make agomelatine a treatment of choice for a large spectrum of depressed patients.

SA-02. Asenapine, a multifunctional antipsychotic. Beyond symptom control in schizophrenia and bipolar disorder supported by an educational grant from Lundbeck

[SA-02-001] Improving patient outcomes in schizophrenia and bipolar I disorder
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Psychiatric disorders are frequently misdiagnosed due to overlapping symptomatology and comorbidities. Early and accurate diagnosis is essential to ensure that the correct treatment is received at the earliest opportunity and that the benefits are maintained over the long-term. There is also a need for diagnostic markers that may allow earlier, accurate diagnosis. Despite important advances in pharmacotherapy for bipolar I disorder, a substantial number of individuals do not achieve full remission, experiencing treatment-resistant symptoms, frequent relapse, and poor functioning. There remains a need for more effective, and better tolerated, antipsychotic, antidepressant, and mood-stabilising therapies with faster onset of action, including improved treatment of comorbid psychiatric and medical disorders, and of cognitive deficits. Successful management of bipolar I disorder may be further hindered by poor treatment adherence due to intrinsic disease symptoms (eg, poor insight), problems with intolerable side effects, use of numerous concomitant medications, and poor social support systems. Non-adherence to treatment regimens is generally reported to range from 40 to 60%. An ideal treatment for bipolar I disorder should be able to rapidly control symptoms and achieve clinical, as well as functional, remission.

[SA-02-002] Asenapine, a multifunctional antipsychotic
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Asenapine is a new treatment option with some specificproperties. It is derived from a tetracyclic chemical class that is different from other antipsychotics, and has a unique sublingual mode of administration. Asenapine has a unique multi-functional human receptor pharmacology with three distinctive components. It is a potent D2-receptor antagonist and, like other antipsychotics, has a high 5-HT2A/12 binding affinity ratio—a key driver for antimanic and antidepressant efficacy. Additionally, asenapine has ‘untypical’ receptor properties, such as the combination of potent 5-HT2A/12 and 5-HT7/5-HT6 receptor antagonism, when compared to first- and second-generation antipsychotics, at therapeutic doses. This triple action multi-functional pharmacology has driven hypotheses for potential additional therapeutic benefits of asenapine. For example, 5-HT2A/12 receptor blockade may contribute towards alleviating depressive symptoms. Furthermore, the preclinical pharmacology of asenapine provides a rationale for enhancing cognition. Unlike the tricyclic antipsychotics, asenapine does not have excessive anticholinergic effects, respectively. Efficacy of asenapine has been demonstrated in the management of bipolar disorder, but translation of asenapine’s unique pharmacology into additional therapeutic benefits should be determined in patients. The pre-clinical profile provides rationale for study in depressed patients.

[SA-02-003] Effective remission with asenapine for patients with bipolar I disorder
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Asenapine is a novel, tetracyclic antipsychotic medication delivered in a fast-dissolving sublingual tablet. In two 3-week, double-blind, randomised, placebo-controlled studies in patients with bipolar I disorder experiencing manic or mixed episodes, asenapine-treated patients showed a significantly greater reduction than placebo-treated patients in the Young Mania Rating Scale (YMRS) total score, as early as Day 2. A subsequent 9-week, double-blind, head-to-head, non-inferiority extension study demonstrated that over 12 weeks of treatment asenapine maintained efficacy and was comparable to olanzapine in terms of improving YMRS total score, and in rates of response and remission. A further 40-week, double-blind, extension study showed that the efficacy of asenapine treatment (secondary endpoint) was maintained up to 1 year. A post-hoc analysis was performed to assess the effect of asenapine on depressive symptoms experienced by patients during an acute manic phase. In patients with significant depressive symptoms (baseline MADRS total score >20) a highly significant improvement in MADRS total score with asenapine treatment relative to placebo was observed; an effect that was not shown in patients in the olanzapine group. Asenapine offers a new treatment option for patients with bipolar I disorder. The strong clinical efficacy of asenapine has been demonstrated in acute manic and mixed episodes. Asenapine efficacy is comparable to olanzapine over 12 weeks and is maintained up to 1 year. Furthermore, reduction of depressive symptoms was shown in a post-hoc analysis.

Wednesday 6 June 2012

SA-04. Designing new antidepressants: A focus on multimodality supported by an educational grant from Lundbeck

[SA-04-001] What is the rationale for designing multimodal antidepressants?
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Major depressive disorder (MDD) is characterised by aberrations in many intertwined pathways: monoaminergic dysfunctions; inflammatory pathways (increased levels of proinflammatory cytokines); hypothalamic-pituitary-adrenal (HPA) axis abnormalities; impairments in neuroplasticity markers; and disturbances in circadian rhythmicity. Monoaminergic dysfunctions have dominated clinical development of antidepressant drugs, as witnessed by the role of selective serotonin reuptake inhibitors (SSRIs) and dual-action antidepressants during recent decades [1]. However, treatments with improved response and tolerability are needed. Several attempts have been undertaken to develop antidepressants based on pathogenetic principles related to hyperactivity of the HPA axis, such as CRH1, glucocorticoid and vasopressin1B receptor antagonists [2]. So far, these developments have been disappointing. Candidate targets have been identified that reduce the increased signs of neuroinflammation in MDD [3]. Based on this, new targets could include cytokine antagonists, Cox-2 inhibitors, acetylsalicylic acid, ketamine and
antioxidants. Clinical evidence for these candidate compounds is, however, still circumstantial. In clinical practice, recent studies have shown that augmentation of SSRIs with atypical antipsychotics leads to enhanced antidepressant response [4]. There is increasing clinical evidence for the augmentation strategy involving combination of an SSRI and mirtazapine [5, 6]. This response could be explained by assuming a synergistic effect between inhibiting reuptake of 5-HT and adding an antidepressant that is a 5-HT2A/2C and 5-HT3 receptor antagonist. From preclinical studies, there is evidence for the efficacy of multi-target serotonergic compounds, such as combination of an SSRI with 5-HT1A agonism, 5-HT2C antagonism, 5-HT3 antagonism, 5-HT6 agonism and 5-HT7 antagonism in different varieties [7]. When studied in isolation, 5-HT1A agonists may have modest antidepressant effects, as may 5-HT2C- and 5-HT3 antagonists. There is a rationale for representing these two pharmacological modes of action into one molecule, constituting a multimodal drug. This may lead to synergistic effects and a strong antidepressant response.

References

SA-04-002 Optimising receptor activity and reuptake inhibition in multimodal antidepressants – examining the evidence to date

C. Sanchez, USA

The new multimodal compounds vilazodone and Lu AA21004 are thought to work via a combination of both receptor activity and reuptake inhibition. Vilazodone combines serotonin (5-HT) transporter (SERT) inhibition and 5-HT1A receptor partial agonism, increases extracellular 5-HT in vivo in the rat frontal cortex and ventral hippocampus, and is active in preclinical models of anxiety and depression [1]. Lu AA21004 functions as a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the SERT in vitro [2]. In vivo non-clinical studies have demonstrated that Lu AA21004 dose-dependently occupies these targets [2] and enhances extracellular levels of 5-HT, noradrenaline, dopamine, acetylcholine and histamine in the prefrontal cortex [3, 4]. In a rat progesterone-withdrawal model, Lu AA21004 produced an antidepressant-like response, whereas fluoxetine was inactive at corresponding SERT occupancies [5]. Lu AA21004 is effective in animal models of cognitive function, enhancing episodic memory in the rat novel object recognition (NOR) test and contextual memory in the rat fear conditioning test [4]. In contrast to the selective serotonin reuptake inhibitor (SSRI) escitalopram, Lu AA21004 normalises deficits in episodic and spatial memory induced in rats by 5-HT depletion, as measured in the NOR test and spontaneous alteration test, respectively [6]. Thus, Lu AA21004 exerts both its antidepressant-like activity and memory-enhancing effects via mechanisms beyond SERT inhibition [5,6]. Overall target occupancies, neurotransmitter levels and behavioural models, as well as quantitative EEG analyses [7], point towards a unique preclinical profile for Lu AA21004 compared to both vilazodone and current SSRIs.

Policy of full disclosure: The studies were jointly sponsored by H Lundbeck A/S and the Takeda Pharmaceutical Company.

References

SA-04-003 Potential clinical benefits of Multimodals in depression

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The ability of the new multimodal compounds vilazodone and Lu AA21004 to target receptors and enhance neurotransmitters in specific brain areas is expected to have particular clinical benefits, including fewer side effects than are associated with serotonin-noradrenaline reuptake inhibitors. It is anticipated that the multimodal effects of Lu AA21004 could reduce treatment-emergent sexual dysfunction (TESD) (via 5-HT3 antagonism and 5-HT1A agonism) and improve cognitive function (via 5-HT3 and 5-HT7 antagonism) [1-4]. Vilazodone is an effective treatment for adults with MDD, as shown by significant improvements compared with placebo in the MADRS and HAM-D-17 in two pivotal, 8-week, randomised, double-blind, Phase III studies [5, 6]. Vilazodone was generally well tolerated, with diarrhoea and nausea being the most common treatment-emergent AEs, and had minimal impact on sexual functioning. In a proof-of-concept study, Lu AA21004 was comparable to a high-dose venlafaxine in improving depressive symptoms (MADRS and CGI-S/SA-04-002) at 6 weeks [7]. Lu AA21004 also significantly reduced the risk of relapse compared with placebo in a long-term study in patients with MDD (24–64 weeks) [8]. In elderly patients (≥65 years) with MDD, Lu AA21004 significantly improved depressive symptoms (HAM-D-24) and cognitive performance (DSST and RAVLT) compared with placebo at 8 weeks [9]. Lu AA21004 was well tolerated in the short-term and maintenance studies [7, 8], with placebo-level TESD [7]. In elderly patients, the AE profile was similar to placebo for Lu AA21004, with nausea being the only AE that was significantly higher [9]. Several AEs were significantly higher than placebo with the active comparator duloxetine. To date, vilazodone and Lu AA21004 have shown evidence of efficacy in improving depressive symptoms, together with a lack of serotonin-related AEs such as TESD. Ongoing clinical trials will further assess the potential benefits of their multimodal pharmacological profiles.

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