SSRI augmentation strategies
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Chapter 2

Clinical efficacy of antidepressants in depression
Introduction

History
Once the therapeutic effects of iproniazid and imipramine in major depression were recognized, pharmaceutical companies intensified research programs to develop superior antidepressants. Progress has undeniably been made with respect to side effects and safety. We are only on the verge, however, of dealing with issues such as efficacy and onset of action.

The first class of antidepressants, to which iproniazid and pargyline belong, increase norepinephrine, dopamine, and serotonin levels in the brain by interfering with their metabolic pathways through inhibition of the mitochondrial enzyme monoamine oxidase (MAO). MAO inhibitors (MAOIs) are effective in major depression, although they do have pronounced side effects. Moreover, their mechanism of action is prone to hazardous interactions that occasionally lead to hypertensive crises, serotonin syndrome, and severe intoxications.

The second class of antidepressants, tricyclic antidepressants (TCAs) such as imipramine, block the reuptake of monoamines. TCAs are effective antidepressants and interactions with other exogenous compounds are less severe than with the MAOIs. Nevertheless, many unwanted side effects have been reported, most of which are related to the complex pharmacological profile of TCAs. The most serious unwanted side effect is that TCAs are not safe in overdose, which may lead to life-threatening situations.

Several classes of antidepressants have evolved from the classic tricyclic antidepressants, which may be superior in terms of safety profile and lack of side effects. With regard to efficacy, however, little progress has been made. All antidepressants have a delayed onset of action (2-6 weeks) and the percentage of nonresponders is relatively large (30-40%). Research is therefore increasingly focused on improving efficacy and onset of action. In order to reach this goal, several pharmacological concepts have been investigated over the last decades. The present chapter discusses these concepts, which range from single- to multiple-action strategies.

Confounding factors in antidepressant research

Subclassification and comorbidity
The clinical evaluation of antidepressant drugs is hampered by the multiplicity of the disease itself. Depression is an ‘umbrella’ term for several clusters of clinical symptoms. Great effort has been made to develop a structural subclassification system, e.g. DSM-IV. Diagnostic criteria may be too coarse, however, to guarantee that a coherent group of patients is entering the clinical studies.

An extra confounding factor is comorbidity with anxiety and other psychiatric disorders, which blurs the boundaries of the illness and further complicates rational treatment. Better insight into the biological mechanisms underlying the different subforms of depression and comorbid disease will hopefully help to improve the diagnostic criteria.
Response and onset of action
Evaluation of antidepressant activity is also complicated by differences in design and scoring methods between clinical studies. Rating scales, such as the Hamilton Rating Scale for Depression (HAM-D), may improve objectivity but substantial differences between open and controlled trials have often been reported. In addition, although objective scoring is improved by rating scales, differences in scoring between investigators enhances noise, which in turn increases the statistical power needed to show differences in efficacy when antidepressant drugs are compared.

Co-medication
Ideally, a drug’s therapeutic effect is measured in a biological matrix that is free of interfering exogenous substances. In practice, depressed patients are seldom drug-naive. An extensive washout period certainly helps, but pharmacological interference cannot be excluded completely; this phenomenon is sometimes neglected in the overall outcome analysis. Moreover, participants in clinical trials often receive additional medication to relieve the symptoms of comorbid disease. Benzodiazepines are likely to interfere with the pharmacology of an antidepressant, which complicates its clinical evaluation considerably. Although undesirable, this situation is sometimes inevitable.

Etiology, gender, genetics, and pharmacokinetics
Several other factors may influence the pharmacology of antidepressants. Differences in etiology, gender, genetics and pharmacokinetics potentially complicate the evaluation process, but are often neglected or not examined due to low statistical power. Confounding factors like these will certainly gain increased attention in future studies.
Antidepressant drugs

Classical antidepressants
MAOIs and TCAs belong to the first generation of antidepressant drugs. Several augmentation strategies to improve the therapeutic efficacy of these drugs have been attempted in the past, but these strategies are beyond the scope of this chapter and will therefore not be discussed here.

1. Selective compounds: SSRIs

Several lines of evidence indicate an involvement of serotonin in depression. The notion that LSD, a potent serotonin receptor antagonist, could induce mood changes in humans gave rise to the idea that serotonin could be involved in the etiology of mood disorders (Schildkraut 1965, Woolley and Shaw 1963, Gaddum 1963). This idea was strengthened by the observation that reserpine, a monoamine depleter, was able to induce depressive symptoms in humans (Carlsson et al. 1957). The effectiveness of MAOIs and TCAs in the treatment of depression gave further support for a role of serotonin in depression. Finally, this insight has resulted in the development of a new generation of antidepressants, the selective serotonin reuptake inhibitors (SSRIs, structures 1).

SSRIs and the serotonergic system
The serotonergic innervation of the brain mainly originates in the dorsal raphe nucleus (DRN) and the median raphe nucleus (MRN). These nuclei innervate a variety of structures within the brain, with a topical organization with respect to several brain areas. Whereas the prefrontal cortex is mainly innervated by the DRN, the dorsal hippocampus is mostly innervated by the MRN.

SSRIs increase extracellular levels of serotonin immediately upon administration (Fuller 1994). Yet their therapeutic effect is typically delayed for several weeks. This apparent discrepancy may be explained as follows. At least two types of serotonin (5-HT) autoreceptor are found on the serotonergic neuron. 5-HT$_{1A}$ receptors are present in the somatodendritic area; activation of these receptors decreases neuronal firing, which results in less serotonin being released from the axon terminals. 5-HT$_{1B}$ receptors are located on the terminals of serotonin neurons; when they are activated, serotonin release is directly inhibited. There is growing evidence that postsynaptic 5-HT$_{1A}$ receptors are also involved in the control of serotonin release, through a large feedback loop from terminal to cell body region (Bosker et al. 1997). It is very likely that these autorestraining processes counteract the initial effect of SSRIs. Following chronic administration of SSRIs it has been shown that at least the 5-HT$_{1A}$ receptors (presynaptically as well as postsynaptically) desensitize (Cremers et al. 2000). Arguably, this adaptive process enhances the effect of the SSRI on serotonergic neurotransmission. This cascade of events may partly explain the delayed onset of action of SSRIs.
SSRIs and pharmacokinetics
The pharmacokinetics of SSRIs are generally well documented, although no correlation has been found between plasma levels and the antidepressant effect. Clinically effective plasma levels have been described, however (Baumann and Rochat 1995). The SSRIs form a heterogeneous group in terms of affinity for liver enzymes. Citalopram does not influence the metabolism of other drugs, while other SSRIs have prominent interactions (Sproule et al. 1997).

Clinical trials: SSRI versus TCA and SSRI versus SSRI
Many studies have been performed to evaluate the efficacy of SSRIs in the treatment of various subtypes of depression. An elaborate discussion of individual studies is beyond the scope of this chapter, however.
Several meta-analyses of short-term comparative studies have investigated the efficacy of SSRIs compared with TCAs in major depression (Anderson 1998, Anderson and Tomenson 1995, Bech and Cialdella 1992, Bech 1989, Mendlewicz 1992, Montgomery et al. 1994, Song et al. 1993, Steffens et al. 1997, Tignol et al. 1992). The majority of these papers did not observe differences in efficacy between the two classes of antidepressant drugs. In one meta-analysis (Anderson 1998) it was found that some TCAs, in particular amitriptyline, may be more effective than SSRIs in depressed patients. A study of combined fluvoxamine data...
showed that the response rate with this antidepressant was comparable to that seen with tricyclics and tetracyclics (Mendlewicz 1992).


**Tolerability and long-term efficacy**

Several studies have analyzed the adverse-effect profile of SSRIs. In addition to gastrointestinal effects, headaches and ‘stimulant adverse effects’ like agitation, anxiety, and insomnia were frequently reported (Baldwin and Johnson 1995, Boyer and Blumhardt 1992, Cooper 1988, Doogan 1991, Wagner et al.1994).

Since depression is a chronic recurrent condition, long-term treatment is often required in order to minimize the chance of relapse. Several studies have been performed on relapse during placebo treatment, after initial successful treatment with SSRIs. All studies show that chronic treatment with SSRIs was superior with respect to reappearance of depression and the time to relapse. No evidence was found for differences between SSRIs or between SSRIs and TCAs in terms of relapse features (Anderson and Tomenson 1995, Doogan and Caillard 1992, Franchini et al.1997, Keller et al.1998a, Keller et al.1998b, Montgomery and Dunbar 1993a, Montgomery et al. 1993b, Montgomery and Kasper 1995a, Robert and Montgomery 1995, Rush et al.1998).

Although the long-term efficacies of SSRIs and TCAs are similar, the tolerance of SSRIs is clearly superior to TCAs (Song et al.1993, Montgomery et al. 1994, Anderson and Tomenson 1995, Anderson 1998, Meanna et al. 1992).

**Augmentation with 5-HT$_{1A}$ receptor antagonists**

SSRIs are believed to exert their antidepressant effect partly through desensitization of 5-HT$_{1A}$ receptors (Blier et al.1987). Following this line of thought, it was hypothesized that co-administration with a 5-HT$_{1A}$ receptor antagonist would instantaneously mimic this desensitization, thereby enhancing efficacy and reducing the lag time of the antidepressant treatment (Artigas 1993). Since selective 5-HT$_{1A}$ receptor antagonists were not available for clinical use, investigators have used the mixed β-adrenoceptor/5-HT$_{1A}$ receptor antagonist pindolol in order to test this hypothesis (structure 1.5).
Evaluation of this hypothesis has yielded mixed results depending on the setup of the clinical trial. The first trials on the effect of co-administration of pindolol with SSRIs in patients suffering from major depression have all been performed in an open and not placebo-controlled manner. All open trials on co-administration of pindolol with several different SSRIs have reported positive effects on latency to improvement and effectiveness in refractory depression (table 1). In line with the hypothesis, no augmenting effects were observed when pindolol was co-administered with tricyclic antidepressant drugs devoid of serotonin reuptake inhibitory properties.

In contrast with these preliminary studies, double-blind placebo controlled trials have yielded controversial results (table 2). When increased efficacy was evaluated versus placebo based on reductions in HAM-D scores or response rate at end-point, only 3 out of 9 studies were in support of enhanced efficacy. A decreased latency in therapeutic response was only observed in 5 out of 9 cases, whereas no superiority was observed in treatment resistance.
<table>
<thead>
<tr>
<th>SSRI</th>
<th>Dose SSRI</th>
<th>Dose pindolol</th>
<th>Number of subjects</th>
<th>Treatment resistance (TR) or treatment (T)</th>
<th>Outcome (response)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>7</td>
<td>T</td>
<td>5/7</td>
<td>Artigas et al. 1994</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>9</td>
<td>T</td>
<td>7/9</td>
<td>Blier and Bergeron 1995</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>3</td>
<td>T</td>
<td>1/3</td>
<td>Blier et al. 1997</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>3</td>
<td>TR</td>
<td>3/3</td>
<td>Artigas et al. 1994</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>8</td>
<td>TR</td>
<td>Δ-HAMD 32-10</td>
<td>Blier and Bergeron 1995</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20-40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>3</td>
<td>TR</td>
<td>1/3</td>
<td>Dinan and Scott 1996</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>3</td>
<td>TR</td>
<td>Δ-HAMD 29-11</td>
<td>Blier and Bergeron 1995</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-60 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>6</td>
<td>TR</td>
<td>1/6</td>
<td>Dinan and Scott 1996</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>50-100 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>8</td>
<td>T</td>
<td>0/8</td>
<td>Blier et al. 1997</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>200 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1</td>
<td>TR</td>
<td>1/1</td>
<td>Artigas et al. 1994</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-100 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>5</td>
<td>TR</td>
<td>0/5</td>
<td>Blier and Bergeron 1995</td>
</tr>
<tr>
<td>Sertraline</td>
<td>50-100 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>4</td>
<td>TR</td>
<td>¼</td>
<td>Dinan and Scott 1996</td>
</tr>
<tr>
<td>Trimipamine</td>
<td>75-100 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>5</td>
<td>T</td>
<td>0/5</td>
<td>Blier et al. 1997</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>900 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>2</td>
<td>TR</td>
<td>0/2</td>
<td>Blier and Bergeron 1995</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>100 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>20</td>
<td>T</td>
<td>15/20</td>
<td>Barkish et al. 1997</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>60 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1</td>
<td>TR</td>
<td>1/1</td>
<td>Artigas et al. 1994</td>
</tr>
<tr>
<td>Imipramine</td>
<td>200 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1</td>
<td>TR</td>
<td>1/1</td>
<td>Artigas et al. 1994</td>
</tr>
</tbody>
</table>

*Table 1. Efficacy of pindolol co-administration in open trials*
Clinical efficacy of antidepressants in depression

<table>
<thead>
<tr>
<th>SSRI</th>
<th>Dose SSRI</th>
<th>Dose pindolol</th>
<th>Duration of study (weeks)</th>
<th>Number of subjects</th>
<th>Treatment resistance (TR) or treatment (T)</th>
<th>Increased efficacy</th>
<th>Decrease latency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1.5</td>
<td>28</td>
<td>TR</td>
<td>-</td>
<td>-</td>
<td>Perez et al. 1999</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20-40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>2</td>
<td>8</td>
<td>T</td>
<td>-</td>
<td>-</td>
<td>Moreno et al. 1997</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>5</td>
<td>21</td>
<td>30 % TR</td>
<td>+</td>
<td>-</td>
<td>Maes et al. 1999</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>6</td>
<td>86</td>
<td>50 % TR</td>
<td>-</td>
<td>-</td>
<td>Berman et al. 1997, 1999</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>6</td>
<td>111</td>
<td>T</td>
<td>+</td>
<td>+</td>
<td>Perez et al. 1997</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>6</td>
<td>80</td>
<td>T</td>
<td>-</td>
<td>+</td>
<td>Tome et al. 1997</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>4</td>
<td>63</td>
<td>T</td>
<td>+</td>
<td>+</td>
<td>Zanardi et al. 1997</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>20 mg/day</td>
<td>5 mg t.i.d.</td>
<td>4</td>
<td>100</td>
<td>T</td>
<td>-</td>
<td>+</td>
<td>Bordet et al. 1998</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>40 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1.5</td>
<td>20</td>
<td>TR</td>
<td>-</td>
<td>-</td>
<td>Perez et al. 1999</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>200 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1.5</td>
<td>6</td>
<td>TR</td>
<td>-</td>
<td>-</td>
<td>Perez et al. 1999</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>150 mg/day</td>
<td>2.5 mg t.i.d.</td>
<td>1.5</td>
<td>26</td>
<td>TR</td>
<td>-</td>
<td>-</td>
<td>Perez et al. 1999</td>
</tr>
</tbody>
</table>

Table 2. Efficacy of pindolol co-administration in double-blind placebo-controlled clinical trials

Although several trials have observed beneficial effects of co-administration of pindolol with SSRIs, there is increasing evidence that these effects may not be due to antagonism of somatodendritic 5-HT$_{1A}$ receptors by pindolol. Several preclinical studies indicate that pindolol has agonistic properties at 5-HT$_{1A}$ receptors in the raphe nuclei in vivo. Moreover, plasma levels of pindolol are low and the drug does not penetrate the brain easily due to its polar character. It is therefore questionable whether the dose of pindolol used in clinical studies is sufficient to mimic desensitization of 5-HT$_{1A}$ autoreceptors. More studies with specific and potent 5-HT$_{1A}$ receptor antagonists are definitely needed to support this interesting concept.
Augmentation with 5-HT$_{1A}$ receptor agonists

5-HT$_{1A}$ receptor partial agonists have weak antidepressant properties. Preclinical studies have shown that 5-HT$_{1A}$ receptor agonists induce rapid desensitization of 5-HT$_{1A}$ receptors (Kreiss and Lucki 1997). Theoretically, co-administration with a 5-HT$_{1A}$ receptor partial agonist may improve the efficacy and lag time of an SSRI, depending on the size and rate of desensitization induced by the 5-HT$_{1A}$ receptor partial agonist.

Clinical evaluation of this concept has shown beneficial effects, although the evidence is not conclusive (Bouwer and Stein 1997, Jacobsen 1991, Joffe and Schuller 1993, Harvey and Ballon 1995, Landen et al. 1998). More studies are needed to explore this interesting but somewhat paradoxical idea.

2. Selective norepinephrine reuptake inhibitors (reboxetine)

As with serotonin, a role for norepinephrine in depression was suggested by the depressogenic features of reserpine. Abundant evidence is present linking dysfunction of the norepinephrinergic system to depression (Leonard 1997b). In addition, several TCAs are also very potent norepinephrine reuptake inhibitors.

The idea that inhibition of norepinephrine uptake, alongside serotonin reuptake inhibition, could be beneficial in treating depression prompted the development of selective norepinephrine reuptake inhibitors, of which reboxetine is currently the only marketed drug (structure 2.1).

Reboxetine and the noradrenergic system

The noradrenergic system originates mainly in the locus coeruleus. α$_2$-autoreceptors are located on both axon terminals and cell bodies, thus establishing an effective self-regulation system similar to that seen in the serotonergic neuron.

Post-mortem studies of the frontal cortex of suicide victims revealed that both the density and affinity of these receptors were increased (Callado et al. 1998, Meanna et al. 1992). In addition, α$_2$-adrenoceptors may become supersensitive during depression (Charney et al. 1981, Spyraki and Fibiger 1980).

Although chronic administration of desimipramine has been shown to effectively reduce the supersensitivity of α$_2$-adrenoceptors, a recent preclinical study with reboxetine failed to demonstrate changes in receptor function following chronic treatment (Charney et al. 1981, Sacchetti et al. 1999).

β-adrenoceptors are located postsynaptically. Upregulation of these receptors has consistently been observed in patients with depression, whereas downregulation of these receptors is regarded as a marker for antidepressant activity (Leonard 1997a).

The relevance of α$_2$- and β-adrenoceptor downregulation/desensitization for reboxetine’s antidepressant effect has yet to be established.
Pharmacokinetics of reboxetine

Reboxetine is administered on a daily basis at a dose ranging from 8 to 20 mg. Due to its relative short half-life, the daily dose must be divided over the day. The bioavailability of reboxetine is more than 60%, and it has no active metabolites (Table 3).

<table>
<thead>
<tr>
<th></th>
<th>Dose (mg/day)</th>
<th>Bioavailability</th>
<th>Protein binding</th>
<th>$V_d$ (l/kg)</th>
<th>Half-life range (h)</th>
<th>Steady state (ng/ml)</th>
<th>Active metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reboxetine</td>
<td>8-20</td>
<td>&gt;60</td>
<td>97</td>
<td>0.5</td>
<td>12-16</td>
<td>50-160</td>
<td>No</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>75-225</td>
<td>92</td>
<td>27</td>
<td>2.23</td>
<td>2-11</td>
<td>50-150</td>
<td>Yes</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>50-200</td>
<td>85</td>
<td>13</td>
<td>5.3</td>
<td>8</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Trazodone</td>
<td>200-600</td>
<td>60-80</td>
<td>89-95</td>
<td>5-9</td>
<td>700-1600</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Nefazodone</td>
<td>50-600</td>
<td>&gt;20</td>
<td>99</td>
<td>0.2-1</td>
<td>2-8</td>
<td>150-1000</td>
<td>Yes</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15-45</td>
<td>50</td>
<td>85</td>
<td>4.5</td>
<td>13-34</td>
<td>20-40</td>
<td>No</td>
</tr>
</tbody>
</table>


Reboxetine versus TCAs

Several trials have investigated the efficacy of reboxetine compared with TCAs. In one short-term study, reboxetine was found to be at least as effective as imipramine (Montgomery 1997). Analysis of pooled data from four double-blind outpatient studies also showed no differences between reboxetine and imipramine (Massana and Moller 1998a). Another study, comparing imipramine and reboxetine in depressed and dysthymic elderly patients, reported better efficacy of reboxetine in dysthymic patients but not in depressed patients (Dubini et al. 1997, Katona et al. 1999).

Only one short-term study has compared reboxetine with desimipramine. Equal or superior activity of reboxetine was observed (Montgomery 1997).
Reboxetine versus SSRIs
Fluoxetine is the only SSRI that has been compared with reboxetine. Short-term evaluation has shown that the efficacy of reboxetine is similar to fluoxetine (Massana 1998b, Montgomery 1997). Pooling of four double-blind comparison studies, however, revealed increased efficacy of reboxetine compared with fluoxetine in depressed outpatients imipramine (Massana and Moller 1998a). Subset analysis on severe depression in several trials showed that reboxetine was superior to fluoxetine (Massana 1998, Montgomery 1999a).

Tolerability and long-term efficacy
Reboxetine has been shown to be well tolerated in short-term studies. Adverse events, which have been more frequently observed in reboxetine- versus placebo-treated patients, were dry mouth, constipation, insomnia, increased sweating, tachycardia, vertigo, urinary hesitancy and/or retention, and impotence (Mucci 1997). Comparison of reboxetine with imipramine and desipramine revealed a beneficial profile with respect to a number of common side effects like hypotension, dry mouth, and tremor (Ban et al. 1998, Berzewski et al. 1997). When reboxetine was compared with fluoxetine, patients were observed to be less likely to experience ‘stimulant adverse effects’ as well as gastrointestinal effects (Mucci 1999). Reboxetine was shown to be effective in the long-term treatment of depression, given its superior efficacy in a 1-year placebo-controlled study (Montgomery 1997).
Multiple action compounds

**Rationale**
Anderson and colleagues have compared the efficacy of SSRIs and TCAs. No overall differences were found between the groups, although amitriptyline was superior in efficacy compared with SSRIs (Anderson 1998, Anderson and Tomenson 1994). Similar results were found when the SSRI fluoxetine was compared with nortriptyline (Roose et al. 1994). Based on the high affinity of these compounds for both the serotonin and norepinephrine reuptake site, it was speculated that compounds acting on both serotonin and norepinephrine would be superior to single-action antidepressants such as the SSRIs and reboxetine (see Chapter 5). This idea has prompted the development of a group of dual-action antidepressants, which can be subdivided as follows:

I) dual-action reuptake inhibitors (venlafaxine, milnacipran, nomifensin*, and Bupropion*)  
II) receptor antagonist/reuptake inhibitors (trazodone and nefazodone)  
III) heterocyclics with no affinity for the re-uptake site (mirtazapine).

* This chapter is focusing on serotonin and norepinephrine. The dopamine reuptake inhibitors nomifensine and bupropion will therefore not be discussed here.

**3.1 Serotonin-norepinephrine reuptake inhibitors: venlafaxine**

**Pharmacology of venlafaxine**
Venlafaxine has considerable affinity for both the norepinephrine and serotonin reuptake sites, and is therefore called a serotonin-norepinephrine reuptake inhibitor (SNRI) (structure 3.1). The mechanism of action may be deduced from the SSRIs and reboxetine, insofar as venlafaxine can desensitize serotonin autoreceptors and may induce rapid β-adrenoceptor desensitization. In contrast to the classical TCAs, venlafaxine does not bind to histaminergic, cholinergic, or adrenergic receptors, thereby avoiding side effects such as hypotension and sedation.

**Pharmacokinetics of venlafaxine**
Venlafaxine is marketed as regular venlafaxine (venlafaxine-IR). Due to the fast elimination of venlafaxine (elimination half-life of four hours), it is also available in an extended-release formulation (venlafaxine-XR) that enables venlafaxine to be administered once daily. Venlafaxine does not substantially inhibit CYP2C9, 2D6, 1A2, 3A3, and 3A4, and is therefore not likely to interfere with the metabolism of other drugs (Ereshefsky 1996). Venlafaxine has an ascending dose-response curve (Preskorn 1994). This observation is consistent with preclinical data demonstrating that norepinephrine uptake inhibition is seen at doses exceeding those for serotonin reuptake inhibition. Clinical observations also strengthen this idea. Norepinephrine uptake inhibition becomes relevant at doses above 150 mg/day, and clinical superiority with respect to SSRIs is apparent at doses from 225 mg/day (Muth et al. 1986, Clerc et al. 1994).
Venlafaxine versus TCAs
Venlafaxine (25-75 mg twice daily) has been compared with imipramine in a double-blind 13-week study in outpatients with mild-to-moderate intensity (Lecrubrier et al. 1997). Compared with imipramine, venlafaxine-treated patients showed greater reductions in Montgomery-Asberg Depression Rating Scale (MADRS) total scores from week 4 until the end of the study, showing a significant difference in favor of venlafaxine at week 4. Additionally, response rates and clinical global impression (CGI) indices over time were superior for venlafaxine recipients compared with imipramine recipients.

Venlafaxine-XR has been compared with TCAs in a meta-analysis (Einarson et al. 1999). Therapeutic success was defined as a 50% decrease in HAM-D or MADRS scores. Using this approach, the authors showed that venlafaxine-XR was significantly superior to TCAs.

Venlafaxine versus SSRIs
Several trials have been conducted comparing venlafaxine and venlafaxine-XR with SSRIs. A number of these studies indicate that venlafaxine could be superior to SSRIs.

In a 6-week study comparing venlafaxine with fluoxetine in severely depressed inpatients, superior efficacy was observed for venlafaxine (Clerc et al 1994), while an 8-week study also revealed an enhanced response in patients on venlafaxine compared with fluoxetine (Dierick et al. 1995). Another study, however, did not find that the efficacy of venlafaxine was superior to fluoxetine in depressive outpatients (Costa e Silva 1998).

Venlafaxine-XR enhances tolerability and ease of administration. A study investigating the efficacy of venlafaxine-XR versus fluoxetine suggests that venlafaxine-XR brings about greater remission than fluoxetine. In addition, CGI indices were higher in venlafaxine- versus fluoxetine-treated patients (Rudolph and Derivan 1997). Additionally, a meta-analysis has shown that venlafaxine-XR was superior to SSRIs as a group when success rates based on criteria of a 50% decrease in HAM-D and MADRS scores were evaluated (Einarson et al. 1999).

Tolerability and long-term efficacy
As venlafaxine is a very potent inhibitor of serotonin reuptake, it shares several adverse events in common with the SSRIs. The most common adverse events are nausea, dizziness, and somnolence. Just like SSRIs, venlafaxine can induce sexual dysfunction after several weeks of
treatment. When the daily dose of venlafaxine exceeds 225 mg, adverse events may be induced that differ from SSRIs (e.g. hypertension, sweating, and tremors).
3.2 Noradrenaline/serotonin reuptake inhibitors: milnacipran

Pharmacology of milnacipran
Like venlafaxine, milnacipran blocks norepinephrine reuptake sites in addition to serotonin reuptake sites (structure 3.2). Arguably, its mechanism of action is comparable to that of venlafaxine. Differences in efficacy between milnacipran and venlafaxine may be attributed to different pharmacokinetics.

Pharmacokinetics of milnacipran
The bioavailability of milnacipran after oral administration is around 85%. The variation in plasma levels between patients is low, and steady-state conditions are realized with a single daily dose. No active metabolites have been found in humans (Table 3).

Milnacipran versus TCAs

Several clinical trials have compared milnacipran with amitriptyline, imipramine, and clomipramine.
Milnacipran was found to be inferior or equal to amitriptyline, depending on the milnacipran dose used in the trials. At a dose of 50 mg/day, milnacipran was clearly inferior to amitriptyline in terms of onset of action and efficacy after 4 weeks. At a dose of 100 mg/day, onset of action was still inferior but the efficacy after four weeks was comparable to amitriptyline (Ansseau et al. 1989a). Evaluation was based on reductions in MADRS and HDRS (Hamilton Depression Rating Scale) scores, as well as CGI efficacy scores. In a later trial that compared milnacipran 200 mg/day with amitriptyline, CGI efficacy scores were significantly greater in milnacipran-treated patients than in amitriptyline-treated patients (Ansseau et al. 1989b).
Several studies have compared the efficacy of imipramine, clomipramine, and milnacipran in major depression (Clerc et al.1990, Kasper et al. 1996, Matsubara et al. 1996, Puech et al. 1997, Steen and den Boer 1997, Yamashita et al. 1995). Despite the suboptimal dose of milnacipran (50 mg/day), pooled data from these studies did not reveal significant differences between milnacipran and the two tricyclic antidepressants. HDRS and/or MADRS scores were used to assess antidepressant efficacy (Kasper et al. 1996).
In a Japanese trial, treatment with milnacipran (50-150 mg/day) was superior to imipramine after one week of treatment, although no differences were observed at the end of the study (week 4) (Yamashita et al. 1995, Matsubara et al. 1996). Analysis was based on the following scales: HDRS, CGI, and CPRGDRSUC (Clinical Psychopharmacology Research Group Depression Rating Scale for Doctor’s Use). The efficacy of milnacipran (50 mg/day) versus imipramine in elderly people was not significantly different in terms of HDRS, MADRS scores, and other indices in an 8-week trial (Tignol et al 1998).

The efficacies of milnacipran and clomipramine were comparable in several trials, albeit with a slight advantage demonstrated for clomipramine. In one study, where milnacipran (100 mg/day) was compared with clomipramine in major depressive patients, no differences were observed at any time during 3 weeks of treatment (Clerc et al. 1990). Two trials, each lasting 26 weeks, have yielded controversial results. In the first study, no clinical efficacy of either milnacipran or clomipramine could be demonstrated, probably due to the high withdrawal rates and the inclusion of therapy-resistant patients (Steen and den Boer 1997). The second trial, however, clearly favored clomipramine in terms of end-point efficacy, onset of action, and response in severely depressed patients. Interestingly, both studies used an optimal dose of milnacipran 200 mg/day. Significant differences were found in the latter study in terms of the HDRS scores. MADRS and CGI scores were slightly in favor of clomipramine but the differences were not significant (Leinonen 1997).

**Milnacipran versus SSRIs**

Milnacipran has been compared with fluoxetine and fluvoxamine in several clinical trials (Ansseau et al. 1994, Ansseau et al. 1991, Guelfi et al. 1997, Lopez-Ibor et al. 1996). No differences were observed at the end-point (12 weeks) when milnacipran (50 and 100 mg twice daily) was compared with fluoxetine, in terms of HDRS, MADRS, and CGI scores. Milnacipran recipients responded more rapidly than fluoxetine recipients, however, as measured by reductions in HDRS and MADRS scores at week 4 (Guelfi et al. 1997, Lopez-Ibor 1996). In another study, fluoxetine was superior to milnacipran (100mg once daily) after 6 weeks in outpatients suffering from major depression. Reductions in MADRS, HDRS, and CGI scores were significantly different between fluoxetine and milnacipran recipients. Since milnacipran was dosed once daily in this study, and the usual dosage is twice daily, pharmacokinetics may explain the unfavorable results seen with milnacipran (Ansseau et al. 1994).

A comparison of fluvoxamine with milnacipran (75-100 twice daily), either with or without a loading dose, did not produce any significant differences in reductions of MADRS, HDRS, or CGI scores after 4 weeks in major depressive inpatients (Ansseau et al. 1991). Milnacipran (50 mg twice daily) produced larger reductions in MADRS but not in HDRS scores when compared with fluvoxamine (Lopez-Ibor 1996). When data from two comparative studies of milnacipran (50 mg twice daily) versus either fluoxetine or fluvoxamine were pooled, they indicated significantly better results for milnacipran than for the SSRIs. Reductions in HDRS and MADRS scores were significantly greater for milnacipran (Lopez-Ibor 1996).
Tolerability and long-term efficacy
Milnacipran was associated with a higher incidence of vertigo, sweating, anxiety, hot flushes, and dysuria when compared with placebo. When the adverse effects of TCAs were compared with those of milnacipran, patients on TCAs reported a significantly greater number of events of dry mouth, constipation, tremor, sweating, somnolence, tiredness, and vertigo. Only nausea was observed more frequently in SSRI-treated patients than in milnacipran-treated patients (Puech et al. 1997).
4.1 Mixed serotonin antagonist/reuptake inhibitors: trazodone

Pharmacology of trazodone

Trazodone is a potent 5-HT_{2A} and 5-HT_{2C} receptor antagonist (structure 4.1). In addition, it is a weak inhibitor of serotonin reuptake (Table 2). Its metabolite, mCPP, is an agonist at 5-HT_{2C} receptors but an antagonist at 5-HT_{2A} receptors, thus it partly counteracts the effect of trazodone (Fiorella et al. 1995). Taking into account its pharmacokinetic profile, the antidepressant effect of trazodone is most likely related to serotonin reuptake inhibition. Nevertheless, antagonism of 5-HT_{2} receptors may be beneficial, since these receptors are upregulated in suicide patients with a history of depression (Mann et al. 1986).

### Table 2

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*Table 2. In-vitro affinities for receptors and synaptosome reuptake inhibition. Data are IC_{50}, K_{i}, and K_{d} values (nM). Data from (Davis et al. 1997, Venlafaxine package insert 1999, Montgomery 1999b, Owens et al. 1997, Spencer and Wilde 1998, Moret et al. 1985, Taylor et al. 1995).*

5-HT; potency on serotonergic re-uptake inhibition. NE ; potency on norepinephrine re-uptake inhibition. DA ; potency on dopaminergic re-uptake inhibition. α_{1&2}, H, HT_{2A}, HT_{1A} and Musc.; potencies on alpha adrenergic 1 and 2, histaminergic, serotonin 2A and 1A and muscarinic receptors.

\[ \text{Figure 4.1 Trazodone} \]

Pharmacokinetics of trazodone

Trazodone has a short elimination half-life. The daily dose of 200-600 mg must therefore be divided over the day (Table 1).
Trazodone versus TCAs
A meta-analysis has compared the efficacy of trazodone with imipramine. Using HDRS rating scales, no differences were found between the two drugs (Workmann and Short 1993). Moreover, a review of 25 clinical studies on the efficacy of trazodone in depression has reported equal efficacy for imipramine and trazodone (Patten 1992). Additionally, other TCAs did not differ significantly in terms of efficacy when compared with trazodone (Marek et al. 1992).

Trazodone versus SSRIs
Trazodone has good antidepressant properties compared with SSRIs, but it has no effect in panic disorder and OCD (Obsessive Compulsive Disorder) (Marek et al. 1992, Pigott et al. 1992).

Tolerability and long-term efficacy
Dizziness, drowsiness, dry mouth, and nausea are the most frequently reported adverse effects when trazodone was compared with placebo.
4.2 Mixed serotonin antagonist/reuptake inhibitors: nefazodone

Pharmacology of nefazodone
Nefazodone is a potent 5-HT$_{2A}$ receptor antagonist with moderate antagonism at the $\alpha_1$ – adrenoceptors (structure 4.2). It has a considerable affinity for serotonin and norepinephrine reuptake sites too, but these properties were recognized much later (Table 4). Nefazodone may be superior to TCAs in combining serotonin and norepinephrine reuptake inhibition with 5-HT$_{2A}$ receptor antagonism. Upregulation has been reported for 5-HT$_{2A}$ receptors in suicide victims with a history of depression (Mann et al. 1986).

Pharmacokinetics of nefazodone
Nefazodone is absorbed rapidly and completely after oral administration. Due to extensive first-pass metabolism, the bioavailability of nefazodone is approximately 20%. Nefazodone is widely distributed throughout the body, including the central nervous system. The volume of distribution ranges from 0.22 to 0.87 l/kg. Nefazodone is metabolized into several pharmacologically active metabolites such as hydroxynefazodone, mCPP, $p$-hydroxynefazodone, and a triazolodione metabolite (Davis et al. 1997). The daily dose of nefazodone is 50-600 mg, given once or in two divided doses. As with milnacipran, it has an ascending dose-response curve. Nefazodone’s efficacy at lower doses (300-400 mg/day) may be comparable to that of the SSRIs, but it could exceed the latter’s efficacy at higher doses (500mg/day). Analysis of data in the literature has shown that higher doses of nefazodone (> 500 mg/day) do not improve antidepressant efficacy (Dale Horst and Preskorn 1998).

Nefazodone versus TCAs
mg/day), nefazodone was as effective as imipramine, whereas low dosages (50-300 mg/day) were less efficacious (Fountaine et al. 1994, Mendels et al 1995, van Moffaert et al. 1994). Amitriptyline has shown superior efficacy compared with nefazodone in patients with moderate-to-severe depression and in bipolar affective disorder (Ansseau et al. 1994b).

Nefazodone versus SSRIs
Nefazodone has been compared with paroxetine, sertraline, and fluoxetine in several clinical trials (Armitage et al 1996, Baldwin et al 1996, Cassano et al. 1993, Feiger et al. 1996, Rioux et al. 1996). No indications for differences in efficacy have been observed between nefazodone and any of the SSRIs.

Tolerability and long-term efficacy
The most frequently reported adverse events observed with nefazodone are nausea, somnolence, dry mouth, dizziness, constipation, asthenia, light-headedness, and blurred vision. Compared with TCAs, nefazodone was observed to induce less dry mouth, constipation, and blurred vision. No abnormal weight gain has been observed with nefazodone, although weight gain was reported for TCAs and trazodone.
When nefazodone was compared with SSRIs, more activating symptoms (agitation, anxiety, tremor, insomnia, and nervousness), diarrhea, sweating, anorexia, nausea, and male sexual dysfunction were observed in SSRI versus nefazodone recipients. Dry mouth, dizziness, constipation, visual disturbances, and confusion were more common in nefazodone versus SSRI recipients (Davis et al. 1997).
5.1 Mixed serotonin/noradrenaline antagonist: mirtazapine

Pharmacology of mirtazapine
It is thought that the dual mode of action of mirtazapine operates via the blockade of $\alpha_2$-adrenergic receptors in combination with 5-HT$_2$ and 5-HT$_3$ receptor antagonism (structure 5.1). This mechanism of action refers to the interplay between the norepinephrine system and the serotonin system in the brain. The norepinephrine neuron carries $\alpha_2$-autoreceptors in the terminal as well as in the cell body region.

Antagonism of these receptors by mirtazapine has been shown to enhance norepinephrine neurotransmission. Noradrenaline interacts with the serotonergic system in two ways. First, $\alpha_2$-heteroreceptors are present on the terminals of serotonin neurons, activation of which attenuates serotonin release. Second, $\alpha_1$-heteroreceptors are present in the cell body region of the serotonergic system, activation of which increases the firing rate of the serotonergic neurons, thus enhancing serotonin neurotransmission. Mirtazapine blocks presynaptic $\alpha_2$-adrenoceptors, which enhances noradrenaline release in the raphe nuclei. Arguably, $\alpha_1$-adrenoceptors on serotonin cell bodies in the raphe nuclei become increasingly activated, thereby enhancing the firing rate of the serotonergic neurons. Antagonism of 5-HT$_2$ and 5-HT$_3$ receptors has been hypothesized to further concentrate the enhanced serotonin neurotransmission towards 5-HT$_{1A}$ receptors.

Pharmacokinetics of mirtazapine
The pharmacokinetic parameters of patients have been summarized in Table 1. Based on the recommended daily dose of 15-45 mg, average steady-state plasma levels of mirtazapine range between 30-300 nM. Since protein binding of mirtazapine is approximately 85%, free mirtazapine levels will be between 4.5 and 45 nM. The free brain concentration of mirtazapine will maximally range between 4.5 and 45 nM. Since mirtazapine is not a very potent $\alpha_2$-adrenoceptor antagonist ($K_i \sim 100$ nM, $K_d \sim 140$ nM), binding of mirtazapine to these receptors will not be substantial at clinical doses. The latter argument may urge for a reconsideration of the proposed mechanism.
Mirtazapine does not inhibit CYP450 enzymes and is therefore not expected to interact with the metabolism of other drugs (Table 3).

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Table 5: Relative inhibition of CYP450. Data from (Spencer and Wilde 1998, Lindsay de Vane 1998).

Clinical trials: mirtazapine versus TCAs
Comparisons of mirtazapine with tricyclic antidepressants have mainly focused on amitriptyline, imipramine, clomipramine, and doxepine. In a review by Davis and Wilde (Davis and Wilde 1996), it was reported that mirtazapine has a similar efficacy to TCAs in both outpatients and inpatients with major depression. Several trials comparing mirtazapine with amitriptyline have observed similar HDRS response rates between the two compounds (Bremner 1995, Mullin et al. 1996, Smith et al 1990, Zivkov and de Jongh 1995). Concurrent meta-analyses have confirmed the equal efficacy of both drugs (Stahl et al. 1997, Fawcett and Barkin 1998, Kasper et al 1997, Kasper 1995). Although efficacy was observed to be similar, relapse rates were lower and sustained remission rates were higher for mirtazapine in a placebo-controlled continuation trial (Montgomery et al 1998).
Mirtazapine has been compared with imipramine in inpatients in a study that claimed a superior response rate for imipramine (Bruijn et al. 1996). When the efficacy on several symptom clusters was investigated, mirtazapine appeared to be effective in clusters related to anxiety and sleep, whereas imipramine was effective on core symptoms of depression (Bruijn et al 1999).
No indications for a different efficacy for mirtazapine and clomipramine were found in two double-blind randomized trials (Richou et al. 1995, Peyron 1996).
Response rates at study end-point were similar in mirtazapine and doxepine recipients in a double-blind multicenter trial (Martilla et al. 1995).

Clinical trials: mirtazapine versus SSRIs
Mirtazapine had a superior onset of action compared with fluoxetine. The reductions in HAM-D score were significantly greater at weeks 3 and 4. Response rates (>50% reduction in HAM-D score) were also significantly higher at week 4 (Wheatley et al. 1998).
When compared with paroxetine, mirtazapine was significantly superior in terms of reduction in HDRS scores at various time points (Benkert et al. 1998). The decrease in HAM-D score
was higher for mirtazapine at week 1. Mirtazapine was also significantly superior to fluoxetine at weeks 1 and 4 when responder dates were evaluated.

A multicenter, double-blind, randomized study in inpatients and outpatients with major depressive disorder has compared mirtazapine with citalopram. The decrease in baseline MADRS scores was greater for mirtazapine than for citalopram at week 2. Additional scorings such as the Hamilton Rating Scale for Anxiety (HAM-A) and CGI also showed superior reductions for mirtazapine versus citalopram at week 2. Response rates, as defined by CGI, were better for mirtazapine at weeks 1 and 2 (Agren et al. 1998).

Tolerability and long-term efficacy

The results of clinical trials suggest that patients are more likely to comply with mirtazapine than with TCA treatment. An overview of the available data showed that amitriptyline was inferior to mirtazapine in terms of long-term dropouts due to adverse events (Montgomery 1995b).
Conclusions
The latest generation of antidepressants may have several advantages in comparison to MAOIs, TCAs, and SSRIs.

- Safety profile and interaction with the metabolism of other drugs are much improved compared with MAOIs and TCAs.
- Unfortunately, elimination rates (except for mirtazapine) have increased, making it necessary to use multiple daily doses. By using extended-release formulations such as venlafaxine-XR, however, the inconvenient multiple dosages can be avoided. On the other hand, rapid elimination is beneficial when patients change antidepressants.
- Selective norepinephrine reuptake inhibition (Reboxetine) may be superior to selective inhibition of the serotonin reuptake site, although enhanced efficacy with respect to TCAs has not been observed in the majority of comparative studies.
- Clinical studies have shown that some, but not all, of the multiple-action antidepressants tend to have better short-term efficacy than TCAs and SSRIs (Table 4).
- The mixed serotonin/norepinephrine reuptake inhibitor venlafaxine has shown superior efficacy compared with TCAs and SSRIs in the majority of short-term trials. Unexpectedly, milnacipran, with almost the same pharmacological profile as venlafaxine, was not found to be superior to the SSRIs and TCAs. The less convincing results for milnacipran may be related to the pharmacokinetic properties of the compound.
- Although not reviewed in this chapter, combined dopaminergic/noradrenergic compounds (nomifensine and bupropion) do not seem to be superior to SSRIs and TCAs in depression. These drugs, although originally marketed for depression, have both been withdrawn as antidepressants and were therefore not evaluated extensively.
- Antidepressants with a mixed profile of Selective Serotonin Reuptake inhibition and 5-HT\textsubscript{1A} antagonism and agonism could have beneficial effects over SSRIs, though their exact efficacy has to be evaluated with selective and potent ligands. Comparison versus TCA’s has not been performed yet.
- The mixed serotonin antagonist/reuptake inhibitors nefazodone and trazodone do not have an advantage over regular treatment with TCAs and SSRIs. Trazodone may be as effective, or slightly superior to, TCAs whereas nefazodone has equal or inferior efficacy compared with TCAs. Compared with SSRIs, nefazodone was equally effective.
- Mirtazapine is comparable to the TCAs on short-term efficacy, but a majority of studies indicate that mirtazapine is superior to SSRIs.
Clinical efficacy of antidepressants in depression

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Table 4. Short-term comparative efficacy of new antidepressants versus tricyclic antidepressants and selective serotonin reuptake inhibitors based on reduction in HDRS and CGI.

In conclusion, it can be stated that the majority of new antidepressants tend to be superior to SSRIs in short-term trials. Compared with the TCAs, venlafaxine may be the only multiple-action compound with somewhat better antidepressant properties.

Depression is a recurrent condition. Future trials should therefore evaluate the efficacy of newer antidepressants over a longer period of time (years), thereby evaluating patient compliance as well as sustained antidepressant efficacy. In addition, patient sub-group analysis of trials would indicate the long- and short-term efficacies of antidepressants over the depression sub-population. Only in this way can the clinical efficacy of the new antidepressants be evaluated thoroughly.
References


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