Based on:

Introduction

Mental illness accounts for about one-third of adult disability globally (Anderson et al., 2011) causing considerable societal and personal suffering, and high social and economic costs. For instance, major depressive disorder affects an estimated 121 million people worldwide and is one of the leading causes of disability on a global scale (Demyttenaere et al., 2004). By 2020, depression is expected to be the second leading contributor to all-cause disability worldwide, second only to heart disease (World Health Organization (WHO), 2013).

Despite important progress in psychiatry not all patients respond well to available treatments. Studies using data of both published and unpublished clinical trials show that the effects of the most common treatments in psychiatry have been overestimated. This seems to be true for psychotherapy (Cuijpers et al., 2010; Cuijpers et al., 2011) as well as for the pharmacologic treatments of many major psychiatric disorders (Herrmann et al., 2011; Kirsch et al., 2008; Turner et al., 2008; Thase, 2007; Velligan et al., 2009). In addition to growing concerns about efficacy, psychotropic drugs can cause adverse effects, including weight gain, increased risk of diabetes and heart disease, metabolic syndrome, neurological disorders, sudden cardiac death, and may potentially increase suicide risk (Henderson, 2008).

There are also other concerns in (mental) health care. The costs are getting out of control, now taking 17.6 percent of gross domestic product (GDP) in the USA and 12.0 in the Netherlands (OECD, 2012). One possible strategy to cut costs is inviting patients to take a more active role in their recovery, for instance by applying therapeutic lifestyle changes like exercise, diet and relaxation (Egger et al., 2007; Walsh, 2011). The contribution of lifestyle to modern chronic disease has been estimated at 80% (Yusuf et al., 2004) and even 95% (Ruiz-Nunez et al., 2013). There is growing evidence for the efficacy of lifestyle changes for improving health, but besides running therapy, there is only limited experience with applying lifestyle changes in (mental) health care (ACPM, 2009; Walsh, 2011; Sarris et al., 2012; Berk et al., 2013).

Another concern is the quality of the therapeutic relationship, which seems threatened by managed care, focus on protocols and evidence-based medicine, and a tendency to reductionism, narrowing the view to diseases or symptoms and losing sight of the whole person in his / her context. The original definition of evidence-based medicine is ‘(1) the conscientious use of current best evidence in (2) making decisions about the care of individual patients or the delivery of health services, (3) taking preferences and needs of patients into account’ (Sackett et al., 1996; Sackett et al., 2000). However, the last part of this definition is often neglected. This, together with a tendency towards uniformity and efficiency (in the form of guidelines, treatment protocols and clinical pathways) can lead to a ‘one size fits all approach’. However, there is a growing awareness of the need for a more holistic perspective beyond the current paradigm that is primarily focused on brainscience and psychopharmacology (Bracken et al., 2012), taking the whole person into account (Ahn et al., 2006). This can be observed in new concepts like ‘personalized medicine’ (Galas & Hood, 2009; Ozomaro et al., 2013; Van der Gref, 2011), ‘shared decision making’ (Elwyn et al., 2000) and ‘patient-centered care’ (Gill, 2013). The need for a more holistic / integrated approach to medicine has been proposed by the Dutch psychiatrist Querido in 1955 (Boenink & Huyse, 1997). In 1977 George Engel formulated his biopsychosocial model (Engel, 1977). Since then some models for a more integrated system of care have been developed, such as INTERMED (Stiefel et al., 2006).
These models, however, are mostly theoretically acknowledged but still rarely applied in patient care (Astin et al., 2003).

**Integrative medicine: a new paradigm**

In response to the before-mentioned concerns a consortium of academic health centers in the USA launched a new concept of health care, called integrative medicine, in the late nineties of the past century. Integrative medicine is the central theme of this thesis with an emphasis on its application to (Dutch) psychiatry.

Integrative medicine is the practice of medicine that (1) reaffirms the importance of the relationship between practitioner and patient, (2) focuses on the whole person, (3) is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to (4) achieve optimal health and healing (The Consortium, 2004). Today 55 academic health centers (e.g. Duke university, Harvard, Stanford) in the USA are active members of this consortium. Many research groups, health centers, educational, advocacy and policy activities related to integrative medicine now exist in different countries around the world (e.g. Australia, UK, Germany). The part of psychiatry / mental health care, however, seems undervalued.

Integrative psychiatry is integrative medicine applied to mental health care (Sarris et al., 2013). It is also based on those four pillars. It (1) emphasizes the importance of the therapeutic relationship between clinician and patient using shared decision making and a personalized approach. It (2) focuses on treating the ‘whole person’ from a holistic perspective, considering mind-body and its systems as interrelated, with biological, mental, emotional, cultural, ecological and spiritual / religious aspects. It (3) seeks to provide the ‘best of both worlds’ combining conventional medicine with non-conventional medicine (this includes lifestyle, complementary and alternative medicine; see next paragraph ‘definitions’) based on evidence for their safety and efficacy. Its focus (4) is on increasing qualities and strengths (salutogenesis) as well as decreasing symptoms (pathogenesis) and it aims for increasing general wellbeing and mental health (Lake et al., 2012).

This approach to medicine might provide some solutions to the concerns mentioned in the previous paragraph. The first two principles can increase adherence to the treatment plan, improve the therapeutic relationship (Stevingson, 2001) and enhance treatment outcome (Koenig, 2000; Nikles et al., 2005; Gill, 2013), as treatment outcome has been shown to be highly dependent on the quality of the therapeutic alliance (Wampold, 2001; Driessen et al., 2010; Baldwin et al., 2007; De Jong, 2011), while a personalized approach may also improve outcome (e.g. Ozomaro et al., 2013).

The third principle might lead to new treatment options and less adverse side effects of conventional medicine. Besides possible health gain for individual patients, there are also financial reasons for applying this principle. Recent findings from economic modeling research suggest that incorporating lifestyle, complementary and alternative medicine into conventional treatment may yield cost-effective long-term outcomes (Herman et al., 2005; Bornhoft et al., 2006; Pelletier et al., 2010; Kooreman & Baars, 2011). Although the evidence base for alternative medicines is generally weak, evidence for the effectiveness of lifestyle and complementary medicine is stronger and emerging (see next paragraphs).

Improved outcomes may also be achieved by not only looking at symptoms and problems and trying to eradicate them (pathogenesis), but also at the strengths
and qualities of patients and finding ways to increase them (health promotion or salutogenesis; Lindstrom & Erkkson, 2005). One example is positive psychology (Seligman & Csikszentmihalyi, 2000; Fredrickson, 2001). Another is the induction of therapeutic lifestyle changes. It is cheap and can increase self-esteem, responsibility for one’s own health and more independence from therapists (Walsh, 2011; Sarris, 2011; Egger et al., 2007; Berk et al., 2013). It may not only reduce psychopathology, but it may also enhance (mental) health and wellbeing by fostering positive emotions like calmness, empathy and self-actualization (Shapiro & Carlson, 2009; Walsh & Shapiro, 2006). In this way therapeutic lifestyle changes can contribute to the fourth principle of integrative psychiatry.

**Definitions**

There is no consensus on definitions of non-conventional (lifestyle, complementary or alternative) medicine, which increases confusion (Gaboury et al., 2012). In this thesis we use the following definitions (Box 1).

**Box 1: Definitions and examples of different classes of non-conventional medicine**

<table>
<thead>
<tr>
<th><strong>Lifestyle medicine</strong></th>
<th>Preventing and treating chronic diseases by inducing therapeutic lifestyle changes (Egger et al., 2007; ACPM, 2009).</th>
<th>Running therapy, diet, yoga and mindfulness</th>
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<td><strong>Complementary medicine</strong></td>
<td>Forms of diagnostics, treatments and prevention strategies that are based on theories accepted in biomedicine and are substantiated by some scientific evidence (two or more RCTs), but for different reasons (cultural or practical) do not form part of biomedicine (Lake, 2007).</td>
<td>Herbs, vitamins and food supplements</td>
</tr>
<tr>
<td><strong>Alternative medicine</strong></td>
<td>Forms of diagnostics, treatments and prevention strategies that make use of other than the basic concepts of biomedicine. There is little proof for the efficacy of these treatments and / or there is considerable controversy about the scientific validation (Lake, 2007).</td>
<td>Healing and homeopathy</td>
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Lifestyle medicine is also called ‘therapeutic lifestyle change’ or ‘preventive medicine’. We include it among non-conventional medicines because a majority of integrative clinics have a program of lifestyle medicine (Horrigan et al., 2012) including exercise, diet, nutrition, relaxation, yoga and meditation, whereas most conventional clinics do not provide any of these. Nonetheless, there are some lifestyle changes that are part of conventional medicine, e.g. smoking cessation and losing weight.
Evidence, mechanism and acceptance

To clarify the differences between conventional, complementary, lifestyle and alternative medicine, we distinguish three main aspects in table 1: mechanism (is the proposed working mechanism of the treatment plausible?), efficacy (how much evidence is there for its efficacy?) and acceptance (to what degree are these treatments accepted and implemented by conventional health care?).

Conventional medicine’s efficacy and mechanisms are obviously most researched and accepted. Hypotheses on mechanisms follow generally accepted basic concepts of science / medicine. Most conventional clinicians agree that treatments should be evidence-based (e.g. established efficacy in at least two high quality randomised clinical trials; RCTs), and many of the conventional treatments are, although not all of them. Estimates of the percentage of conventional treatments that are actually evidence-based vary from 15% (Smith, 1991) to 38% (Imrie & Ramey, 2001) and 53% (Ellis et al., 1995). Pelletier (2003) assessed the percentage of decisions in various medical specialties that follow the rules of EBM; his summary ranges from 11% to 70%.

Table 1: Characteristics of (non-)conventional medicine

<table>
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<th>Conventional Medicine</th>
<th>Non-conventional medicines</th>
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<tr>
<td></td>
<td></td>
<td>Lifestyle</td>
</tr>
<tr>
<td>Convincing mechanism</td>
<td>present</td>
<td>present</td>
</tr>
<tr>
<td>Evidence for efficacy</td>
<td>well documented</td>
<td>varying levels</td>
</tr>
<tr>
<td>Acceptance by conventional healthcare providers</td>
<td>high</td>
<td>partial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Complementary</td>
</tr>
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<td>Alternative</td>
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Research shows that lifestyle medicine (Egger et al., 2007) is insufficiently appreciated, taught and utilized in (mental) health care, even though there is growing evidence for its efficacy and there are few side effects (ACPM, 2009; Ornish, 2009). A lifestyle program consisting of diet / nutrition, exercise and relaxation has been proven effective for reversal of coronary heart disease and early stage prostate cancer (Ornish et al., 1990; Ornish et al., 2005). Promoting lifestyle changes is also an effective intervention for mental health (Walsh, 2011). Evidence shows improvements in overall (mental) health and reduced relapse risk (Angell, 2009; Walsh, 2011; Sarris, 2011; Berk et al., 2013). Mindfulness meditation seems effective for mood disorders (Piet & Hougaard, 2011), anxiety (Coelho et al., 2007; Kim et al., 2009), negative symptoms of schizophrenia (Lake, 2007), addiction (Bowen et al., 2006), sleep disorders (Ong et al., 2008), eating disorders (Kristeller & Hallet, 1999) and trauma (Niles et al., 2011). Other lifestyle changes have been researched less
rigorously, but still with promising results. For instance, yoga seems effective for depression, anxiety and sleep disorders (Balasubramaniam et al., 2012; Uebelacker et al., 2010; Cramer et al., 2013a; Cramer et al., 2013b) and possibly for schizophrenia as an adjunct to pharmacological treatment (Vancampfort et al., 2012). Most lifestyle medicine is still underutilized in conventional health care settings, although acceptance is growing (e.g. mindfulness).

For some complementary medicines there is a lot of evidence for their mechanism and effectiveness, especially for nutrients (such as S-adenosyl methionine (SAMe) and folic acid for mood disorders) and herbs (e.g. St. John’s wort for depression and Ginkgo biloba for cognitive decline). For other complementary medicines the evidence is less convincing but emerging (e.g. omega-3 fatty acids in mood disorders and rhodiola for stress and fatigue). An extensive overview of the efficacy of complementary medicines in bipolar disorder and schizophrenia is presented in chapters 4 and 5.

Alternative medicine generally lacks convincing evidence for its effectiveness. The proposed mechanism is often based on theories that are not part of basic concepts in biomedicine. Alternative medicine is therefore generally not accepted and not applied in conventional medicine.

Therapies do not necessarily stay in one category. They can move from alternative to complementary and even to conventional (e.g. EMDR and mindfulness) when evidence emerges. They can also move into the other direction when evidence emerges that these treatments do not work (e.g. vitamin B3 as a stand-alone treatment for chronic schizophrenia). Therapies can also move to another category when the proposed working mechanism changes. For example acupuncture: a review of eight Cochrane reviews found evidence for its effectiveness in nausea and pain (Lee & Ernst, 2011), but there is a lot of debate about the mechanism. Originally, in China, it was proposed to work through stimulating acupuncture points and energy channels, called meridians. With increasing levels of evidence for effectiveness, some authors have suggested other mechanisms more familiar to conventional medicine (the pain of needles might stimulate endorphins or other neurotransmitters; Sun et al., 2008). With emerging evidence and a mechanism more plausible (for conventional doctors), acupuncture can now be classified as complementary medicine instead of alternative. This is reflected by a growing acceptance (many pain centers of conventional hospitals now provide acupuncture).

The use of complementary and alternative medicine

Since integrative medicine was introduced, there has been increasing interest from the medical and scientific community. This interest has particularly focused on three elements; reaffirmation of the therapeutic relationship (first principle of integrative psychiatry), the holistic approach (second principle) and the focus on health and healing (fourth principle). But there is criticism as well, especially about the use of complementary or alternative medicines (part of the third principle), which remains controversial and subject to heated debates. Therefore, this thesis is primarily focused on this third principle of integrative medicine.

There are more reasons to take a critical look at complementary and alternative medicines. Complementary and alternative medicines are widely used by patients for a range of mental health conditions. Large surveys confirm that consumer use has steadily increased over several decades (Barnes et al., 2008).
Survey findings suggest that 43% of patients in developed countries with an anxiety disorder (Bystritsky et al., 2012) and 53% with depression (Wu et al., 2007) use complementary or alternative medicine. These patients perceive such treatments as improving their physical, emotional, cognitive, social, and spiritual functioning, reducing symptom severity and promoting recovery and wellness (Russinova et al., 2009). We replicated these findings in an outpatient clinic in the north of the Netherlands and found a similar percentage (42%; Hoenders et al., 2006). In developing countries in Africa and Asia 80% of the population depends on complementary and alternative medicine for their primary health care (World Health Organization, 2006).

Many seriously mentally ill individuals who use complementary or alternative medicine perceive such treatments as improving their physical, emotional, cognitive, social, and spiritual functioning, reducing symptom severity and promoting recovery and wellness (Sirois, 2008). However, few patients disclose this use to their psychiatrist, family physician or other conventional healthcare provider (Thomson et al., 2012) in fear of being ridiculed (Vandercreek, 1999). In our study, 61% of psychiatric outpatients did not disclose their use of complementary / alternative medicine to their conventional doctor / healthcare provider (Hoenders et al., 2006). This may lead to potential health risks such as interactions between medicines and herbs, some of which indeed have been reported (Ernst, 2003). Only 3% of the user population is aware of this potential risk (Walter & Rey, 1999).

Lack of uniformity and practice guidelines

At present, the practice of integrative medicine / psychiatry is highly varied and idiosyncratic. Such practice depends on the personal philosophies, values and clinical perspectives of its practitioners, and the goals of diverse training programs, clinics or hospitals where integrative treatment approaches are employed (Horrigan et al., 2012). Such wide variety seems undesirable as regards effectiveness, efficiency and scientific evaluation. There is a need for treatment guidelines for the judicious use of complementary and alternative medicine in conventional care and more uniformity in the practice of integrative psychiatry.

There are additional reasons for the need for guidelines in integrative psychiatry. Despite the emerging evidence for the efficacy of complementary medicines, in the Netherlands many doctors do not inform their patients about complementary or alternative medicine and avoid prescribing it or referring to it, because of the controversy surrounding it or because they are not familiar with these medicines and their effectiveness. In a written enquiry 65% of psychiatrists and residents state that ‘they want to learn more about complementary / alternative medicine’ (Hoenders et al., 2006). Others have claimed that these medicines are quackery and that the effects are based on placebo and ‘ridiculous principles’ (Renckens, 2004). Such prejudice against new developments is undesirable; decisions should be made on empirical evidence instead of subjective opinions. A critical evaluation of complementary and alternative medicine is needed because of the before-mentioned high usage patterns in the general population and safety issues. Moreover, it seems urgent to facilitate the spread of reliable information, as the majority of patients get information on these medicines now through the Internet, family or social networks. The quality of this information varies greatly, leading to potentially harmful and dangerous situations (Crone & Wise, 2000). The Dutch Minister of Health has announced more severe punishment for practitioners who
harm their patients either by applying unsafe therapies or by delaying the start of conventional treatment (Klink, 2009). Thus, in the Netherlands patients and doctors are informed about what cannot be done concerning complementary and alternative medicine, while it remains unclear what could or should be done. Despite calls from the World Health Organization (World Health Organization, 2003) and the European Parliament (European Parliament, 1997), until now the Dutch government did not formulate policy on this subject.

Research on integrative psychiatry

Psychiatric research in the past 50 years has focused primarily on neurobiological mechanisms, pharmacotherapy, and (to a lesser extent) psychotherapeutic techniques. More recent research has also explored the effects of lifestyle medicine and complementary and alternative medicine (Horrigan et al., 2012; Sarris, 2011; Walsh, 2011, Kemper et al., 2008; Ravindran et al., 2009) although this field is still in its infancy.

For assessing the effects of treatments (conventional, lifestyle, as well as complementary and alternative medicine), researchers have almost exclusively relied on RCTs. This is because the RCT has strong features that control for bias and confounding (e.g. randomization), which results in high internal validity. Therefore, it has been considered the gold standard for determining treatment effects. As a corollary, however, external or ecological validity is often compromised (Howard et al., 1996; Natan et al., 2000). One example of this potential lack of external validity is the observation that patient samples of RCTs are often dissimilar from those seen by practicing clinicians, because inclusion criteria are stringent (Natan et al., 2000; Persons & Silberschatz, 1998). Other examples are the stringent use of standardized treatment protocols, leaving no space to adapt the treatment to the individual patient, and the randomization procedure that prevents the patient to choose the treatment of preference. Today many researchers propose a more balanced position, acknowledging the strong features of RCTs but at the same time stressing the need for other types of research (Bluhm, 2009; Slade & Priebe, 2001; Van der Lem et al., 2012; Walach et al., 2006).

There are some other drawbacks to conventional research methods. Most efficacy studies only take a single therapeutic factor into account. But different factors may reinforce or counteract each other. Moreover, conventional randomized studies generally show treatment effects at the group level, while at the individual level great differences in effectiveness exist. Finally, RCTs usually provide little insight into the causal mechanisms by which interventions exert their effect. The typical intervention study has measurements before and after the intervention, but not in between. As a result, little can be concluded about the process of change and how improvements are established (Hilliard, 1993).

This leads to additional research questions, such as questions of effectiveness (does this treatment work in daily practice?), questions of individuality (does this treatment work for this particular patient?) and questions of mechanism (why does this treatment work?). This is especially true for complex interventions such as physiotherapy, surgery and complementary and alternative medicine (Walach et al., 2006). To answer such questions, effectiveness studies are needed, for example modifications of the orthodox randomized trial (called ‘real-world’ randomized trials or pragmatic trials) or analyses of large administrative databases (Simon et al., 1995). Also single-subject studies with time-series analysis can be useful to answer these questions.
Introduction

(Molenaar & Campbell, 2009; Hilliard, 1993; VandenBroucke et al., 2006; Nikles et al., 2005). At present there is a scarcity of this kind of research approaches in medicine and psychiatry (Sarris et al., 2013). Advances in research and the clinical practice of psychiatry will take place when formal research methodologies permit the rigorous evaluation of complex interventions involving multiple therapeutic modalities (which mirrors true clinical practice) to treat real-world clinical populations. Mental health research needs to span both the natural and social sciences (Van Os, 2012; De Jong, 2013). Evidence based on RCTs has an important place, but to adopt only concepts from one body of knowledge is to neglect contributions that other well-established methodologies can make (Slade & Priebe, 2001). In other words: besides an integrated treatment approach, a truly integrative research focus is also needed. While methodologically challenging, this approach may potentially elucidate the relative contributions of social, psychological, biological and spiritual factors in each unique patient’s response to combined treatment modalities.

This thesis

Part I of this thesis is about the conceptual foundation of integrative (mental) health. In chapter 1 we argue that the success of integrative medicine is related to the fact that integration is not only a current tendency in medicine, but also fitting recent changes in psychotherapy, science, religion and philosophy of which integration seems to be the most common feature. In chapter 2 we compare conventional and complementary/alternative medicine as regards their perspective, paradigm, organization, scientific method and procedures. We show that theoretically, conventional and alternative medicine are categorically opposed to each other in many respects, but in practice they seem to differ merely dimensionally, with the exception of the commonly used theoretical models (paradigms), which do seem to differ fundamentally. We argue that the difference in paradigms can be bridged using an integrative model that accommodates both.

Part II is about the implementation of integrative medicine in Dutch mental health care. In chapter 3 we present a treatment guideline using an algorithm for the judicious safety-conscious application of complementary and lifestyle medicine in psychiatry, based on the Dutch law, scientific research, jurisprudence and rules of professional bodies (e.g. the Royal Dutch Association of Medical Doctors).

Part III is about the effectiveness of complementary medicine and integrative psychiatry. First, we discuss the effectiveness and safety of complementary medicine for bipolar disorder (chapter 4) and schizophrenia (chapter 5) based on (systematic) reviews. Then, in a single-subject time-series analysis, we investigate the temporal dynamics of symptom and treatment variables in a lifestyle-oriented approach to anxiety disorder (chapter 6). Finally, in chapter 7 we discuss pitfalls in the assessment, analysis, and interpretation of routine outcome monitoring (ROM) data using results from our outpatient clinic for integrative mental health.

In the last part we discuss the results of the research presented in this thesis. We respond to criticism on integrative medicine / psychiatry and give recommendations for future research and practice.
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Introduction


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Part I: Conceptual foundation