Integrative Psychiatry
Conceptual foundation, implementation and effectiveness

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Colofon

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* The Borobudur stupa mandala is situated in Central Java, Indonesia. It was constructed out of vulcanic stone in the 8th century by three generations of the Sailendra Buddhist Dynasty. It is the largest surviving Buddhist mandala in the world that displays all three 'yanas' of Buddhism: Theravada, Mahayana and Varjayana. Due to a large vulcanic eruption in the 9th century it lay covered with volcanic ash and mud for over 1000 years. It was completely overgrown by jungle vegetation when, in the 19th century it was rediscovered and excavated by Dutch and English colonial explorers. Dutchman Theodor van Erp initiated in 1902 the first attempt to restore it. Between 1975 and 1982 it was completely rebuilt and renovated by the Indonesian government and UNESCO. It is recognized as a world heritage site since 1991.

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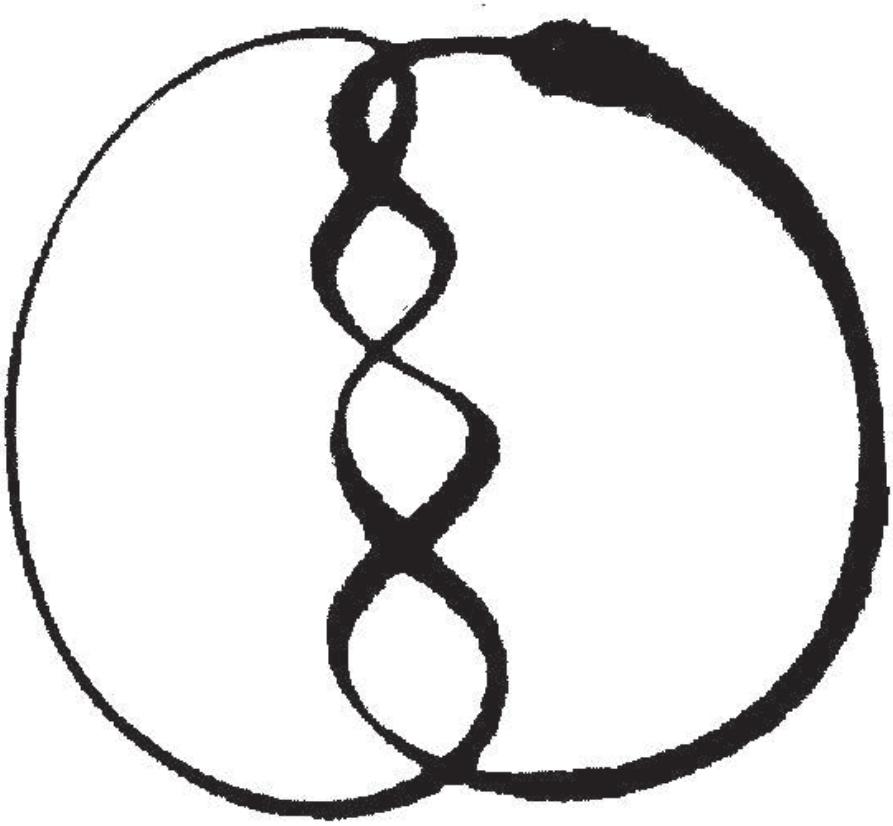

[1]

[1] Deze afbeelding, getiteld ‘oneindigheid in duplo’, is een Japanse penseelschildering gemaakt in één vloeiende beweging met Sumi-E techniek door Jan Pijpker in 1987. Het is het logo van (Centrum) Integrale Psychiatrie.

Introduction

Based on:

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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 Studies using data of both published and unpublished clinical trials show that the effects of the most common treatments in psychiatry have been overestimated.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 Greef, 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 & Erikkson, 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

Lifestyle medicine	Preventing and treating chronic diseases by inducing therapeutic lifestyle changes (Egger et al., 2007; ACPM, 2009).	Running therapy, diet, yoga and mindfulness
Complementary medicine	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).	Herbs, vitamins and food supplements
Alternative medicine	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).	Healing and homeopathy

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

	Conventional Medicine	Non-conventional medicines		
		Lifestyle	Complementary	Alternative
Convincing mechanism	present	present	present	Absent
Evidence for efficacy	well documented	varying levels	varying levels	absent or conflicting
Acceptance by conventional healthcare providers	high	partial	low	very low

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

(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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Part I: Conceptual foundation

Chapter 1

Integrative medicine: a bridge between biomedicine and alternative medicine fitting the spirit of the age

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Abstract

Complementary and alternative medicine (CAM) are increasingly used by people in first world countries, almost always in combination with biomedicine. The combination of CAM and biomedicine is now commonly referred to as 'integrative medicine' (IM). In Groningen, The Netherlands, we founded a center for integrative psychiatry, offering conventional and complementary mental health care. Like other centers for integrative (mental) health we have mostly received positive reactions although there have been negative and even hostile reactions as well, using phrases like 'quackery' and 'betrayal'. We will try to illustrate that these polarising qualifications, in which 'the good' is being positioned against 'the bad' in an over-simplified manner, are unnecessary and not useful. Moreover, it is unlikely that this polarisation will stall the growth of IM. It seems that integration is not only a current tendency in medicine, but also a trend fitting the contemporary spirit of the age in which integration seems to be the most common focus. It can be observed in religion, philosophy, spirituality and psychotherapy as well. This article will discuss the difference between differentiation and integration and will show that the focus on differentiation or integration varies with time, mostly rising as a reaction to each other. The transition from one period to the next is often met with resistance and criticism. If the integrative movement is to survive, it cannot do without differentiation and must find a middle way in which appropriate attention is being paid to keeping the integrated parts sufficiently differentiated and allowing them to keep their own identity.

Introduction

The Latin word 'integralis' means: 'forming a greater entity'. Integration stands for 'fusing or making collaborate different parts into a larger whole' or 'including into a whole'. The opposite of integration is differentiation; the process whereby a homogeneous entity is being divided in parts with different qualities. Integration and differentiation are not mutually exclusive. They should rather be understood as movements of the same wave, or phenomena taking turns. When there is too much integration, the different parts lose their identity or experience a lack of autonomy. This provokes differentiation, leading them to profile themselves independently from each other. When there is too much differentiation, they lose sight of each other and each other's interests, which increases the risk of polarisation and conflict. This will invariably lead to a need for more integration.

This process can also be observed in medicine. At the end of the 19th and the beginning of the 20th century, the need for differentiation led to a change in medical laws and regulations in various countries (for instance the Flexner report in 1910 in the United States and the Health Care Implementation Act in 1865 in the Netherlands). These changes created a strict separation between recognised treatments on the one hand (which later became known as biomedicine or conventional medicine) and other forms of medicine (which later became known as complementary / alternative medicine). Besides the distinction between biomedicine and complementary / alternative medicine, a debate also arose between professionals who favoured a reductionistic and biomedical approach of medicine and colleagues who preferred a more holistic or integrative approach. In the seventies and eighties of the 20th century George Engel was an influential physician from the last group. In response to the dominant reductionistic view of medicine, he formulated a biopsychosocial model. His criticism (Engel, 1992) of the biomedical model encompassed among other things: that illness perception can be insufficiently explained by biochemical changes (for instance, illness perception varies with culturally shared cognitions about diseases, illness-related behaviours and social support); that clinicians pay too little attention to personal factors and communication skills (for instance with regards to stimulating therapy adherence); and that behavioural and social variables can and do influence the course of an illness.

After more than a century of separation and conflicts between conventional, biomedical medicine and alternative, holistic medicine, from 2000 on there is a tendency towards integration under the denominator of 'integrative medicine' (Hollenberg, 2006; Hsiao et al., 2006; Jobst, 1998). Integrative medicine can be defined as 'the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, health care professionals and disciplines to achieve optimal health and healing (Consortium, 2009). The most controversial part is the use of 'all appropriate therapeutic approaches' as it includes the use of complementary and alternative medicine (CAM) within conventional hospitals/ (care) delivery systems' (Hoffer & Hoenders, 2010). 'Complementary' stands for forms of diagnostics, treatments and prevention strategies that are based on theories accepted in biomedicine. These are usually substantiated by scientific argumentation, but for different reasons do not form part of biomedicine. Examples are massage therapy and the use of herbs and food supplements. Alternative treatments, such as healing and homeopathy, make use of other than the basic concepts of biomedicine. There is little proof for the efficacy of

these treatments or there is considerable controversy about the scientific validation (Lake, 2007).

In integrative medicine the principles of evidence-based medicine are applied to conventional, complementary and alternative treatments. This implies that in choosing an intervention, one should take into account the highest level of available scientific evidence about the different treatment options; the values, preferences and frame of reference of the patient; and the professionalism and experience of the therapist (Sackett et al., 2000). The number of options in integrated medicine is larger than in regular health care (Hoenders et al., 2011; Lake, 2007; Lake & Spiegel, 2006), since CAM treatments are not excluded beforehand.

The European Parliament (1997) and the World Health Organization (2003) plead in favour of promoting integrative medicine (Chung et al., 2011). However, this call is meeting a lot of resistance. There is an enormous heterogeneity in views and behaviour concerning CAM (Hirschkorn & Bourgeault, 2005). The movement is even sometimes labelled as ‘quackery’ and the people who practice or promote CAM are sometimes disqualified as betrayers. This can be observed when reading the ‘rapid responses’ to the editorial introducing this concept in biomedicine (Rees & Weil, 2001) and more recently in a letter by Ernst (2012). Our center for integrative psychiatry also met these kind of criticisms (Kuipers & Gijsman, 2006). In this essay we will try to illustrate that these polarising qualifications, in which ‘the good’ is being positioned against ‘the bad’ in an over-simplified manner, are unnecessary and not useful. The fact is that integration is not only a current tendency in medicine, but also a phenomenon that has manifested itself in the history of mankind in all types of fields and all sorts of ways. Not as an enemy of differentiation, but as a natural reaction to it.

Manifestations of a society aimed at integration

‘Integration’ and ‘differentiation’ both play a central role in the dynamics of life. Cells merge and split; people marry and separate; companies are fused and subdivided; and power blocks are formed and fall apart. The process of merging and separation is taking place on each level of life. It forms a returning theme in the history of humanity, and takes different forms in different fields, over and over again. In this article, we provide several typical examples from different spheres of life, restricting ourselves to the themes related to our own field: world view (philosophy, religion and spirituality), health care (treatment demand, pathways to care and psychotherapy), and scientific research.

Philosophy

The contemporary philosophy that evolved roughly after the Second World War is called 'postmodernism' (Anderson, 1999; Bertens, 1994; Scruton, 2006). The core of this trend is the idea that objectivity and the absolute truth do not exist. There are many theories, ideologies, religions, convictions and principles, but history teaches us that none of these has profiled itself in such a way that it can be rightfully called ‘leading’, ‘all-encompassing’ or ‘universal’.

Lyotard (1979) called this ‘the end of the big stories’. There is no winner and thus, there is no such thing as the ultimate truth or essential knowledge. As a result, postmodernism is not exclusively aimed at acquiring knowledge, but especially points at its ignorant, emotional, narrative, theory-bound and thus unstable

foundation. If there is no absolute criterion, it is also not determined which goals we should pursue. According to one of the post-modern philosophies, existentialism, we are therefore doomed to freedom (Sartre, 1965). According to another philosophy, social constructivism, we are free to choose what we make of our lives, because everything changes all the time (Bertens, 1994). This implies fear and insecurity, but also provides unrestricted space to numerous equal, parallel ways to deal with things. Mainly because of this freedom, post-modern philosophy is offering a visionary framework for integrative thinking and acting.

Religion and spirituality

Even though polarisation and hostilities between the major world religions still exist, and even though inter-religious tension is a risk factor for war and armed conflict (De Jong, 2010), there is a clear tendency of integration in the field of religion, especially in the Western world. This is caused by the secularisation of society, which has led to a decrease in popularity of institutionalised forms of religion, such as the Church. This has created a need for new forms of spirituality and interpretation, in which Eastern and shamanistic traditions and philosophies have played a considerable role in the last decennia. The way this new form of spirituality is being created, is characterised by diversity and the post-modern lack of claims on one exclusive source of the truth. This is accompanied by the freedom to choose how an individual would like to fulfil his spiritual needs.

Research shows that spirituality has a strong positive association with health (Koenig, 2000; Koenig, 2001). It also consistently shows that giving meaning to what happens to us, is more important for the wellbeing of a person than any particular religion. The experience of finding purpose is more important for the wellbeing of people than the capacity to clarify or to give a logical explanation for things (Lewis et al., 2005; Scannell et al., 2002; Steger & Frazier, 2005).

Demands for care

Also regarding to health needs and demands for care, a tendency towards integration can be observed. The expression ‘supply creates demand’ implies that when people are making a choice, they take into account and use all available options. A demand for care is therefore determined for the most part by the available supply. Especially because of the internet, all health-related knowledge has become accessible to everyone. This has had a huge impact on the kind of health care demands people make. Nowadays patients want to choose their own treatment (Coulter & Willis, 2004) and are increasingly requesting an integrated package of regular, complementary and alternative treatment methods (Hök et al., 2007), not bothered by the differences in paradigms and working styles of CAM and biomedicine (Hoenders et al., 2008) and the ethical and scientific challenges resulting from it (Oguamanam, 2006).

Eisenberg et al. (1998) showed that CAM is being used on a large scale in the United States, usually in combination with regular treatments, and that there is an increase in use. In 1990, 34% of the Americans used CAM; by 1997 this percentage had increased to 42%.

Even though patients do increasingly express demands for integrative care, they seem to anticipate that caregivers still restrict themselves to their own field of interest. About 60-75% of patients appear to conceal the use of CAM to their doctor because of fear of disapproval or ridicule (VandeCreek et al., 1999). This is in sharp contrast with the fact that patients would like to receive information about CAM from

their conventional providers. It would be advisable if doctors would address this need respectfully, since an open attitude towards nonregular treatment methods is essential (Hök et al., 2007): It improves the therapeutic relationship (Stevinson, 2001) and increases the impact of medical interventions (Koenig, 2000). It is also important to enquire about the use of CAM for medical-ethical reasons. Uncontrolled use of CAM can be dangerous, because of possible side-effects and interactions with regular medicines (Ernst, 2002). In a study in Australia less than 3% of the population was aware of this (Walter & Rey, 1998). In this regard it is worrisome that one in five patients combines herbs or foods supplements with medication (Eisenberg et al., 1998). An open conversation about CAM can take away misunderstandings and thereby prevent potentially dangerous situations.

These considerations led to our own research (Hoenders et al., 2006), which showed that 42% of almost 600 psychiatric outpatients in the Northern Netherlands had used CAM. This figure is similar to older prevalence figures in psychiatric patients (53%) (Knaudt et al., 1999). We also studied the prevalence of CAM use among patients of General Practitioners (GPs). A survey of 900 patients showed that they had used CAM in 62% of cases (Borgemeester et al., 2008). Both groups of patients report less than half of the cases of CAM use to their conventional doctor. This is also in agreement with prevalence rates offered by other researchers (VandeCreek et al., 1999; Wetzel, 1998). Half of the psychiatric patients and 65% of the GP patients would like to receive more information about CAM and prefers that their conventional therapist would offer this. In contrast, the psychiatrists and GPs who were surveyed in this study heavily underestimated the use of CAM among their patients, and only one third of them was in favour of offering this information themselves. For one quarter of the psychiatrists and one third of the GPs CAM had an outspoken negative connotation. So, it seems that despite most patients favour CAM and integrative health care, a considerable number of conventional doctors are not willing to work in this way, creating a tension between health needs and supply.

Psychotherapy

Eventually, the struggle between different schools of thought in Western psychotherapy had come to an end. It was replaced by a so-called ‘Dodo bird verdict: Everybody has won, and all must have prizes’ (Luborsky et al., 2002). This was done because empirical evidence had shown that the ‘specific ingredient’ in any given therapy – that which theoretically makes it work – adds little to the nonspecific elements of psychotherapy (Asay & Lambert, 1999). Moreover, this research has shown that clinical success is more a function of differences among therapists than among therapies (Wampold, 2001), and the success of therapists is primarily related to the quality of their alliance with patients (Baldwin et al., 2007; Luborsky et al., 2002).

This revaluation of nonspecific therapy factors is also being stimulated by an increasing collaboration between behaviour-oriented sciences such as neurology, biology and experimental, social and clinical psychology. The results of this interdisciplinary research questions the existence of the free will: the neo-cortex appears to be less dominant and therefore has less influence on our behaviour than it would like us to believe (Dijksterhuis, 2008; Lamme, 2010). It seems that we are predominantly controlled by automatic neural networks. Someone who would like to change his behaviour does not benefit much from a wonderful all-encompassing theory, but needs the discipline to replace all old automatisms with new ones that fit into his own (small, but subjectively significant) story (Appelo, 2011; Brewin, 2006).

The treatment method that facilitates this type of learning, is no longer forcefully dictated by a particular viewpoint or school of thought. In line with the principles of evidence-based medicine, this integrative method results from the interaction between the (preferences of the) patient, the (expertise and experience of the) therapist and the number of effective interventions that are available at that moment. This gives psychotherapeutic practice an integrated, eclectic character (Korrelboom & Ten Broeke, 2004).

Another form of integration in psychotherapy is that of East and West. Eastern philosophies are increasingly being integrated into Western (psycho-)therapies; examples are mindfulness and Acceptance and Commitment Therapy (ACT) (Kabat-Zinn, 2003). So, it seems that also in psychotherapy there are many developments with a tendency towards integration.

Scientific research

Although there still are well-defined schools of thought in the world of science with their own methodological preferences, we also see, especially in health care, a growing space for the equal coexistence of different research methods (Plochg et al., 2007; Walach et al., 2006). This is facilitated by the criticism of the doctrine of the randomised controlled trial (RCT) as a 'sacred' scientific research method (Ottenbacher & Hinderer, 2001). This criticism is predominantly based on the difference between internal validity, or efficacy (does a method or intervention work as such?) and external validity, or effectiveness (is it beneficial in a certain context?). Proven efficacy does not say much about effectiveness, as what works in a large group on average does not per se apply to all individuals in various contexts. On the other hand, effectiveness does not simply imply efficacy, because what works for a person in a particular situation, cannot always be generalised to a group.

If an intervention with only one mode of action is being studied, as is the case with medication, and if a subject does not prefer the experimental condition over the control condition (because he cannot know the difference between the two), it is indicated to establish the internal validity of the intervention first. In this case, the RCT is the research method of choice. If however the expectation of the result and the preference of subjects play a role and these are not the same for the experimental and the control condition (as is the case with almost all psychological and non-placebo-controlled medication research in health care), establishment of the external validity is indicated first. Observational, quasi-experimental and mixed-methods research is the method of choice in this case (Barry, 2006; Plochg et al., 2007). This offers possibilities for CAM (Barry, 2006) as most CAM users have a strong preference and therefore it is difficult to do RCTs for CAM therapies. Although in biomedicine it is common to start with randomised trials first, possibly later followed with effectiveness studies, in CAM it seems acceptable to work the other way around. To start assessing the effectiveness in a certain context and verifying it later in a RCT. This also makes sense as in biomedicine new pharmacological compounds are only allowed on the market after assessing efficacy and safety in RCTs, but most CAM are already being used, even though efficacy has not been established yet. So, it seems that it depends entirely on the research question, kind of treatment and circumstances, which kind of research design is needed. No design (not even RCT) can be considered best in all circumstances (Walach et al., 2006). This calls for an integrated research approach.

Discussion

This essay suggests that the integrative movement in health care does not stand on itself. It is a phenomenon that is manifesting itself worldwide and in different aspects of daily life. It follows a period in which differentiation took central stage but did not lead to absolute, unquestionable truths.

The conclusion that integrative health care fits the spirit of the time therefore seems justified. However, there is a chance that, with continuing integration, this movement will develop into another direction. The different parts in this case might eventually lose their identity, develop a need for autonomy and try to promote more differentiation. The dynamics of the processes of differentiation and integration show that both poles are connected (similar to the perpetual dynamics and balance between yin and yang in Eastern philosophy or the Western theory of dialectics). If the integrative movement wants to survive, it will have to make sure that the balance is not lost.

In other words: a continuing integrative movement cannot do without differentiation and must find a middle way in which appropriate attention is being paid to keeping the integrated parts sufficiently differentiated and allowing them to keep their own identity. Then, integrative health care predominantly means a good and equal collaboration between parts that are well differentiated. In this regard it would be useful if everyone who is involved in the process, critically contributes to the debate and raises the alarm once the balance between differentiation and integration is getting lost. In the last few years a distorted balance due to a lack of criticism or supervision has become visible in various spheres – e.g., the worldwide financial crisis and fraud in scientific research.

Finally, it would be interesting to raise the question why in the process of integration and differentiation people may feel the need for polarisation and rowing against the flow, instead of contributing to the debate. We think that the main reason why people would protest against integration is that they do not consider themselves sufficiently profiled and recognised in the process of differentiation. After all, it looks like integration works against one's own identity. Especially when a person's identity has not been satisfactorily established during the process of differentiation, he may fear that integration will destroy it. This phenomenon is visible in the viewpoint of Kuipers and Gijsman (2006), who present as an argument against the psychiatric branch of the integrative movement, that it has taken regular psychiatry already a lot of efforts to be seen as a normal part of medicine. The resistance against integration is then related to the lack of a clear identity. Developing such an identity is a good thing. But fighting against something else is, in our opinion, not an appropriate method to reach this goal. It would be better to invest in the profiling of your own message and methods. Once we feel that we are being carried away, against our will or not, in an integrative movement, we do not have to be afraid that we will lose ourselves in it. We can get out of it on our own, or take part in the larger whole and help create something that is more than the sum of its parts, all the while making sure that we can still recognise ourselves in what we are doing. That will assist in finding and keeping the middle road between preservation of one's own identity and integration into a larger whole.

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Chapter 2

Western and Traditional Medicine: a comparison of paradigms and working methods

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Introduction

In the West half the population uses non-conventional medicines (complementary and alternative medicine, CAM; also referred to as Traditional Medicine, TM) annually (Bodeker & Kronenberg, 2002), almost always in combination with Western Medicine (WM) (Astin, 1998). For instance in the Netherlands CAM is used by 42% of psychiatric outpatients (Hoenders et al., 2006a). Most of them favour integration of CAM and WM (Hoenders et al., 2006a). In the East, traditional medicines like Chinese and Tibetan medicine and Ayurveda are increasingly being researched with Western research methods (like the RCT; randomized clinical trial) often with remarkable results. Of course, these medicines have already proved their value in thousands of years. But now in this information era with increasing exchange between East and West and an emphasis on scientific research, there seem to be great opportunities for collaboration, exchange and even integration of WM and TM; the different medicines of the world.

But although the practical integration of western medicine (WM) and complementary and alternative medicine is growing (Hoenders et al., 2008), their paradigms and therapeutic methods often differ greatly. At first sight they even appear impossible to reconcile. Is theoretical and therapeutic integration of WM and CAM really an illusion or is the presumed gap mainly related to our points of view? We did a literature search on this issue and this is what we found (Hoenders et al., 2006b).

Comparison of CAM and Western Medicine

Many authors compared the Western biomedical paradigm with alternative paradigms (McFarlane, 1996; Goldstein, 2003; Kaptchuk & Eisenberg, 1998). Table 1 shows five factors that in our opinion characterize the differences most clearly, with references to the original authors.

These distinctions are in most cases not categorical but dimensional, for example, the ‘procedures’ aspect ‘technology versus natural sources’. A great deal of current WM medications is directly derived from herbs and plant extracts, such as procaine and digitalis. This obscures the boundary between 'natural' and 'technical'.

The same counts for the ‘expert’ issue. It is clear that during surgical intervention the patient is under anaesthesia and the doctor is the expert. However, afterwards the patient himself has to work actively on rehabilitation. The patient's contribution varies from minimal to a great deal considering the circumstances.

With regard to the ‘therapist-patient relationship’, mainstream psychotherapy currently strongly recognizes the importance of non-specific factors (Duncan & Miller, 2006).

Table 1: General differences between CAM and WM

Factor	Western Medicine	CAM / TM
Perspective	Reductionism[1]	Holism
	Pathogenesis (focusing on factors that cause disease)	Salutogenesis (focusing on health, well-being, and one's self-healing capacity)[2]
Paradigm	Mechanism[3]	Vitalism[4]
	Giving antidote (allopathy)	Stimulating healing response (homeopathy)[5]
Procedure	Therapist is expert and responsible	Patient is expert and responsible[6]
	Therapeutic relationship is minor detail[7]	Therapeutic relationship is central[8]
	Technology	Natural sources[9]
Research method	'Outer science'[10] / 'evidence'[10]	'Inner science'[11] 'experience'[9]
	RCT, efficacy[10]	N of 1, effectiveness[12]
Organisation	Legitimate, official[13]	Unofficial[14]
	Training[14]	'Calling'[15]
	Costly	Cheap[16]

[1] Engel, 1980; Van Der Steen, 1991
[2] Goldstein, 2003; Cassidy, 2001; Weil, 2000
[3] Jonas, 2002
[4] Goldstein, 2003; Kaptchuk & Eisenberg, 1998; Micozzi, 2001; Gulmen, 2004
[5] Vickers & Zollman, 1999
[6] Weil, 1996; Gangchen Rinpoche, 1997
[7] Snyderman & Weil, 2002
[8] Astin, 1998
[9] Kaptchuk & Eisenberg, 1998
[10] Sackett et al., 2000
[11] Wilber, 2000; Bensing, 2000; Happle, 1998; McFarlane, 1996
[12] Ho & Van Der Steen, 2005; Kaptchuk, 2001
[13] Barrett et al., 2000
[14] Happle, 1998
[15] Bruce, 2002
[16] Sarnat & Winterstein, 2004; Boon et al., 2004

Regarding research, in Western medicine it is largely based on positivism, reductionism, objectivism and determinism. This is sometimes called ‘outer science’. It strives for standardization and generalization. In furnishing scientific proof, the RCT is the golden standard. Alternative therapies are particularly based on subjective experience, intuition and belief. The assumption is that the truth is found by way of personal experience (McFarlane, 1996). This is sometimes called ‘inner science’ or ‘first-person science’ (Wilber, 2000). This approach seems particularly suitable for observations or 'single-case' studies (n = 1). In research terms, it is related to the difference between *efficacy* (the ideal outcome in controlled circumstances) and *effectiveness* (the clinical outcome in natural circumstances). According to Bensing (2000), ‘outer’ and ‘inner science’ are two different worlds. Some say ‘inner science’ is by definition irrational and irreconcilable with rational science (Happle, 1998). Conversely, the criticism of RCTs is that they artificially reflect a complex clinical practice and that the importance of the individual patient becomes devaluated by this (Tataryn & Verhoef, 2005). Moreover, the ‘RCT as golden standard’ is, to our opinion, culture-bound and is implemented less outside of Western culture. After all, for instance various Eastern spiritual philosophies, consider the *inner* experience as the ultimate basis for attaining knowledge about reality. Assumptions are tested according to other (inner) research methods (McFarlane, 1996).

Despite these differences, it is clear that in the last decade Eastern philosophies have found more acceptance in the Western world and in psychiatry, for example, mindfulness and other Buddhist techniques in the (third generation of) behaviour therapy (Brewin, 2006). Additionally, the unassailable status of the RCT is more frequently put into question, and research methods suitable for ‘inner science’ are proposed more often (Ho & Van Der Steen, 2005; Kaptchuk, 2001). So, also where it concerns research methods, the differences found are not as absolute as they initially seemed to be. The same gradual distinctions seem to be valid for all other factors and aspects. Therefore, theoretical and therapeutic integration of WM and CAM seems relatively easy. But is it?

There seems to be an exception. The contrast between ‘mechanism’ (often accompanied by reductionism) and ‘vitalism’ (often accompanied by holism) is categorical and has been one of the greatest controversies in philosophy. It still leads to heated discussions between WM and CAM. This absolute contrast is of a meta-theoretical nature and therefore cannot be solved through standard scientific logic (Hein, 1971). Supporters of each paradigm and perspective cannot be convinced by scientific evidence to the contrary because their points of view concern an existential premise, a conviction regarding the question of ‘why’ things are as they are (Coulter & Willis, 2004).

However, looking deeper, this controversy seems also relative. For example, a mechanical, work-related frame of mind does not rule out religion and spirituality in private life. Furthermore, a vitalistic philosophy as the leading therapeutic principle can occasionally imply a mechanical working method.

Conclusion

Besides practical integration practised by patients already for a long time, the theoretical and therapeutic integration of WM and CAM is also possible. The findings of our literature search argue for using the biopsychosocial model as originally proposed by Engel (1980; 1992) to facilitate this process. This model fits well because it maintains a middle ground between the biomedical approach and the holistic-vitalistic approach and because its basis is in biological systems theory. This theory attempts to surpass (the opposition between) mechanism and vitalism, partly by nuancing both (Hein, 1972). And it is precisely this nuancing that seems important in our post-modern, multicultural society.

In our opinion we should support integration of WM and CAM in a professional, critical manner and with an open mind so that we can arrive at a complete, efficient, effective integrated healthcare system in which everyone, regardless of his or her culture, race, philosophy of life or need, can receive the help he or she needs.

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Part II: Implementation

Chapter 3

The Dutch complementary and alternative medicine (CAM) protocol: to ensure the safe and effective use of CAM within Dutch mental health care

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Abstract

Background:
Complementary and alternative medicine (CAM) is subject to heated debates and prejudices. Studies show that CAM is widely used by psychiatric patients, usually without the guidance of a therapist and without the use of a solid working method, leading to potential health risks.

Aim:
The judicious use of CAM alongside conventional psychiatry in an outpatient psychiatric clinic.

Methods:
A search through scientific and legal articles and discussion in focus groups.

Results:
In the Center for Integrative Psychiatry (CIP) of Lentis in the Netherlands some carefully selected CAM are offered under strict conditions, alongside conventional treatments. Because of the controversy and the potential health risks, Lentis designed a protocol that is presented.

Introduction

In 2002 Silvia Millecam, a famous Dutch actress, died of breast cancer after refusing conventional medical treatment while trusting herself to practitioners treating her with CAM. The Dutch Healthcare Inspection did an extensive inquiry into the matter. Three doctors were put to trial for malpractice and were convicted by the Medical Disciplinary Tribunal. Two of them lost their medical licence. In the years that followed there were heated debates on the use of alternative medicine in the Netherlands.

Supporters of CAM claim that conventional treatments have too many side effects, lack effectiveness and room for patients' wishes and needs. On the other hand, opponents state that CAM is quackery and that the effects are based on placebo and 'ridiculous principles' (Renckens, 2004). This reaction reminds us of earlier resistance to change in medicine; for instance, in 1911 Herrick was almost laughed out of medicine for stating that atherosclerosis causes myocardial infarction (Olshansky & Dossey, 2003).

Previous and current bias against new developments is undesirable because both patients and doctors are uncertain about safety and effectiveness of CAM. This is all the more important because about half of the population in a variety of western countries (Bodeker & Kronenberg, 2002) and almost half of Dutch psychiatric outpatients use CAM annually (Hoenders et al., 2006). A majority of patients gets information on CAM via internet, friends or family. The quality of this information varies greatly, leading to potentially harmful and dangerous situations (Crone & Wise, 2000).

In the Netherlands many doctors do not inform their patients about CAM and they certainly avoid prescribing or referring to CAM. Recently 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 (NRC Journal, 2009). Therefore, in the Netherlands patients and doctors are informed about what *cannot* be done concerning CAM, while it remains unclear what could or should be done. Despite calls from the World Health Organization (WHO, 2003) and the European parliament (European Parliament, 1997), until now the Dutch government did not formulate a policy on this matter.

In an effort to fill this gap and inspired by the North American consortium of 55 academic health centers for integrative medicine (CAHCIM, 2004), Lentis (a community mental health facility in the North of the Netherlands) founded a Center for Integrative Psychiatry (CIP) in 2006. It consists of an outpatient clinic, a research department, an educational department, and organizes an annual conference (with approximately 1000 attendees) (Hoenders et al., 2008). Its main purpose is to provide safe and effective integrative mental health care.

What is Integrative Psychiatry?

Integrative psychiatry is based on the principles of 'integrative medicine': reaffirming the importance of the relationship between practitioner and patient; focusing on the whole person; using all therapeutic approaches (conventional and CAM) based on the principles of evidence-based medicine (EBM); and achieving optimal health and healing.

The debate in the Netherlands focuses mainly on the principle of EBM, i.e. the use of CAM within conventional treatment centers, and the correct definition of evidence-based medicine. In this regard it is noteworthy that Sackett et al. (2000) defined EBM as: (1) the best available evidence for effective and safe treatment options, (2) the preferences and needs of the patient, and (3) the clinical expertise of the professional. These three together should be decisive in making treatment choices.

This definition is in contrast with the present-day more reductionist explanation of evidence-based medicine in which the first and third principle are emphasised without paying much attention to the patient's preference (Offringa et al., 2003). The original definition therefore accommodates therapies that still lack (sufficient) evidence-based proof. It is also important to realize that according to some researchers only about one third of culturally and professionally accepted interventions in western medicine is proven effective by RCTs (Booth, 2006; Tataryn & Verhoef, 2001).

Prejudices

Some reasons why opponents feel doctors should not use CAM seem to be based on prejudices. Table 1 compares the most common prejudices *against* CAM with information from scientific studies.

Table 1: Prejudices against CAM

Prejudice	Refutation
1. Only few people use CAM	1. 30-70% of the population uses CAM[1] and 42% of Dutch psychiatric outpatients[2]
2. My patients do not use CAM because they never ask or tell me about it	2. 60-75% of patients using CAM do not tell their doctor out of fear of a negative response[3]
3. CAM users are less educated and easily influenced	3. CAM users are typically female, highly educated, high income with chronic disease[4]
4. They use CAM instead of conventional medicine	4. 80-95% combines[2]
5. They use CAM because of negative reasons (against conventional medicine)	5. Besides disappointment about side effects and limited results, also positive reasons play a part: good relationship with therapist and a shared belief about health and disease (holism)[5]
6. CAM effects are due to placebo	6. Several CAM are more effective than placebo[6]
7. CAM and EBM are incompatible	7. CAM can be offered based on the principles of EBM[7]
8. CAM are not endorsed by influential institutions	8. The CAHCIM[8], the WHO[9] and the EP[10] endorse the integration of effective CAM in conventional clinics

[1] Bodeker & Kronenberg, 2002
[2] Hoenders et al., 2006
[3] Van De Creek et al., 1999
[4] Astin, 1998; Eisenberg et al., 1998
[5] Furham, 1996
[6] Ernst, 2006; Lake & Spiegel, 2006; Mischoulon & Rosenbaum, 2008
[7] Wilson & Mills, 2002; Hoenders et al., 2010
[8] CAHCIM, 2004
[9] World Health Organization, 2003
[10] European Parliament, 1997

Similarly, those in favor of CAM also seem to have prejudices. Those are mentioned in table 2. We therefore argue that CAM needs serious attention, both within conventional treatment centers and in the alternative field.

Table 2: Prejudices for CAM

Prejudice	Refutation
1. If it does not work, at least it will not harm	1. Some supplements or herbs can cause severe side effects or interactions[1]
2. Natural substances are more healthy than chemicals	2. Nature contains severe toxins, besides natural medicines
3. CAM do not need to be researched; I know it works from experience	3. Experience is not enough; research is needed to distinguish from placebo and bias[2]
4. CAM are not suitable for research because of their specific nature	4. Science can be applied to all phenomena; it is essential to choose the right design[3]

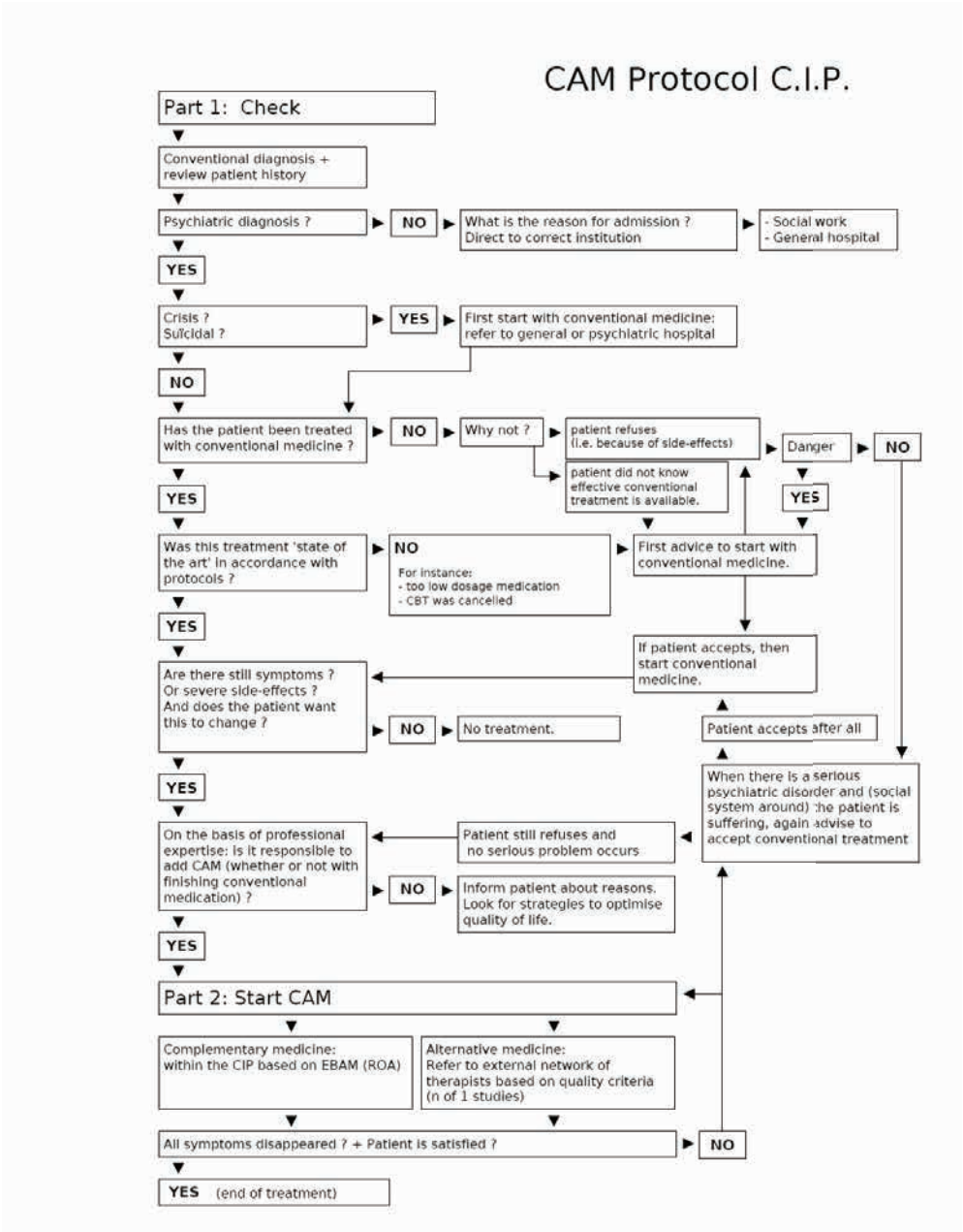
[1] Ernst, 2003
[2] Sackett et al., 2000
[3] Walach et al., 2006

The CAM protocol

One of the primary tasks of our center was to formulate a scientific model based on the requirements that it would (1) answer patients' needs and wishes; (2) respect their freedom of choice; (3) would offer western medicine and CAM that are safe and effective; (4) would protect against quackery and abuse; (5) should be based on Dutch law, the jurisprudence of the Medical Disciplinary Tribunal and the rules of the Dutch Association of Medical Practitioners (KNMG); and (6) be based on scientific evidence.

The authors reviewed documents, the scientific literature and collected information with the help of focus groups (De Jong et al., 2010). This resulted in the CAM protocol (Hoenders et al., 2010). In this protocol we distinguish (between) complementary and alternative medicine. The first is defined as "approaches based on mainstream biomedical theory and supported by research evidence but not part of mainstream practice because of social, political or ideological reasons". Examples are St. John's wort and massage. Alternative medicine is defined as "approaches that are based on concepts that are outside mainstream Western medicine". Examples include homeopathy and healing (Lake, 2007). Based on an analysis of the results we produced the algorithm shown in figure 1.

Figure 1: Decision tree



This is the working method of the Center for Integrative Psychiatry. The first step of the algorithm clarifies that CAM can only be used after an extensive and precise stepwise process. They can only be started if conventional treatments have been applied before or at least advised as suggested by guidelines and protocols. In addition, CAM is considered if there is no danger when a patient refused treatment (for instance: a manic or psychotic patient with severe symptoms will be strongly advised first to accept conventional medication even when asking for CAM).

After deciding to start CAM, the second step is based on the principles of EBM (i.e. alternative treatments with a lower level of evidence can be provided on a patient's request when there is no contraindication). However, these treatments will not be offered within the CIP. Patients will be referred to an external network that provides these treatments in conjunction with proven treatments provided by CIP and not instead of them. In addition, there are the following required conditions:

- The therapists are members of a (para)professional organization with a formal procedure for complaints and malpractice.
- The therapists base their treatments and their way of working on the professional guidelines of the organization.
- The therapists conform themselves to legal demands concerning patient files.
- The clinic or office where patients are being treated meet privacy and hygiene demands, as common in conventional medicine.
- The therapists have malpractice insurance.
- There has to be at least monthly contact between the CIP and the alternative practitioner.
- After finishing the alternative treatment there will be at least one contact with the CIP to evaluate.
- The alternative therapists agree to be included in scientific evaluation by routine outcome measurement (ROM) of the effect of the treatments and agree with publication, regardless the results.

Center for Integrative Psychiatry

In the Center for Integrative Psychiatry of Lentis only conventional and complementary medicine that have been proven effective and safe are being practised. That means that they have to be based on (reviews of) several well-designed scientific studies. Examples are St. John's wort for depression (Linde et al., 2008), valerian for insomnia (Mischoulon & Rosenbaum, 2008), relaxation for anxiety (Eppley et al., 1989), mindfulness-based stress reduction (Baer, 2003; Grossman et al., 2004) and mindfulness-based cognitive therapy for depression (Teasdale et al., 2000), massage for stress, anxiety and depression (Moyer et al., 2004), exercise for depression, anxiety and sleep disorders (Craft & Landers, 1998), heart-rate variability training for anxiety and stress-related and depressive symptoms (Karavidas, 2008; McCraty et al., 2001), single vitamins as a supplement to medication for depression (like folic acid) (Taylor et al., 2008), food supplements like s-adenosylmethionine (SAMe) for depression (DelleChiaie et al., 2002), melatonin for sleep disorders (Zhdanova & Friedman et al., 2008), inositol for depression, panic and obsessive compulsive disorder (Belmaker & Levine , 2008), and dietary changes for depression (Freeman, 2010). These treatments, integrated with conventional psychiatry, have been offered since three years to psychiatric outpatients.

Alternative medicine like homeopathy, reiki or healing are not being offered. However patients can be referred to these treatments under strict conditions, which are explained above. All treatments are evaluated by routine outcome measurement (ROM). In addition, we study the outcome of innovative treatments with individual outcome measurements (IOM) such as N-of-1 design, single-subject experimental design and time-series analysis. ROM consists of six questionnaires: psychopathology, quality of life, resiliency, costs, satisfaction and one self-report personalized outcome indicator, chosen by the patient. Patients fill out these forms before treatment starts, every half year, at the end of treatment, and half a year after their discharge. Patients with IOM fill out diaries concerning items that are most relevant to their treatment and symptoms, to assess subjective improvement on core symptoms and complaints.

Conclusion

Because of the increasing demand of patients for alternative medicine and integrative treatments and because of social, political, scientific and ethical reasons, and inspired by the CAHCIM, Lentis has founded a CIP. Here it offers selected complementary treatments alongside conventional ones under strict conditions. By doing so, the CIP responds to a call from the Word Health Organization and European Parliament, even though the Dutch government still hasn't made policy on this subject. Because of the controversy surrounding CAM, because of the lack of clear information and because we do not only need an open attitude but also a critical one, the CIP has formulated the CAM protocol. It believes that in this way CAM can be offered in a safe and effective way within conventional treatment centers. It hopes in this way to better serve and respect the individual needs and preferences of the diversity of patients who need mental healthcare in our Dutch multicultural society. It believes the protocol also protects against quackery, abuse and false hope.

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Part III: Effectiveness

Chapter 4

Bipolar disorder and complementary medicine: current evidence, safety issues, and clinical considerations

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Abstract

Background:
Bipolar Disorder (BD) is a debilitating syndrome that is often undiagnosed and under-treated. Population surveys show that persons with BD often self-medicate with complementary and alternative medicine (CAM) or integrative therapies in spite of limited research evidence supporting their use. To date no review has focused specifically on non-conventional treatments of BD.

Objectives:
To present a comprehensive review of non-conventional (complementary and integrative) interventions examined in clinical trials on BD, and to offer provisional guidelines for the judicious integrative use of CAM in the management of BD.

Methods:
PubMed, CINAHL, Web of Science and Cochrane Library databases were searched for human clinical trials in English during mid-2010 using Bipolar Disorder and CAM therapy and CAM medicine search terms. Effect sizes (Cohen's d) were also calculated where data were available.

Results:
Several positive high-quality studies on nutrients in combination with conventional mood stabilizers and antipsychotic medications in BD depression were identified, while branched-chain amino acids and magnesium were effective (small studies) in attenuating mania in BD. In the treatment of bipolar depression evidence was mixed regarding omega-3, while isolated studies provide provisional support for a multi-nutrient formula, n-acetylcysteine, and L-tryptophan. In one study acupuncture was found to have favorable, but non-significant effects on mania and depression outcomes.

Conclusions:
Current evidence supports the integrative treatment of BD using combinations of mood stabilizers and select nutrients. Other CAM or integrative modalities used to treat BD have not been adequately explored to date; however, some early findings are promising. Select CAM and integrative interventions add to established conventional treatment of BD and may be considered when formulating a treatment plan. It is hoped that the safety issues and clinical considerations addressed in this article may encourage the practice of safety-conscious and evidence-based integrative treatment of BD.

Introduction

Bipolar disorder (BD) is a debilitating heritable mental illness that has profound personal and socioeconomic effects. Emerging research findings reviewed in this paper suggest that non-conventional therapies may have a potentially significant role in improving quality of life, reducing side-effects, improving adherence with conventional medications, and reducing the severity of bipolar symptoms. Complementary and Alternative Medicine (CAM) consists of therapies such as acupuncture or naturopathy, and medicinal interventions such as herbal medicines or nutrients (Sarris & Wardle, 2010). CAM is commonly used by people diagnosed with mood disorders with up to 50% of psychiatric outpatients using one or more CAM therapies in a given year (Knaudt et al., 1999; Hoenders et al., 2006). Studies reveal especially high CAM use rates in women, the highly educated, the elderly, and those with chronic diseases (Keaton et al., 2009; Kessler et al., 2001; Wu et al., 2007). Aside from specific CAM interventions used in conjunction with pharmacotherapies (reviewed in this paper), according to users, CAM may provide general beneficial effects on physical and mental health and quality of life (Sirois, 2008). Furthermore, research has shown that administration of CAM within an holistic model can be beneficial for mental health (Cooley et al., 2009). Thus, adjuvant use of CAM within an integrated whole-person framework (combined with pharmacological and psychosocial interventions) holds the potential to reduce the severity of bipolar symptoms and risk of relapse.

Despite this, few studies have been done on non-conventional treatments of BD. Other than a review by Andreescu and colleagues (Andreescu et al., 2008), there is a paucity of peer-reviewed publications reporting clinical trial outcomes and safety issues associated with non-conventional treatments of BD. While their article is significant for providing the first review in this area, its focus is primarily on unipolar depression and it does not review nutritional interventions in detail, many of which are effective adjunctive interventions when combined with conventional pharmacotherapies (Sarris et al., 2009). The Andreescu et al. review is also limited by excluding studies published over 10 years ago. In the present paper we critically review evidence for CAM and integrative treatments of bipolar depression, mania and hypomania, and make recommendations for provisional clinical guidelines.

Methods

PubMed, CINAHL, Web of Science and Cochrane Library databases were searched during mid 2010 firstly for research in the overarching area of bipolar disorder; then for human clinical trials using the terms “Bipolar Disorder”, “Bipolar Depression”, “Bipolar Mania”, “Mania”, “Hypomania”, “Cyclothymia” together with terms for CAM therapies and products (e.g. herbal and nutritional medicine), and dietary and lifestyle factors. A forward search of identified papers was subsequently performed using Web of Science cited reference search. Reasons for exclusion included: a higher level of evidence being available or inadequate methodological rigor. Included clinical trials were open or controlled human studies that recruited people diagnosed with BD, examined CAM as a monotherapy or as an adjuvant with a conventional medication, and measured outcomes using established psychiatric rating scales. The term “significant” was used in studies with p values of <0.05. Effect sizes were calculated in all RCTs where data were available. From the results of the clinical

trials we calculated an effect size as Cohen's *d* (Cohen, 1988) by firstly subtracting the differences between the intervention and placebo scores on the scale used, then dividing this by the pooled standard deviation at baseline (clinical effect: 0.2 = small, 0.5 medium, > 0.8 large). Studies involving exercise and psychological therapies were omitted from analysis as, for purposes of this review, they are considered mainstream interventions (however they are briefly discussed in the Clinical Considerations section). Results are grouped under omega-3 fatty acids, amino acids, vitamins and minerals, herbal medicines, and acupuncture.

Bipolar Disorder

Etiology

Bipolar disorder (BD) is a debilitating heritable mental illness that affects approximately 1-2% of adults in their lifetime. When milder subclinical presentations are included the prevalence rate increases to approximately 4% (Merikangas et al., 2007). First-degree relatives of bipolar individuals are significantly more likely to develop the disorder than the population at large and twins have a 70% risk of sharing the disorder (Gurling et al., 1995). Although not yet fully elucidated, BD symptoms are probably caused by dysregulation of serotonergic and dopaminergic pathways, and diminished activity in the hippocampus and pre-frontal cortex (Konradi et al., 2004; Miklowitz & Johnson, 2006). It has been suggested that abnormal activity in hypothalamic circuits involved in maintaining normal circadian rhythms manifest as the affective and behavioral symptoms of BD (Miklowitz & Johnson, 2006).

Diagnosis

According to current conventional Western psychiatric nosology, BD diagnosis is divided into Bipolar Disorder Type I (BD I) and Bipolar Disorder Type II (BD II: see table 1), and can be differentiated from unipolar depression (major depressive disorder: MDD) by the presence of manic or hypomanic (lesser) episodes (American Psychiatric Association, 2000). A manic episode is a complex symptom pattern that may encompass disparate affective, behavioral and cognitive symptoms, including pressured speech, racing thoughts, euphoric or irritable mood, agitation, inflated self-esteem, distractibility, excessive or inappropriate involvement in pleasurable activities, increased goal-directed activity, diminished need for sleep, and in severe cases, psychosis (American Psychiatric Association, 2000).

Table 1. Unipolar depression and bipolar depression: differential diagnoses*

Major Depressive Disorder	Bipolar Disorder I (mania)	Bipolar Disorder II (hypomania)
Two weeks or more of persistent low mood and/or anhedonia (loss of interest in pleasurable activities)	Episodes of mania or a mixed episode lasting 5 or more days. Often presents with cycling between mania and depression	Hypomanic episodes that do not meet criteria for full mania, in addition to cycling to one or more episodes of MDD
Low mood impairs work and/or social functioning, may require hospitalization for severe depression	Manic episodes impairs work and/or social functioning, and often requires hospitalization	Hypomanic episodes not as severe as BD I mania, and do not significantly impair work/social functioning
Changes in body weight, digestion, and sleep patterns	Manic phase (euphoric or irritable mood, grandiosity or psychosis, decreased need for sleep)	Hypomanic phase (euphoric or irritable mood, decreased sleep, increased talkativeness, goal planning and sexual focus)
Psychological changes (e.g. suicidal ideation, guilt, self-worthlessness, agitation)	Depressive phase can present with similar psychological and somatic changes to MDD	Depressive phase can present with similar psychological and somatic changes to MDD (more common in BD II than BD I)
Not due to bereavement, medical comorbidity, drugs or alcohol, or medication	Not due to medical comorbidity, drugs or alcohol, or medication	Not due to medical comorbidity, drugs or alcohol, or medication

* Adapted from DSM-IV TR (APA, 2000)

A history of depressive episodes is not required for a formal diagnosis of BD I according to the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV-TR) (APA, 2000). In contrast, BD II can be diagnosed only in cases when at least one hypomanic episode and at least one depressive episode have been documented. In both disorders moderate or severe depressive episodes typically alternate with manic symptoms, however in “mixed mania” symptoms of mania and depressed mood overlap. Another variant called rapid cycling is diagnosed when at least four complete cycles of depressed mood and mania occur during any 12-month period. A mild variant of BD, cyclothymic disorder, is diagnosed when several hypomanic and depressive episodes take place over a two-year period in the absence of severe manic, mixed or depressive episodes (APA, 2000). The emerging concept of a “mood spectrum” hypothesis suggests that patterns of depressive and manic symptoms occur along a continuum, and that “mood disorders” do not exist as discrete diagnostic entities (Benazzi, 2007; Cassano et al., 2002). Evidence supports that unipolar depression and bipolar II depression occur across a spectrum, with 30% of patients diagnosed with major depressive disorder (MDD) experiencing various bipolar symptoms (e.g. agitation, racing thoughts, decreased sleep) (Benazzi, 2007). While BD I presents as a distinct psychiatric disorder that fulfills specific diagnostic criteria, BD II and cyclothymic disorder are more variable in presentation.

It is estimated that two thirds of individuals diagnosed with BD experience moderate or severe symptoms in any given year (Suppes et al., 2005). Bipolar patients experience depressive symptoms three times more often than mania, and five times more often than rapid cycling or mixed episodes (Judd et al., 2002). A diagnosis of BD is one of the highest risk factors for suicide (Pompili et al., 2009). BD usually presents in a rhythmic manner, oscillating between episodes of mania and depression, with several risk factors and triggers contributing to the rate of relapse and failed response to treatment (see figure 1).

Conventional treatment

Conventional pharmacotherapies are an important and often necessary treatment of both the depressive and manic phases of BD. First-line treatments of BD include mood stabilizers (e.g. lithium carbonate, carbamazepine, and valproate), antidepressants, antipsychotics and sedative-hypnotics (Miklowitz & Johnson, 2006; Suppes et al., 2005). Antipsychotics are used to treat agitation and psychosis, which occur frequently in acute mania, and select antipsychotics have been found to be effective mood stabilizers. Sedative-hypnotics are sometimes prescribed for the severe insomnia that accompanies mania, as well as for daytime management of agitation and anxiety (Cousin & Young, 2007).

Side effects often occur with these medications, having a mixed record of success due to their limited efficacy and high rates of treatment discontinuation (Pompili et al., 2009). Fewer than half of patients who take a conventional mood stabilizer or other psychotropic medications following an initial manic episode report sustained control of their symptoms (Culver et al., 2007). As many as one half of all bipolar patients who take mood stabilizers do not experience good control of their symptoms or refuse to take medications, and approximately 50% discontinue their medications because of serious adverse effects including tremor, weight gain, thyroid dysfunction elevated liver enzymes, and many others (Fleck et al., 2005). People diagnosed with bipolar disorders should be maintained on a consistent long-term pharmacotherapeutic regimen to reduce the rate of re-hospitalization and increase chances of full remission (Perlick et al., 1999). In patients diagnosed with BD, stressors, seasonal change, reduced sleep and stimulants or recreational drug use may provoke an episode of hypomania (although sometimes the trigger may have no apparent cause (Miklowitz & Johnson, 2006). Regular exercise, good nutrition, a strong social support network, and a predictable low-stress environment help reduce relapse risk (Suppes et al., 2005; Benjamin, 2007; Miklowitz & Scott, 2009; Lakhan & Vieira, 2008).

Psychotherapy and psychosocial interventions in stable bipolar patients may potentially reduce relapse risk by providing psychological support, enhancing medication adherence, and helping patients address warning signs of recurring depressive or manic episodes before more serious symptoms emerge (Miklowitz & Scott, 2009). Relapse prevention usually involves use of “lifecharts” and an effective stress management plan. An example is the novel BD relapse prevention program (called MAPS), which has evidence in reducing relapse of mania and BD depression. The Australian developed MAPS program was studied in a clinical trial involving 84 participants with BD, and was conducted over 12 weeks (Castle et al., 2010). Participants were randomized to either the program involving education on BD (symptoms, monitoring triggers, and symptom management skills), in addition to goal setting, medication management, and relapse prevention planning; or a control group consisting of treatment as usual plus telephone calls. Results revealed that

participants who received the group-based intervention were significantly (p=0.04) less likely to have a relapse of mania or depression, and spent less time unwell.

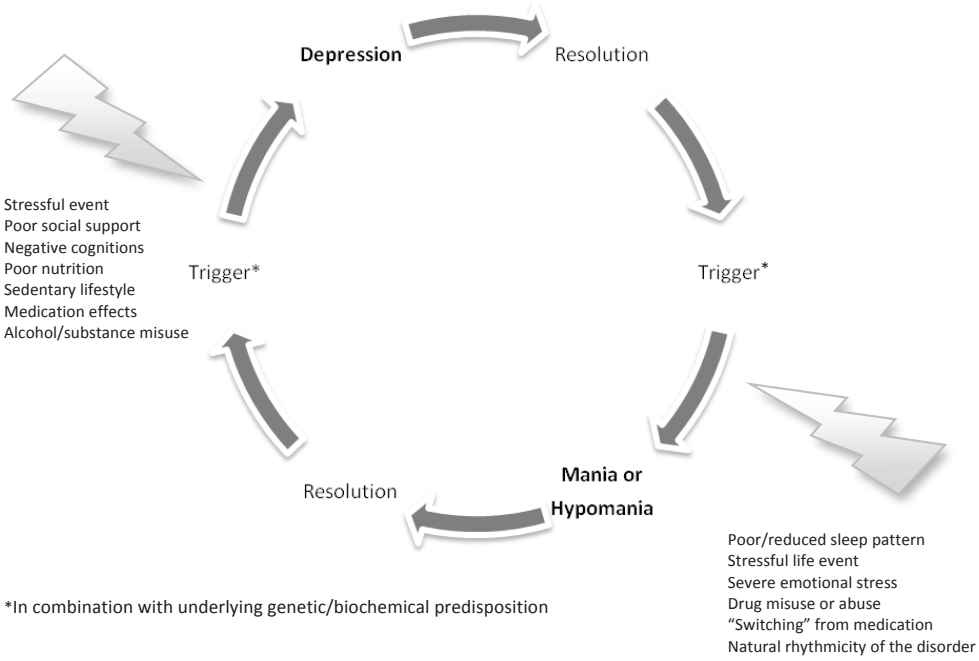
Clinical Considerations

When considering recommending CAM or integrative treatments for BD (in concert with traditional psychotropic medications), it is essential to first carefully examine the evidence for both conventional and nonconventional therapies. In this paper we propose an integrative model that incorporates select CAM therapies in combination with conventional psychotropic medications. We recommend against the use of CAM or integrative therapies whose safety and efficacy is not supported by strong research evidence. This caveat applies even more so to the management of severe symptoms of bipolar depression or mania. Mental healthcare providers should always recommend those therapies supported by the highest level of evidence (Hoenders et al., 2010), and in spite of their limited efficacy and unresolved safety issues, mood stabilizers and select antipsychotics should always be regarded as the first-line treatments of the severe form of bipolar illness (i.e. BD I) (Nivoli, 2011).

Prior to diagnosing bipolar mood disorder a period of mania or hypomania lasting several days must be established in the context of a broader pattern of impairment that may include decreased need for sleep, flight of ideas, grandiosity, excessive or unrealistic spending, or hyper-sexual activity. A life chart can help establish a pattern of cyclic mood changes and associated impairments in social activity, academic performance and work. An important initial consideration when prescribing CAM in persons diagnosed with BD, depends upon which phase are they in (i.e. mania, depression, or remission). A careful history is needed to establish a persisting pattern of mood changes fluctuating between depression and mania or hypomania. Conventional laboratory tests and functional brain imaging studies can be used to rule out medical disorders that can mimic symptoms of depressed mood or mania including, for example, thyroid disease, strokes (especially in the right frontal area of the brain), multiple sclerosis, seizure, or other neurologic disorders (Kumar & Clark, 2002). Irritability or euphoria alternating with periods of depressed mood is sometimes associated with chronic abuse of stimulants, marijuana or other drugs. Thus, screening for substance abuse should be done before a formal diagnosis of BD is made (Swann, 2010).

In persons in the manic phase of BD type I, hospitalization is usually required, at which time adjunctive use of magnesium, choline, branched-chain amino acids, or L-tryptophan may be appropriate adjuvants in combination with mood stabilizers or antipsychotics. When prominent symptoms of anxiety or agitation are present, effective integrative strategies should prioritize treatment of those symptoms. In addition to sedating pharmacotherapies, the use of botanical or nutritional anxiolytics (such as *Piper methysticum*, magnesium, L-theanine, or L-tryptophan) may be beneficial (Lakhan & Vieira, 2008; Sarris et al., 2009a).

Figure 1. Basic cycle of Bipolar Disorder



For patients in the depressed phase the treatment approach is different. It is important to note that depressed symptoms are often misdiagnosed as major depressive disorder when in fact they are the depressive phase of BD. Thus careful screening is essential in all patients presenting with depressed mood including assessment of the length, frequency and severity of depressive episodes, identification of precipitating stressors, and evaluation of suicidality. Assessment should include a urine drug and alcohol screen and a review of their sleep pattern and level of stress. CAM therapies for bipolar depressed patients include select nutrients (S-adenosyl methionine, L-tryptophan, omega-3 fatty acids (mixed evidence) (Sarris et al., 2009b), botanicals (*Hypericum perforatum*, *Rhodiola rosea*, *Crocus sativus*) (Sarris, 2007), select acupuncture protocols (Wang et al., 2008), regular exercise (Barbour et al., 2007), good nutrition (Jacka et al., 2010), and psychological interventions (Cuijpers et al., 2008).

All bipolar patients being treated for depressed mood are at risk of "switching" to mania and should be closely monitored. A personalized relapse prevention program including patient and family education about early warning signs of recurring depressed mood or mania, and a well thought-out plan is an essential component of care for all bipolar patients. Important safety considerations are raised

by the use of CAM therapies that have efficacy in major depressive disorder but that have not been established as safe in bipolar depressed mood and found to not increase the risk of switching to mania. Case reports implicate select natural products used to treat major depressive disorder, such as *Hypericum perforatum* (Moses & Mallinger, 2000), *Ephedra sinica* (Boerth & Caley, 2003), or S-adenosyl methionine (Papakostas et al., 2003) as potentially inducing mania. Several case reports of serotonin syndrome have been associated with the combined use of *Hypericum perforatum* and SSRIs (Sarris et al., 2009c). In addition it should be noted that extracts high in the active constituent hyperforin may induce cytochrome P450 3A4 enzymes and the P-glycoprotein drug efflux pump resulting in reduced serum levels of many drugs including oral contraceptives, anticoagulants, protease inhibitors, and anti-seizure medications (Whitten et al., 2006).

A significant percentage of individuals diagnosed with BD use non-pharmacological modalities adjunctively with prescription medications. However, with the exception of the nutrient interventions reviewed in this article, there is relatively little evidence for the safety and efficacy of the majority of such integrative treatments. Finally, while exercise should be encouraged in all BD patients because of established benefits to general health and mood, those patients taking lithium should consult their physician before starting a rigorous exercise program. Lithium is excreted with perspiration and strenuous physical activity that involves significant sweating may lower lithium levels in the blood; at least one such case has been reported (Waring, 2006).

Clinical Evidence of CAM in Bipolar Disorder

Omega-3 fatty acids

Countries where there is high fish consumption have relatively lower prevalence rates of BD (Hibbeln, 1998). Several clinical trials have studied omega-3 fatty acids including fish oil and purified eicosapentaenoicacid (EPA) and docosahexaenoicacid (DHA), as a mono-therapy or as an adjuvant intervention in BD. An early RCT involving 44 participants using a combination of EPA and DHA (9.6 g/day) with conventional drug therapies revealed positive results on measures of depressed mood in terms of response and remission rates on The Hamilton Depression Rating Scale (HAMD) (d = 1.40) (Stoll et al., 1999; Hamilton, 1960). No significant effect on mania outcomes occurred. A 26-week open-label adjuvant study by Osher and colleagues (2005) in 12 participants with BD I, revealed that eight out of ten participants with one month of EPA were responders on HAMD (d=1.23). It should be noted that while these open-label studies are positive, confidence in these should be tempered as they are not controlled. A 12-week, 3-arm controlled study involving 75 participants using 1 g or 2 g of EPA combined with any class of psychotropic medication revealed a small but significantly greater reduction on the HAMD from either dose, compared with placebo (1 g: d = 0.90, 2 g: d = 0.50) (Frangou et al., 2006). However, no significant effect for mania was achieved on The Young Mania Rating Scale (YMRS) (Young et al., 1978). A later RCT conducted by the research group (Frangou et al., 2007) using 2 g of EPA versus placebo over 12 weeks in 14 female participants with BD I revealed positive, but not statistically significant effects on depression outcomes. A novel 4-week adjuvant study involving 21 participants with BD I by Hirashima and colleagues (2004), revealed no significant differences between EPA 5 g plus DHA 3 g and a non-treatment control. Interestingly however,

brain resonance imaging showed that T2 levels were reduced in the treatment group, denoting increased neuronal cell membrane fluidity.

A larger study (*n* = 121) using 6 g of EPA in combination with at least one mood stabilizer in patients diagnosed with rapidly cycling bipolar disorder also found no benefit over placebo on reducing mania on YMRS (Keck et al., 2006). Further, a small RCT with 15 participants, using 4.4 g of EPA and 6.6 g of DHA/day adjuvantly with 20 mg/kg/day of valproate also revealed no benefit over placebo for reducing mania (Chiu et al., 2005). Two open-label studies have been published on omega-3s in pediatric bipolar disorder: an adjuvancy study and a monotherapy study. Clayton et al. (2009) conducted a 6-week study involving 18 adolescents with BD I or II using omega-3 (DHA 1560 mg and EPA 360 mg per day) and found significantly reduced clinician-rated mania and depression from baseline. A study by Wozniak and colleagues (2007) also revealed significant reductions on YMRS (*d*= 0.90) and BPRS (*d*= 0.83) compared to baseline using 1290 mg-4300mg of fish oil in 20 adolescents who met DSM-IV-TR criteria for BP and had a YMRS score of >15.

Current evidence weakly supports use of omega-3 preparations in combination with conventional psychotropic medications in the depressive phase of BD; however, omega-3s probably have little or no clinical effect in attenuating mania. Although considered a very safe intervention, rare cases of increased bleeding times, but not increased risk of bleeding, have been reported in patients taking aspirin or anti-coagulants together with omega-3s (Sarris et al., 2009b).

Amino acids

Bipolar patients may be genetically susceptible to mood swings when certain amino acids or other micronutrients are lacking in the diet (Kaplan et al., 2007). Findings of two small RCTs suggest that certain branched-chain amino acids (BCAA) may rapidly improve acute mania by interfering with synthesis of norepinephrine and dopamine (Scarna et al., 2003). In one study 25 bipolar patients randomized to a blend of the branched-chain amino acids leucine, isoleucine and valine (60 g/day) versus placebo experienced significant reductions in the severity of mania within six hours (Scarna et al., 2003). Improvements in mania were sustained with repeated administration of the amino acid drink. N-acetylcysteine (NAC) is an amino acid with strong anti-oxidant properties that has been used to treat a range of inflammatory disorders (Dodd et al., 2008). In novel research, Berk and colleagues (2008) conducted a 24-week RCT using 1 g of NAC versus placebo in a sample of 75 participants stable on medication or therapy with DSM-IV-TR diagnosed BD I or BD II. Results revealed that NAC significantly reduced bipolar depression on the Montgomery Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) and the Bipolar Depression Rating Scale with strong effect sizes respectively of 1.04 and 0.83. No significant effect was found on mania outcomes, although it should be noted that YMRS mania levels were very low, thus significant changes were unlikely to occur.

Restricting or excluding L-tryptophan from the diet may increase the susceptibility of bipolar patients to depressive mood swings; however, research findings to date are highly inconsistent (Bell et al., 2005). L-tryptophan has demonstrated beneficial effects in reducing depressed mood in people with unipolar depression (Sarris et al., 2009b). A 1985 2-week study used 12 g of the amino acid in 24 participants with mania (Chouinard et al., 1985). In this two-phase trial, measures of mania were significantly reduced with L-tryptophan on Clinical Global

Inventory (*d*= 1.47) in the initial open phase, and continued but lessened during the controlled phase.

Vitamins and minerals

Magnesium may be an effective adjuvant therapy for treatment of acute mania or rapidly cycling BD. In a small open trial oral magnesium supplementation had comparable efficacy to lithium in rapid cycling bipolar patients (Chiounard et al., 1990). In a small case series intravenous magnesium sulfate used as an adjuvant with lithium, haloperidol and a benzodiazepine in bipolar patients with severe treatment-resistant mania resulted in significant improvement in global functioning and reduction in the severity of mania (Heiden et al., 1999). Many patients treated with intravenous magnesium sulfate remained stable on lower doses of conventional medications. An RCT used 375 mg of magnesium oxide versus glucose placebo over 16 weeks in 20 participants with prior DSM-IV diagnosed mania and > 6 months on a stable mood stabilizer (verapamil). Results revealed a significant reduction on mania compared to control at week 16 (Giannini et al., 2000).

Two clinical trials using inositol (12 g and 5-20 g) adjuvantly with maintenance doses of mood stabilizers have been conducted. Both RCTs (Chengappa et al., 2000; Evins et al., 2006) had small samples (*n*=24 and 26, respectively) and were conducted over six weeks. Results in both studies revealed no significant differences between inositol or placebo on depression or mania outcome scales. Clinical response however was noted in 12/21 participants taking inositol on pooled results of both studies on HAMD and MADRS.

Folic acid has been studied in one early trial as an adjuvant in BD patients stabilized on lithium. A 52-week RCT by Coppen and colleagues (1986) compared 200 mcg of folic acid versus placebo tablets in 102 participants taking lithium. Results revealed that the completers in the folic acid group (*n*=41) had significantly lower BDI scores than the control group, with a strong effect size of 1.07.

A proprietary 36-ingredient formula of vitamins and minerals may significantly reduce symptoms of mania, depressed mood and psychosis in bipolar patients when taken alone or used adjunctively with conventional mood stabilizers. Six out of eleven completers had clinical response with strong effect sizes (HAMD: 1.70, YMRS: 0.83). In one case series 11 bipolar patients who completed a 6-month protocol were able to reduce their conventional mood stabilizers by half while improving clinically (Kaplan et al., 2001). In another case series, 13 out of 19 bipolar patients who continued on the nutrient formula remained stable after discontinuing conventional mood stabilizers (Simmons, 2003). Some patients stopped taking the formula because of nausea and diarrhea and three patients resumed conventional mood stabilizers because of recurring manic symptoms. Researchers believe the formula works by correcting metabolic errors that result in bipolar-like symptoms in genetically predisposed individuals when certain micronutrients are deficient in the diet (Popper et al., 2001; Kaplan et al., 2001).

Choline is necessary for the biosynthesis of acetylcholine, and abnormal low brain levels of acetylcholine may contribute to some cases of mania (Leiva, 1990). Findings of a small open study suggest that phosphatidylcholine (15 gm to 30 gm/day) may reduce the severity of mania and depressed mood in bipolar patients (Stoll et al., 1996). It should be noted that two non-responders were also taking hypermetabolic doses of thyroid medication. Clinical improvement correlated with increased intensity of the basal ganglia choline signal as measured on proton

magnetic resonance imaging (MRI). The effect of choline on depressive symptoms was variable (Stoll et al., 1996).

Findings of a small open study suggest that patients diagnosed with BD who exhibit mania or depressed mood may respond to low doses (50 micrograms with each meal) of a natural lithium preparation (Fierro, 1988). Post-treatment serum lithium levels were undetectable in patients who responded to trace lithium supplementation.

Findings from animal research and a small open study suggest that bipolar patients who take potassium 20 mEq twice daily with their conventional lithium therapy experience fewer side effects, including tremor, compared to patients who take lithium alone (Tripuraneni, 1990). No changes in serum lithium levels were reported in patients taking potassium. Pending confirmation of these findings by a larger double-blind trial, potassium supplementation may provide a safe, cost-effective integrative approach for the management of bipolar patients who are unable to tolerate therapeutic doses of lithium due to tremor and other adverse effects (patients who have cardiac arrhythmias or are taking anti-arrhythmic medications should consult their physicians before considering taking a potassium supplementation).

Herbal medicines

Findings of a large 12-week placebo-controlled trial involving a sample of 58 BD patients suggest that a proprietary Chinese compound herbal formula consisting of at least 11 herbs may enhance the effect of conventional mood stabilizers for treatment of the depressive phase of BD (Zhang et al., 2005). Bipolar depressed (but not manic) patients randomized to the herbal formula plus carbamazepine experienced significantly greater reductions in the severity of depressed mood compared to matched patients receiving a mood stabilizer only. These findings were replicated in a subsequent study, which confirmed that bipolar depressed patients treated with the herbal formula improved more than patients treated with a placebo, with a strong effect size (d=0.98) between treatments at week 12 (Zhang et al., 2007).

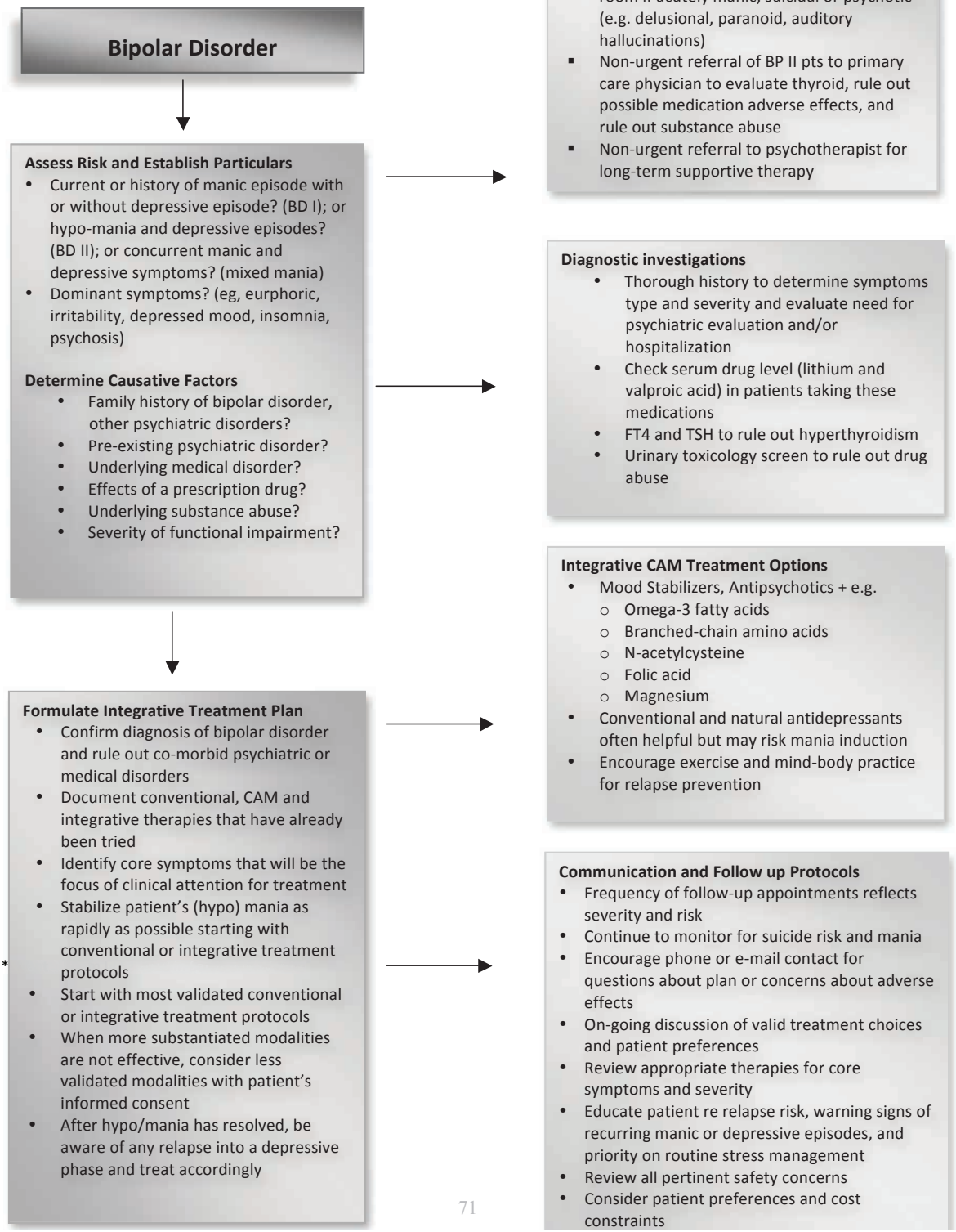
Table 2. Adjuvant nutrient interventions in Bipolar Disorder

Intervention	BD (depression)	BD (mania)	Level of evidence	
			Depression	Mania
Omega-3	✓		**A**	**D**
N-acetylcysteine	✓		**B**	**C**
BCAA		✓	**NK**	**B**
Inositol	✓		**C**	**NK**
Choline	✓	✓	**C**	**C**
Folic acid	✓		**B**	**C**
Magnesium	✓	✓	**C**	**A**
Chelated minerals	✓		**B**	**C**

✓ = Potential use in bipolar mania or bipolar depression
NK= Not known
BCAA= Branched-chain amino acids
A= Several repeated clinical trials (with some positive results)
B= Unreplicated positive study
C= Small study, or inconclusive results
D= Several clinical trials reveal mainly negative results

Early studies suggested that the Ayurvedic plant medicine *Rauwolfia serpentina* and an alkaloid derivative, reserpine, was an effective treatment of BD by augmenting the anti-manic efficacy of lithium without risk of toxic interactions (Bacher & Lewis, 1979; Berlant, 1986). However, therapeutic use of this plant in various Western countries is restricted due to the presence of the alkaloid reserpine, which has potent effects on blood pressure and the CNS. A previous review published in *JACM* (Sarris et al., 2009d) of placebo-controlled trials comparing *Hypericum perforatum* to placebo or conventional antidepressants concluded that the herbal medicine might be beneficial for mild to moderate depressive symptoms. Although this herb may potentially be beneficial in the depressive phase of BD, no studies on this have been conducted to date. Several case reports of mania induction with St. John's wort (Moses & Mallinger, 2000; Fahmi et al., 2002) and potential serious interactions with many drugs (Izzo, 2004) have resulted in limited use of this herbal for the treatment of BD.

Figure 2. Treatment decision tree



Acupuncture

The art of acupuncture has been used for millennia in Eastern cultures for treating a range of illnesses including mental disorders. Research in the area of unipolar depression has revealed mixed but mainly positive results. A two-part clinical trial has been conducted examining the safety, effectiveness, and acceptability of adjunctive acupuncture in the treatment of hypomania and depression associated with bipolar disorder (Dennehy et al., 2009). In the first study 20 patients experiencing symptoms of mood elevation were given targeted acupuncture (points specific to symptoms) versus 'sham' acupuncture (non-acupoint needling) over 12 weeks, while for 26 patients experiencing symptoms of depression targeted acupuncture was compared to (off the meridian) acupuncture for nonpsychiatric health concerns over 8 weeks. While the results revealed that acupuncture treatment reduced symptoms (mood elevation in Study I, depression in Study II), a non-significant difference occurred between treatments, with all patients experiencing improvement over the course of study.

Conclusions

Bipolar disorder may potentially be effectively managed using an integrative approach. While use of select nutrients combined with medication in BD is supported by strong evidence, to date herbal medicines have not been adequately evaluated. Surprisingly, other CAM modalities potentially used by bipolar patients are currently not supported by clinical trial evidence. Interventions such as manual therapies (e.g. acupuncture, massage), dietary modification, meditation, or mind-body practices (e.g. tai chi or yoga) are supported by some evidence in psychiatric disorders; however, their beneficial effects in patients diagnosed with BD are currently unknown or inconclusive. However, while these interventions may not be 'directly effective' in the treatment of BD, they have general beneficial effects on physical and mental health and quality of life, are probably associated with reduced stress and improved functioning in general, and thus may potentially reduce the severity of bipolar symptoms and risk of relapse. We hope this article illuminates the current evidence of CAM for the integrative management of BD, and may encourage further discussion and research in this area.

Conflict of Interest

No conflicts of interest noted.

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Chapter 5

Natural medicines in schizophrenia: a systematic review

H.J. Rogier Hoenders, Agna A. Bartels-Velthuis, Nina K. Vollbehr, Richard Bruggeman, H. (Rikus) Knegtering, Joop T.V.M. de Jong

(in preparation)

Abstract

Introduction:
Despite progress in treatment options in the last century, the results of pharmacological treatment of schizophrenia are frequently unsatisfactory. Therefore some patients use natural medicines, although it is unclear whether natural medicines are effective and safe. We assessed the evidence for natural medicines with and without antipsychotics in treating symptoms or reducing side effects of antipsychotics in schizophrenia.

Method:
A systematic review until April 2013. Only RCTs with a Jadad score of 3 or higher were included.

Results:
105 RCTs were identified. Evidence was found for glycine, sarcosine, NAC, some Chinese and ayurvedic herbs, ginkgo biloba, estradiol and vitamin B6 for improving symptoms of schizophrenia when added to antipsychotics (glycine not when added to clozapine). Inconclusive or no evidence was found for omega-3 fatty acids, D-serine, D-alanine, D-cycloserine, B vitamins, vitamin C, dehydroepiandrosteron (DHEA), pregnenolone (PREG), inositol, gamma-hydroxybutyrate (GHB) and des-tyr-gamma-endorphin when added to antipsychotics. Omega-3 fatty acids without antipsychotics might be beneficial in the prevention of schizophrenia. In one large study, ayurvedic herbs seemed effective without antipsychotics. Other agents without antipsychotics (vitamin B3, vitamin C, sarcosine, glycine, Protilerin) were not effective or had only been tested in single or small trials. Ginkgo and vitamin B6 seemed to be effective in reducing side effects of antipsychotics (tardive dyskinesia and akathisia). The evidence for reducing side effects of antipsychotics by omega-3 fatty acids, melatonin and DHEA appeared to be inconclusive. All natural agents produced only mild or no side effects.

Conclusion:
High-quality research on natural medicines for schizophrenia is scarce. However, there is emerging evidence for improved outcome for glycine, sarcosine, NAC, some Chinese and Ayurvedic herbs, ginkgo biloba, estradiol and vitamin B6, all with only mild or no side effects. Most study samples are small, the study periods are generally short, the studies only cover a modest part of the world's population and most results need replication.

Introduction

Despite much progress in treatment options in the last century, the pharmacological treatment of schizophrenia and other psychotic disorders is often unsatisfactory as expressed in long-lasting positive, negative, cognitive and affective symptoms and problems in social and occupational functioning. Psychotic symptoms are often only partially resolved (Rummel-Kluge, 2010), and especially cognitive and negative symptoms seem refractory to present pharmacological options (Buckley & Stahl, 2007). Newer (second-generation) antipsychotics are in general equally effective as first-generation antipsychotics in treating positive symptoms, the promise of greater efficacy against negative symptoms of newer antipsychotics has not been fulfilled (Leucht et al., 2012). Many patients continue to suffer persistent symptoms and symptom relapses during treatment with antipsychotics, particularly when they fail to adhere to prescribed medications (Van Os & Kapur, 2009). Besides, patients often experience undesired treatment (side) effects, most commonly weight gain, sexual dysfunction, glycaemic and lipid dysfunction, extra-pyramidal symptoms (EPS) and sedation (Stahl, 2008).

As a result, many patients with psychotic disorders use non-conventional medicines or treatments in the hope of decreasing undesired treatment effects or in search for a more successful recovery. Nonconventional medicine includes lifestyle changes, and complementary and alternative medicine (CAM) (Hoenders et al., 2013). Complementary medicine comprises 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 various reasons - cultural or practical - do not form part of biomedicine (Hoenders et al., 2011). Alternative medicine comprises forms of diagnostics, treatments and prevention strategies that make use of other than the basic concepts of biomedicine. Sofar, there is little proof for the efficacy of the latter treatments and / or there is considerable controversy about the scientific validation (Lake, 2007). Part of complementary medicine refers to natural medicine: using only agents that are produced by a living organism (plant, tree, seed, vegetable, fruit, animal, human), instead of non-natural (i.e. chemical) agents: agents that cannot be found in nature and that can only be obtained from laboratory experiments (Porter, 1998). Some patients prefer natural medicines as they assume that natural is better than chemical and causes fewer side effects. This is obviously not (always) true as the natural environment contains agents that can be toxic to humans and it is the molecular structure and dosage of a substance rather than its source that determines its effect on human health (Topliss et al., 2002). Besides, herbal medicines can cause undesired effects including interactions with prescription medication (Ernst, 2003a).

Hazra et al. (2010) reported a lifetime and one-year prevalence rate of CAM use of 88% and 68% respectively in Canadian psychotic outpatients. A major difficulty these patients encounter is the heterogeneity in treatment options with CAM, ranging from possibly interesting agents to useless, or even dangerous, ones (Ernst, 2003a). For instance, the concomitant use of antipsychotics and Chinese herbs has been found to induce significantly improved clinical outcomes compared to only antipsychotics. However, a small but significant number of patients treated concomitantly with Chinese herbs have a greater risk of developing worse outcomes (Zhang, 2011).

In recent years the preferences and views of patients have received more attention in making choices in treatment (e.g. shared decision making (Elwyn et al.,

2000) and 'patient-centered care' (Gill, 2013)). The introduction of patient's choice in deciding which antipsychotic to choose has been proposed (Morrison et al., 2012). However, it is difficult for both patients and doctors to make informed decisions, in the absence of reliable information on the emerging evidence for CAM or natural medicine. Considering its high usage in psychotic patients, there is an urgent need for objective information.

The aim of this paper is to provide an overview of evidence for the efficacy and safety of most used and most studied natural medicines for symptoms of schizophrenia or other psychotics disorders, or for side effects of antipsychotics. As the majority of psychosis is related to schizophrenia, in this paper we will use 'schizophrenia' to refer to all forms of psychosis.

Method

Literature search and study selection

Studies were identified by a literature search in Medline, PsycINFO, CINAHL and Cochrane, through April 2013. The search terms (MeSH Thesaurus and free search terms) used were: schizophrenia, psychosis, psychoses, psychotic (disorder), schizophreniform AND (R)CT, review AND complementary medicines, herbs, vitamins, supplements (search terms, in alphabetical order: ascorbic acid, Ayurveda, brahmyadiyoga, branched-chain amino acids [BCAA], Chinese herbs, D-cycloserine, D-serine, dehydroepiandrosterone [DHEA], DHA, EPA, estradiol, fatty acid, fish oil, folic acid, ginkgo biloba, glycine, manganese, methylfolate, N-acetylcysteine, N-methylglycine, niacine, omega-3, rauwolfia serpentina, sarcosine, sarsasapogenin, selenium, TCM, vitamin B complex, vitamin B3, vitamin C, vitamin D, vitamin E, zinc). We used search terms for the most used and most researched agents. A total of 1204 hits (abstracts) were retrieved after systematic deduplication (table 1).

Table 1. Sources of literature retrieval and included number of studies before and after duplicate findings were removed.

Database	Trials	Reviews	Total
Medline	432	541	973
Cinahl	55	16	71
PsycINFO	200	97	297
Cochrane	166	15	181
Total	853	669	1522
Total deduplicated			1204

Next, abstracts about the following topics were included: (i) effects of natural medicines on schizophrenia and psychotic symptoms, (ii) effects of natural medicines for side effects of antipsychotics, (iii) effects of natural medicines in the prevention of the development of psychotic disorders. Exclusion criteria were: (i) non-randomized (controlled) trials, (ii) studies that explore the effects of natural medicines (i.e. mechanism studies), (iii) animal studies, (iv) other disorders or no disorder, (v) conference abstracts, (vi) book chapters, (vii) clinical trial registrations, (viii) comments, addenda, corrigenda and letters, (ix) papers in non-English languages (e.g. Chinese, Japanese, Hebrew, German and Spanish), and (x) duplicate hits which had not been removed systematically. Second, two co-authors (HJRH and AABV)

independently indicated whether papers - based on the abstracts - should (possibly) be included or not. Consultation followed about dubious cases and in case of discordance. Thereupon, 386 studies remained of which the full papers were retrieved and studied. Of these, another 151 were excluded (81 were not a RCT and 70 for different reasons). A flow chart of the study selection is presented in Fig. 1. We found 122 reviews and checked whether we had included the RCTs in their reference lists that matched our inclusion criteria. We added 8 RCTs with a Jadad score of 3 or higher that were not found through our original search. 16 RCTs were excluded because of a Jadad score less than 3. Finally, 105 randomized controlled trials were included. The reviews are not shown in our results table, but their conclusions will be contrasted to our results in the discussion section.

Risk of bias assessment

Two assessors (co-authors AABV and NKV) independently rated the methodological quality of the RCTs found in our original search and those found by checking the reference lists of the reviews. We used the Jadad scale for reporting randomized controlled trials (Jadad et al., 1996). This scale consists of three questions about the methodological quality: whether the study is described as (i) randomized, (ii) double-blind, and (iii) whether (non-) completers are adequately described. The first two questions are each followed by two sub-questions, for which either one point extra may be gained or lost, the total score of the risk of bias assessment thus amounting to a maximum of 5 points (see table 2). RCTs scoring 3 points or higher were included in the study, under the condition that the three main questions were assigned 1 point each. Interrater agreement on the Jadad scores between the assessors before consensus discussion amounted to 0.80. Besides, HJRH independently rated a random selection of 17 papers (15%) from the selected RCTs. Interrater agreement of all three authors was 0.71. Any disagreements between the assessors on the Jadad scoring were resolved through consensus discussion between these three authors. The 105 RCTs exceeding the consensus Jadad score of 3 were included for the current review and are presented in table 3. Based on the hypothesized mechanism, they were divided in six groups: omega-3 fatty acids, B vitamins, eastern herbs, glutamate agonists, antioxidants, and 'other substances'.

For each of the 105 studies that fulfilled the previously mentioned selection criteria the following assessments were made: which natural agent was used; was this combined with antipsychotics, and if yes, which antipsychotics and what dosage; the effect of the natural agent on negative, positive, cognitive, depressive and general symptoms and on side effects of antipsychotics; possible adverse side effects of the natural agent; number of participants in the study; control group characteristics; number of drop-outs; study duration; Jadad score (results are shown in table 3).

Figure 1: flow chart

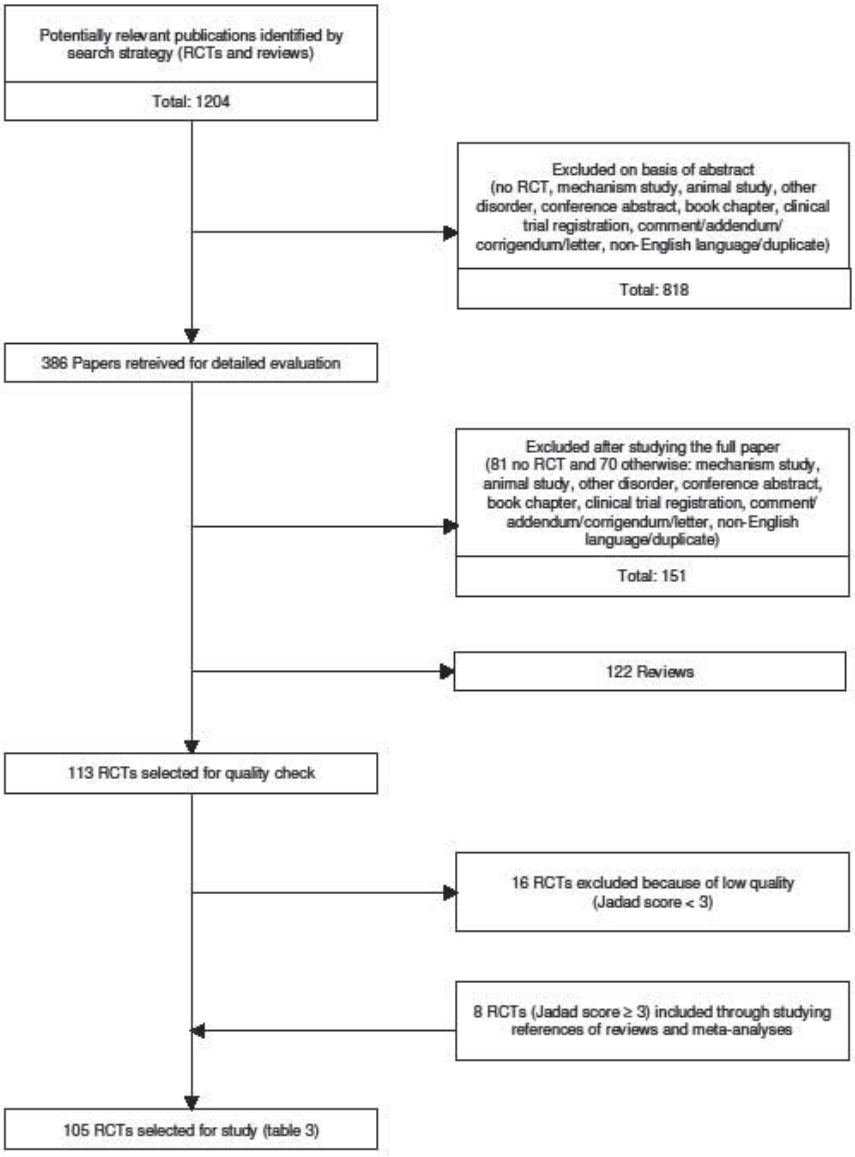

Table 2. Jadad scale for assessing the quality of randomized controlled trials as expressed by a score from 0 (low quality) to 5 (high quality) (Jadad et al., 1996).

Item	Description	Scoring
Randomization	Was the study described as randomized (this includes the use of words such as randomly, random, and randomization)?	1 point
	Was the method to generate the sequence of randomization described and appropriate (table of random numbers, computer generated, etc)?	+ 1 point
	Was the method to generate the sequence of randomization described inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)?	- 1 point
Blinding	Was the study described as double blind?	1 point
	Was the method of double blinding described and was it appropriate (identical placebo, active placebo, dummy, etc.)?	+ 1 point
	Was the study described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy)?	- 1 point
An account of all patients	Was there a description of withdrawals and dropouts?	1 point

Results

A total of 105 RCTs on the effectiveness of natural medicines for schizophrenia that matched our inclusion criteria were identified (see Fig. 1). Based on the hypothesized mechanism, these RCTs were divided into six groups (Table 3).

(i) Omega-3 fatty acids

Polyunsaturated fatty acids (PUFA) are essential for brain functioning (Tsalamanios et al., 2006). They have multiple important biological roles, including membrane functioning, neurotransmission, signal transduction, and eicosanoid synthesis. A growing body of research suggests that PUFA level reduction is related to schizophrenia (Berger et al., 2006). Concordant with these findings, omega-3 PUFA may have positive effects in the treatment and prevention of schizophrenia (Peet, 2008; Emsly et al., 2003; Freeman et al., 2006; Amminger et al., 2010).

Ten RCTs were included (table 3). In studies combining antipsychotics with omega-3 PUFA, one (out of seven) studies on negative symptoms in schizophrenia found some positive effect (in patients using clozapine), three (out of seven) found some positive effect on positive symptoms, one (out of three) on cognitive symptoms, none (out of three) on depressive symptoms, and five (out of nine) on general functioning. Two (out of two) studies on omega-3 PUFA without antipsychotics reported a decrease of positive symptoms, and one of these reported less use of antipsychotics in the second phase of the trial compared to the control group. Three (out of six) reported less side effects of antipsychotics (EPS and or dyskinesia). Two studies reported less use of antipsychotics in the omega-3 PUFA group. Some non-severe side effects of omega-3 PUFA were reported, such as mild gastrointestinal problems and increased bleeding time.

(ii) Glutamate

Besides dopamine, glutamate is thought to play a role in schizophrenia (Tsai & Lin, 2010). Based on the hypothesis that the glutamatergic system may be compromised

in schizophrenia, the use of N-methyl-D-aspartate (NMDA) receptor modulators may compensate for alterations in the glutamate system (Singh & Singh, 2011). Agents with co-agonistic properties to (glutaminergic) NMDA receptors are: glycine (full, endogenous agonist), D-serine (full, endogenous agonist), D-cycloserine (partial, exogenous agonist), D-alanine (partial, endogenous agonist) and sarcosine (sarcosine = methyl-glycine, acting as a reuptake inhibitor of glycine and source of glycine). The glycine transporter-1 (GlyT-1) plays a pivotal role in maintaining the concentration of glycine within synapses at a sub-saturating level. Sarcosine is a GlyT-1 inhibitor meaning that the presence of sarcosine results in increased glycine concentrations. Lower cerebral glycine levels are suggested to be found in patients with schizophrenia. The administration of sarcosine is therefore proposed to relief symptoms of schizophrenia when added to non-clozapine antipsychotics (Lane et al., 2006). Whereas the mechanisms of N-acetylcysteine (NAC) are only beginning to be understood, it is likely that NAC is exerting benefits beyond being a precursor to the antioxidant glutathione, also modulating glutamatergic, neurotropic and inflammatory pathways (Dean et al., 2011).

We included ten RCTs on glycine, six on D-serine, nine on D-cycloserine, one on D-alanine, five on sarcosine and two on NAC.

Glycine improved negative symptoms when combined with antipsychotics in six (out of seven) studies, but not when combined with clozapine (two studies). Positive symptoms improved in one study, worsened in another (with clozapine) and did not change in six (out of eight) studies; cognitive improvement was shown in four, and no change in two (out of six) studies; depressive symptoms diminished in five (out of five) studies; general improvement was shown in four (out of nine) studies. One (out of one) small study (N=8) on glycine suggested improvement of negative as well as positive, depressive and general symptoms when provided without concomitant antipsychotic drugs. No severe side effects of glycine were reported, except some mild gastrointestinal complaints.

D-serine was shown to improve positive, negative, cognitive and general symptoms in two (out of six) studies when added to antipsychotics. The three largest - most recent - studies with highest Jadad score did not show a significant effect of D-serine on any symptom. In five out of six studies D-serine did not improve side effects of antipsychotics. Insomnia, weight gain, palpitations and other side effects of D-serine were reported.

D-cycloserine showed an improvement of negative symptoms in three (out of eight) studies when added to antipsychotics; some improvement of positive symptoms in one and worsening in another study (out of seven); little or no effect on cognitive, depressive or general symptoms and no improvement of side effects of antipsychotics was shown. Five (out of five) studies found no improvement of side effects of antipsychotics. No studies were reported on D-cycloserine without antipsychotics. No side effects of D-cycloserine were reported.

The only study on D-alanine reported positive effects when added to antipsychotics on negative, positive, cognitive and general symptoms, but no effect on depressive symptoms. No effect on side effects of antipsychotics, was found. Side effects of D-alanine (insomnia and nausea) were reported.

All three studies combining sarcosine with antipsychotics (not clozapine) found positive effects on almost all symptom domains. When combined with clozapine (two studies) no treatment effects were found. Also when given without antipsychotics (one study), sarcosine did not improve symptoms. Sarcosine did not improve side

effects of antipsychotics in four out of four studies. Adverse effects of sarcosine included weight gain, insomnia, palpitations, dizziness, and sedation.

One large study (N=140) on NAC added to antipsychotics reported improved positive symptoms but no improvement of negative cognitive or general symptoms and no improvement of side effects of antipsychotics, whereas one small study (N=9) found some improvement of cognitive symptoms. No adverse effects were reported.

(iii) Eastern (Chinese and Ayurvedic) herbs

Eastern herbs are provided in the context of treatment with complete systems of medicine that evolved over thousands of years, such as traditional Chinese medicine (TCM) and Ayurveda. These treatments consist of a treatment including herbal compounds, massage, diet, acupuncture and the regulation of lifestyle (Clifford, 2003; Kaptchuck, 2000). Most clinical studies have been performed on acupuncture (outside the scope of this review) and on the herbal compounds of these medical systems.

Many studies on these eastern herbs were found, but only five got a Jadad score of 3 or higher. One old study (1956) on resperpine found 'clinical improvement' after 11 weeks compared to placebo, in 80 patients not treated with antipsychotics, but with electroconvulsice therapy (ECT). Several side effects were reported: nasal congestion, periorbital edema, diarrhea, epigastric pain, salivating, pseudo-Parkisonian state, severe headaches, deep pains in limbs. Three (out of four) more recent studies found significant effects on general functioning of adding Ayurvedic herbs (bacopa monnieri and nardostachys jatamansi; one study) or Chinese herbs (mixture of 13 Chinese herbs; 2 studies) to antipsychotics. The Ayurvedic herbs were compared to 10 mg of olanzapine in a 76 weeks non-inferiority study including 200 patients. It found no statistically significant difference between both groups looking at improvement of positive, negative and general symptoms. The Ayurvedic group developed less weight gain. Two large studies by Chen (2008, N=200; 2009, N=120) on a mixture of 13 Chinese herbs found improvement of general functioning (both studies) and cognitive and depressive symptoms (in one of two studies) when added to risperidone (max 8 mg/day). One study (Xiao et al., 2011) found no effect of Chinese herb sarsasapogenin compared to placebo when added to risperidone on positive, negative, cognitive or general symptoms in 90 patients during 8 weeks. Many different non-severe adverse effects were reported (e.g. gastrointestinal, drowsiness and insomnia).

(iv) B vitamins

In his paper in Science, Nobel laureate Linus Pauling proposed a way of understanding and treating psychiatric disorders by correcting malfunctions in the body's chemistry, calling this approach 'orthomolecular psychiatry' (Pauling, 1968). His idea was partly built on studies by Osmond (1962) and Hoffer (1963; 1964) reporting good results when treating patients with schizophrenia with large doses of vitamins, especially vitamin B3. Hoffer published two more positive results with B vitamins (Hoffer, 1971; Hoffer, 1972). However, attempts to replicate his findings seem to have failed (Wittkopp, 1972; Ban, 1975). The contradicting findings may be explained since vitamine B is suggested to be only effective in early psychosis and not in chronic schizophrenia (Hoffer, 1965). One of the proposed mechanisms is abnormal one-carbon metabolism due to vitamin deficiencies (Hoffer, 2008). Variable levels of components of one-carbon metabolism (folic acid and vitamin B12) and consequently altered levels of homocysteine and phospholipid docosahexaenoic acid

(DHA) have been reported, in medicated patients as well as medication-naïve first-episode psychotic patients (Kale et al., 2009). Folate status in patients with schizophrenia correlates inversely with negative symptoms (Goff et al., 2004).

We found 20 RCTs on B vitamins added to antipsychotics including one on B3 without antipsychotics. B1 showed some effect on general functioning in one study and on positive and negative symptoms in another. B3 showed improved general functioning in three (out of nine) studies. B6 improved general functioning in four (out of five) studies. In one study general functioning improved after administration of B9. One study reported no effect of B11. Another study showed a positive effect of combined B6, B9 and B12 on positive, negative and cognitive symptoms. B6 improved extra-pyramidal side effects of drugs (tardive dyskinesia (TD) and neuroleptic induced akathisia (NIA)) in four (out of four) studies. In one study on B3 in 57 children without antipsychotics, cognition and general functioning did not improve after six months. Most B vitamins induced modest side effects, especially skin flushing and abnormal liver function induced by vitamin B3 and B6.

(v) Antioxidants

Oxygen is essential in life, but it also generates reactive molecules (called free radicals) throughout the body. These free radicals are potentially harmful as they can damage essential molecules such as DNA and the enzymes necessary for proper functioning of cells. Antioxidants may capture these reactive free radicals and convert them back to less reactive forms of the molecules (Singh et al., 2010). There is a growing body of evidence that oxidative damage (maybe due to defective enzyme systems) may contribute to the course and outcome of schizophrenia (Mahadik & Mukherjee, 1996; Fendri et al., 2006; Mahadik, Evans & Lal, 2001) and is already present in patients with first episode psychosis (Flatow et al., 2013).

Ascorbic acid (vitamin C) is an antioxidant vitamin and plays an important role in protecting free radical-induced damage in the body. It is present in brain tissue and dopamine-dominant areas in higher concentrations compared to other organs (Harrison & May, 2009). Ginkgo biloba, an extract of the leaves of the ginkgo biloba tree) is also suggested to have antioxidant properties (Maclennan et al., 2002) and has been found to improve brain circulation at the microvascular level (Kubota et al., 2001; Sun et al., 2003; Yan et al., 2008), therefore it might improve outcome in schizophrenia.

Long-term treatment with antipsychotics is associated with a variety of movement disorders, including tardive dyskinesia (TD). Both dopamine-receptor super-sensitivity and oxidative stress-induced neurotoxicity in the nigrostriatal system are suggested to be involved in its pathogenesis (Kulkarni & Naidu, 2003). The pineal hormone melatonin is a potent antioxidant and attenuates dopaminergic activity in the striatum and dopamine release from the hypothalamus (Shamir, 2001). Thus, treatment with antioxidative agents may have a beneficial effect for both treatment of psychotic symptoms as well as prevention of TD. Vitamin E has been suggested for TD because it is a lipid-soluble antioxidant that decreases free radical formation (Herrera, 2001).

We found 2 RCTs on vitamin C: one found improved general functioning and reduced side effects (reduced serum malondialdehyde (MDA); a lipid peroxidation product) when added to olanzapine (10 mg), quetiapine (200 mg) or ziprasidone (40 mg) after 8 weeks. One study without antipsychotics found no effect on cognition or motor functioning after 10 days. Both studies reported no side effects of vitamin C. Three out of four studies on ginkgo biloba found improved positive symptoms, two of

three improved general functioning, four out of four no improvement of negative symptoms when added to antipsychotics. All four improved side effects of antipsychotics (behavioral toxicity, symtoms of nervous system, TD). No side effects of ginkgo were reported. One study of melatonin for tardive dyskinesia reported a decrease of TD and no side effects. Six (out of twelve) studies on vitamin E for reducing extra-pyramidal symptoms, while using antipsychotics, showed a decrease of TD (5 studies) and EPS (1 study), those with shorter duration of TD seemed to improve more; no side effects of vitamin E were reported, except mild diarrhea in two studies. Five (out of five) reported no effect on general functioning.

(vi) Other substances
Agents that did not fit in the five categories mentioned above were classified in this residual category. Sixteen high-quality RCTs have been performed on multivitamins, hormones (dehydroepiandrosteron (DHEA), pregnenolone (PREG), estradiol, protilerin), inositol, gamma-hydroxybutyrate (GHB) and des-tyr-gamma-endorphin. Three (out of five) studies on DHEA added to antipsychotics, showed improvement of negative symptoms, one (out of three) on positive symptoms, one (out of two) on cognition, two (out of three) on depression and one (out of three) on general functioning. Two (out of four) improved side effects of drugs. One (out of one) small study (N=12) on protilerin (thyrotropin releasing hormone) found improved general functioning. Three (out of three) studies on estradiol found improved general functioning, two (out of three) improved positive symptoms, one out of one improved cognition and none (out of three) improved negative symptoms. One (out of one) small study (N=14) on inositol found no effect on positive or negative symptoms. Two (out of two) studies on GHB found no general improvement. One (out of one) very small (N=6) study on des-tyr-gamma-endorphin found improvement on general and positive symptoms. No serious side effects induced by any of these agents were reported.

Discussion

This review suggests emerging evidence for the beneficial effects of various natural medicines for schizophrenia. Glycine, sarcosine, NAC, some Chinese and Ayurvedic herbs, ginkgo biloba, estradiol and vitamin B6 seem effective for symptoms of schizophrenia when added to antipsychotics (glycine not when added to clozapine). We found inconclusive or absent evidence for omega-3 fatty acids, D-serine, D-alanine, D-cycloserine, other B vitamins, vitamin C, DHEA, PREG, inositol, GHB and des-tyr-gamma-endorphin when added to antipsychotics. Omega-3 without antipsychotics might be beneficial in the prevention of schizophrenia. Reserpine without antipsychotics seemed effective in one old study. Ayurvedic herbs were reported to be as effective as olanzapine in a recent large study. Other agents as monotherapy (vitamin B3, vitamin C, sarcosine, glycine, protilerin) do not seem effective or have only been tested in single or small trials. For alleviation of side effects, ginkgo and vitamin B6 seem effective for TD and NIA. The evidence for diminishing some side effects of antipsychotics by omega-3, melatonin and DHEA is (still) inconclusive. With regard to the safety of natural compounds, all those were found to produce only mild or no side effects. However, most study samples were small, duration was generally short and studies were not designed or powered to identify side effects. They only covered a modest part of the globe's geography and

most studies need replication.

There is promising but inconclusive evidence for improved outcome by omega-3 fatty acids combined with antipsychotics in schizophrenia, either on symptoms or on side effects of antipsychotics. Earlier reviews report similar conclusions (Tsalamanios et al., 2006; Irving et al., 2011; Boskovic et al., 2011). Most promising evidence for omega-3 is found for preventing transition to first episode psychosis in high-risk individuals. Amminger et al. (2010) found a reduction of the transition rate from 27.5% to 4.8% by prescribing omega-3 fatty acids in people thought to be at risk on developing schizophrenia. However, before conclusions can be drawn, replication of these findings are needed. A randomized controlled multicenter phase III clinical trial of omega-3 PUFA is now in progress (Amminger & McCorry, 2012).

There is some evidence for glycine and sarcosine combined with antipsychotics in reducing negative symptoms, but not when combined with clozapine and also not as monotherapy. No evidence was found for D-cycloserine and D-serine on clinical improvement. Our results concur with two recent reviews (Tsai & Lin, 2010; Singh & Singh, 2011) and are in line with a recently updated Cochrane review (Tiihonen & Wahlbeck, 2006). Conflicting results from studies on drugs targeting the glutamate/NMDA system may be explained by complicated dose-effect relationships, as recently found in studies with the Glyt-1 transporter antagonist bitopertin (Umbricht et al., 2013).

By adding Chinese or Ayurvedic herbs to antipsychotics, general functioning seems to improve. Reserpine might improve outcome, but many side effects are reported. There is controversy concerning the frequently mentioned suggestion that resperine can induce depression (which lead to the monoamine hypothesis of depression; Baumeister et al., 2003). The Mundewadi (2008) study suggests equal effects of Ayurvedic medicine as monotherapy (bacopa monnieri and nardostachys jatamansi) compared to olanzapine but this study needs replication. A Cochrane review (Rathbone et al., 2007) states that ‘the results suggest that combining Chinese herbal medicine with antipsychotics is beneficial’. Another Cochrane review (Agarwal, 2010) concludes that ‘Ayurvedic medication may have some effects for treatment of schizophrenia, but has been evaluated only in a few small pioneering trials’. These results need further exploration and pharmacological differentation as Chinese and Ayurvedic herbs include hundreds of species combined in thousands of different combinations prescribed in a fundamentally different way than Western medicines are (Kaptchuck, 2000; Cliffort, 2003). The combined approach using knowledge from conventional medicine as well as Chinese medicine seems promising as it can lead to innovation (Van der Greef, 2011) and possibly to improved outcomes (Zhang, 2011).

Inconsistent beneficial outcomes of studies on B vitamins were identified, especially when given as a combination of B1, B3, B6, B9 and/or B12 with antipsychotics. One review (Kleijnen and Knipschild,1991) concluded that no adequate support for efficacy of B vitamins in schizophrenia can be identified. Most studies with positive effects in our review, however, were published after 1990. Most convincing evidence was found for vitamin B6 added to antipsychotics, that appears to be effective in diminishing general psychopathology and TD.

The findings on the efficacy of vitamin C for schizophrenia in only two RCTs were inconsistent, so definite conclusions cannot be drawn. The efficacy of vitamin E on TD remains inconclusive as only half of studies in our review found some positive result. Even so, a meta-analysis by Boskovic et al (2011) claimed: ’Vitamin E could

potentially improve TD'. Perhaps this is due to the finding that those with a short history of TD tend to improve more than those with a longer history of TD. A Cochrane review in 2011 (Soares & McGrath) came to a similar conclusion: 'small trials of limited quality suggest that vitamin E may protect against deterioration of TD. There is no evidence that vitamin E improves symptoms of this problematic and disfiguring condition once established'.

Ginkgo biloba is a promising agent that seems to benefit patients with schizophrenia in several ways when added to antipsychotics. Several studies in this review suggest evidence for improving symptoms in various domains including effect on positive symptoms and the reduction of side effects of antipsychotics. Singh et al. concludes in another review: 'ginkgo as add-on therapy ameliorates the symptoms of chronic schizophrenia' (Singh et al., 2010).

On melatonin, there is preliminary evidence from one study for an effect of melatonin to diminish TD. As TD is difficult to investigate with its fluctuating symptom severity, this finding needs replication before more definite conclusions can be drawn.

Some inconsistent evidence was found on improved outcomes by several hormones (DHEA, PREG and testosterone) in schizophrenia, not allowing final conclusions. A Cochrane review on DHEA / testosterone (Elias & Kumar, 2007) arrived at a similar conclusion. For estradiol, a Cochrane review (Chua et al., 2005) found no convincing evidence over placebo. Since then, two more recent studies indicate that estradiol improves positive and general (but not negative) symptoms of schizophrenia when added to antipsychotics. Therefore, the use of estradiol in schizophrenia warrants further study.

There is a need for more high-quality efficacy and (cost-) effectiveness research on natural medicines for schizophrenia. Especially, more large scale RCTs are needed, as most of the studies we included were performed with fewer than 50 participants. Most obvious candidate agents are glycine, sarcosine, Chinese and Ayurvedic herbs, ginkgo biloba, vitamin B6, and omega-3 fatty acids.

Limitations

This review provides a general overview of the effects of different natural agents in treatment of schizophrenia and the treatment of undesired effects of antipsychotics. A limitation of this review is its wide scope, allowing only general descriptions of included studies in six domains. Second, we have only discussed the most well-known and most studied natural agents, as identified with our search strategy. There may be more natural agents investigated for their effects on schizophrenia or on side effects of antipsychotics, that we did not identify. A third limitation is that our search excluded papers in other languages than English, although more studies exist, mainly in Japanese and Chinese. Presumably this might have led to an underestimation of the effects of some natural agents. For instance, Pataracchia (2008) reports on six double-blind trials showing positive results of combining vitamin B3 and vitamin C in the treatment of schizophrenia, but none were published in journals that are included in the databases we assessed. Saku (1991) reports in English about 45 studies (published in Chinese) on the efficacy of Chinese herbs for schizophrenia and psychosis, with and without modern antipsychotics. Beneficial results were reported in studies combining Chinese herbs with low dosage modern antipsychotics. Fourth, we do not know to which extent our findings are influenced by publication bias, for instance in favor of the publication of studies with positive results. Fifth, in the included RCTs there was not much specific information about the kind of

conventional treatment that was continued during study: no information on frequency and type of counselling / therapy and no specific information on dosage and or type of antipsychotics (other than: '..was kept stable during this study..'). Also the dosage of the natural agents and the clinical details on included patients in the study was often not clear (e.g. first or chronic psychosis, treating symptoms or preventing relapse), limiting firm conclusions. Sixth, we only mentioned whether the effects in the studies were significant compared to the control groups. We did not show effect sizes, as the data published in many included studies did not allow to calculate effect sizes. Therefore, the clinical relevance of the results is debatable. Seventh, we did not set a time frame to our search, allowing the inclusion of some rather old studies (some dating more than 50 years ago). Older studies provide data in ways not always in agreement with more modern conventions, although we did assess the quality of all studies. Finally, for this last purpose, we used Jadad, not the Cochrane risk of bias assessment. Therefore possible bias may be less easily identified.

Clinical implications

Clinicians need to be aware of the frequent use of natural medicines without medical prescription, while some patients assume that natural is better than chemical and causes fewer side effects. Although beneficial effects may occur, this is certainly not always the case. Some natural compounds that may be suggested in treatment of schizophrenia are toxic to humans (Topliss et al., 2002), and some herbal medicines can cause side effects or can interact with medication (Ernst, 2003a). Only 3% of the user population is aware of the potential risks of interactions between herbs and prescription medication (Walter & Rey, 1999). So, from a medical perspective it is important to know what patients buy and try. Another concern is the reports on contamination of herbs, for instance from Asia, with heavy metals. However, after investigation of 334 samples, Harris et al. (2011) conclude that 'the vast majority (95%) of medications in this study contained levels of heavy metals or pesticides that would be of negligible concern'. Because of these concerns, patients want their medical doctors to advice them on complementary (or natural) medicines (Gray et al., 1998; Hoenders et al., 2006). The World Health Organization (World Health Organization, 2003) and European Parliament (EP, 1997) have advised their member states to: 'formulate national policy and regulation for the proper use of CAM and its integration into national health care systems in line with the provisions of the WHO strategies on Traditional Medicines; establish regulatory mechanisms to control the safety and quality of products and of CAM practice; create awareness about safe and effective CAM therapies among the public and consumers.' Respecting patients' opinions and informing them may also improve the therapeutic relationship (Stevingson, 2006) and thus enhance treatment outcome (Koenig, 2000; Nikles et al., 2005; Gill, 2013), as this has been shown to be dependent on the quality of the therapeutic alliance (Wampold, 2001; Driessen et al., 2010; Baldwin et al., 2007).

Further research

Research in this area is hampered by a lack of funding. Less than 1% of research budget is spent on non-conventional medicine (Ernst, 2003b). It is unlikely that pharmaceutical companies will provide research grants for natural agents that cannot easily be patented. Other obstacles are national and international biodiversity rules and regulations and lack of standardization of formulation, production and identification of active ingredients from plant products (Ganzera et al., 2001).

Finally
This review provides clinicians and patients with an overview of the results of high-quality scientific studies on the efficacy and safety of natural medicines in schizophrenia and related psychoses. Some agents seem effective and safe. From a clinical perspective however, many questions remain unanswered: what dosage is safe and effective? Are there any interactions with conventional medication? How does one relate to the fact that natural agents can be bought anywhere without prescription? How to assess questions of quality and insurance? We intend to try to answer some of these questions in a subsequent paper focusing on the clinical application of natural medicines in psychiatry.

Conclusion

High quality research on natural medicines for schizophrenia and other psychotic disorders is scarce. However, there is emerging evidence for glycine, sarcosine, NAC, some Chinese and ayurvedic herbs, ginkgo biloba, estradiol and vitamin B6 for improving symptoms of schizophrenia when added to antipsychotics. There is inconclusive or absent evidence for omega-3, D-serine, D-alanine, D-cycloserine, B vitamins, vitamin C, DHEA, PREG, inositol, GHB and des-tyr-gamma-endorphin when added to antipsychotics. Omega-3 without antipsychotics might be beneficial in the prevention of schizophrenia. Ayurvedic herbs seem as effective as olanzapine in one large recent study. Other agents without antipsychotics (vitamin B3, vitamin C, sarcosine, glycine, protilerin) do not seem effective or have only been tested in single or (very) small trials. Ginkgo and vitamin B6 seem effective for side effects of antipsychotics (TD and NIA). The evidence for improved side effects of antipsychotics by omega-3, melatonin and DHEA is (still) inconclusive. All agents produce only mild or no side effects. However, most study samples are small, duration is generally short, they only cover a modest part of the globe's geography and most results need replication.

Table 3. Overview of effects of natural medicines in psychotic disorders

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
Omega-3 fatty acids													
Vaddadi 1989	yes				+ (WMS)		+ (CPRS)	+ EPS (SAS) 0 TD (AIMS)	0	N=48; c-o (21 efamol/pla; 17 plac/efamol)	10 (not specified per group)	2x 16 wks	4
Fenton 2001	yes		0 (PANSS)	0 (PANSS)	0 (RBANS)	0 (MADRS)	0 (CGI)	0 TD (AIMS), EPS (SAS)	+ (respiratory infection and diarrhea)	N=90 (45 EPA, 45 plac)	15 (8 in EPA gr, 7 in plac gr)	16 wks	4
Peet 2001	(1) yes (2) at start no, later in trial yes		(1) 0 (PANSS)	(1) + (PANSS) (2) + (PANSS)			(2) + less use of antipsychotic medication		(1) n.r. (2) 0	2 trials, (1) N=55 (45 ct; 15 ap + EPA, 16 ap + DHA, 14 ap + plac) (2) N=30 (15 EPA, 15 plac)	(1) 10; not specified per group (2) 3 in plac gr, 1 in EPA gr	(1) 3 months (2) 3 months	(1) 4 (2) 4
Emsley 2002	yes		0 (PANSS)	0 (PANSS)			+ (PANSS subscale)	0 EPS (ESRS) + dyskinesia (ESRS)	0	N=40 (20 ap + E-EPA, 20 ap + plac)	1 in E-EPA gr	12 wks	3
Peet 2002	yes		0 (PANSS) + (PANSS for 2gr gr on cloz)	0 (PANSS) + (PANSS for 2gr gr on cloz)		0 (MADRS)	0 (PANSS) + (PANSS for 2gr gr on cloz)	0 EPS (SAS, LUNSERS), akathisia (BAS), TD (AIMS),	0	N=122 (31 plac, 29 1gr E-E, 28 2gr E-E, 27 4gr E-E)	1 in plac gr, 5 in 1 gr gr, 5 in 2gr gr, 2 in 4gr gr	12 wks	4
Emsley 2006, 2008	yes		0 (PANSS)	0 (PANSS)				0 dyskinesia, EPS (ESRS) 0 HDL, LDL, triglycerides, serum prolactin, Hb, blood pressure,	Increase in bleeding time and BMI	N=84 (42 ap + E-EPA, 42 ap + plac)	11 in E-EPA gr, 18 in plac gr	12 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
								heart rate					
Berger 2007 (15-29 year olds)	Risp, Olan or Quet		0 (SANS)			n.r.	0 (BPRS, CGI, GAF, SOFAS)	+ EPS (SAS), less use of AP	0	N=80 (40 ap + E-EPA, 40 ap + plac)	5 in E-EPA gr, 6 in plac gr	12 wks	5
Manteghiy 2008	Risp		0 (PANSS)	0 (PANSS)		0 (PANSS)	0 (PANSS)		Gastrointestinal side effects (in 3)	N=106, 85 c-t (42 ap + Omega-3, 43 ap +plac)	21, not specified per group	6 wks	4
Amminger 2010 (13-25 year olds)	no		+ (PANSS)	+ (PANSS)	0 (resting brain activity)		+ (lower risk of progression to psychosis, PANSS subscale, GAF)		0	N=81 (41 PUFAs, 40 plac)	3 in PUFAs gr, 2 in plac gr	12 wks treatment, 12 mnts follow-up	5
Toktam 2010	Ola						0 (FBS, fasting insulin, HbA_{1c}, HOMA-IR)		n.r.	N=41 (20 ap + omega-3 [4 schizophrenia / schizoaffective], 21 ap + plac [8 schizophrenia / schizoaffective)	n.r.	6 wks	3
Glutamate													
Glycine													
Javitt 1994	yes		+ (PANSS)	0 (PANSS)			0 (PANSS subscale)	0 EPS (ESRS), TD (AIMS)	No SAEs; Temporarily lower-extremity weakness (1)	N=14 (7 ap + glyc, 7 ap + plac)	0	8 wks d-b, 8 wks glyc for everyone	4
Heresco-Levy 1996	yes		+ (PANSS)	0 (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (PANSS subscale)	0 TD (AIMS), EPS (SAS)	0	N=12 c-o (7 glyc/plac, 4 plac/glyc)	1 (on plac, in plac/glyc gr)	2x 6 wks, 2 wks wo before and in between	4
Heresco-Levy 1999	yes		+ (PANSS)	0 (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (BPRS)	0 TD (AIMS), EPS (SAS)	Nausea and vomiting (1)	N=22 c-o (10 plac/glyc, 9 glyc/plac)	3 (2 on plac, 1 on glyc)	2x 6 wks, 2 wks wo before and in between	4
Potkin 1999	Cloz	400-1200	0 (SANS)	- (BPRS subscale)			0 (BPRS)		0	N=24 (12 cloz + glyc, 12 cloz	3 in glyc gr, 2 in	12 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
		mg/day								+ plac)	plac gr		
Evins 2000	Cloz		0 (SANS, PANSS)	0 (PANSS)	0 (PANSS subscale)		0 (BPRS)		n.r.	N=30 (27 ct; 14 cloz + glyc, 13 cloz + plac)	2 on plac, 1 on glyc	8 wks	4
Javitt 2001	yes		+ (PANSS)		+ (PANSS subscale)	+ (PANSS subscale)		0 EPS (SAS), akathisia (BAS), TD (AIMS)	0	N=12 c-o (6 ap+ glyc/plac, 6 ap + plac/glyc)	0	2x 6 wks, 4 wks wo before and 2 wks in between	4
Heresco-Levy 2004	Olan, Risp		+ (PANSS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (BPRS)	+ EPS (SAS), TD (AIMS)	No SAEs; Mild upper gastrointestinal tract discomfort with nausea (2)	N=17 c-o (1 gr ap + glyc/plac, 1 gr ap + plac/glyc)	3 d-o on glyc	2x 6 wks, 2 wks wo before and in between	4
Diaz 2005	yes		0 (PANSS)	0 (PANSS)			0 (BPRS, GAF)	0 EPS (ESRS, SAS)	Nausea and vomiting (1)	N=12 c-o (6 ap + plac/glyc, 6 ap + glyc/plac)	1 on glyc	28 wks	3
Buchanan 2007 (also reported under d-cycloserine)	yes, no Cloz		+ (SANS) for glyc by conventional antipsychotics		0 (neuro-psychological test battery)		0 (BPRS, CGI)	0 EPS (SAS), TD (AIMS)	Nausea and dry mouth	N=165 (55 ap + both plac, 56 ap + d-c + plac, 54 ap + glyc + plac)	10 in plac gr, 10 in d-c gr, 12 in glyc gr	16 wks	3
Woods 2012	no		+ (SOPS)	+ (SOPS)		+ (MADRS)	+ (attention, working memory)		0	N=8 (4 glyc, 4 plac)	1 in glyc gr, 1 in plac gr	12 wks	4
D-serine													
Tsai 1998	yes		+ (SANS)	+ (PANSS)	+ (PANSS subscale, WCST)	0 (HAM-dep)	+ (CGI) 0 (PANSS subscale)	0 TD (AIMS), akathisia (BAS), EPS (SAS)	No SAEs; Insomnia (2), nausea (2), diarrhea (1), constipation (1)	N=31 (17 ap + plac, 14 ap + d-serine)	3 in plac gr, 0 in d-serine gr	6 wks	4
Tsai 1999	Cloz		0 (PANSS, SANS)	0 (PANSS)	0 (PANSS subscale, WCST)	0 (HAM-D)	0 (PANSS subscale, CGI)	0 TD (AIMS), akathisia (BAS), EPS (SAS)	0	N=20 (10 cloz + d-serine, 10 cloz + plac)	n.r.	6 wks	3

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
Heresco-Levy 2005	Olan, Risp		+ (PANSS, SANS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (BPRS)	+ EPS (SAS), TD (AIMS)	0	N=39, c-o (19 ap + d-serine/plac, 20 ap + plac/d-serine)	3	2x 6 wks, 2 wks wo before and 3 wks wo in between	4
Lane 2005 (also reported under sarcosine)	Risp	6 mg/ day or less	0 (SANS)	0 (PANSS)	0 (PANSS subscale)	0 (PANSS subscale)	0 (PANSS subscale)	0 EPS (SAS), akathisia (BAS), TD (AIMS)	No SAEs; e.g. weight gain, palpitations, insomnia, fatigability, orthostatic dizziness, weight loss, tension, salivation	N=65 (23 Risp + plac, 21 Risp + d-s, 21 Risp + sar)	3 in plac gr, 2 in d-s gr, 3 in sar gr	6 wks	5
Lane 2010 (also reported under sarcosine)	yes		0 (PANSS, SANS)	0 (PANSS)	0 (PANSS subscale)	0 (PANSS subscale)	0 (QoL, GAF)	0 EPS (SAS), akathisia (BAS), TD (AIMS)	No SAEs; e.g. weight gain, insomnia, fatigability, sedation, palpitations	N=60 (20 ap + plac, 20 ap + sar, 20 ap + d-s)	1 in sar gr, 4 on d-s, 4 in plac gr	6 wks	5
Weiser 2012	yes		0 (SANS, PANSS)	0 (PANSS)	0 (MATRICS)		0 (PANSS)		Mouth sores	N=195 (97 ap + d-s, 98 ap + plac)	23 in d-s gr, 23 in plac gr	16 wks	5
D-cycloserine													
Rosse 1996	Mol	50 mg t.i.d.	0 (SANS)	0 (BPRS)			0 (BPRS)		n.r.	N=13 (3 mol+10 mg d-s, 6 mol + 30mg d-s, 4 mol + plac)	0	4 wks	
Van Berckel 1999	yes		0 (PANSS)	- (PANSS)			- (PANNS subscale, CGI)	0 EPS (ESRS)	0	N=26 (13 ap + d-s, 13 ap + plac)	1 in d-s gr	8 wks	4
Heresco-Levy 2002	yes		+ (PANSS)	0 (PANSS)		0 (HAM-dep)	+ (PANSS subscale)	0 EPS (SAS), TD (AIMS)	0	N=24, c-o (16 ct, 8 d-c/ plac, 8 plac/d-c)	3 on d-c, 5 on plac	2x 6 wks, 2 wks wo in between	3
Duncan 2004*	yes		0 (SANS, BPRS		0 (CPT, SSTMSP)		0 (BPRS)	0 EPS (SAS)	0	N=22 (10 ap + d-c, 12 ap +	0	4 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
			subscale)							plac)			
Goff 2005*	yes		0 (PANSS, SANS)	0 (PANSS)	0 (e.g. WAIS scales, Stroop, WCST)	0 (HAM)	0 (GAS, QoL)	0 EPS (SAS), TD (AIMS)	n.r.	N=55 (27 ap + d-c, 28 ap + plac)	13 in d-c gr, 16 in plac gr)	24 wks	4
Yurgelun-Todd 2005	yes		+ (PANSS)	0 (PANSS)	+ (temporal lobe activation) 0 (frontal lobe activation)				n.r.	N=12 (6 ap +d-s, 6 ap +plac)	0	8 wks	4
Buchanan 2007 (also reported under glycine)	yes, no Cloz		0 (SANS)		0 (neuro-psychologic al test battery)		0 (BPRS, CGI)	0 EPS (SAS), TD (AIMS)	0	N=165 (55 ap + both plac, 56 ap + d-c + plac, 54 ap + glyc + plac)	10 in plac gr, 10 in d-c gr, 12 in glyc gr	16 wks	3
Goff 2008	yes, no cloz		+ (SANS)	0 (PANSS)	0 (cognitive test battery)		0 (CGI)		0	N=38 (19 ap + d-c, 19 ap + plac)	3 in d-c gr, 2 (3 at f.u.) in plac gr	8 wks, f.u. + 2 wks	5
Gottlieb 2011	yes			0 (SAPS, PSYRATS) + (first d-c, greater reductions in delusional severity)	0 (ABA, PRT-BT) + (first d-c, greater reductions in belief conviction)				0	N=21, c-o (11 ap + d-c/plac, 10 ap + plac/d-c)	1 in plac – d-c gr	3 wks, 3 visits, 2 doses (visit 1 and 2)	4
D-alanine													
Tsai 2006	yes		+ (SANS)	+ (PANSS)	+ (PANSS subscale)	0 (HAM-D)	+ (CGI) 0 (PANSS subscale)	0 TD (AIMS), akathisia (BAS), EPS (SAS)	No SAEs; insomnia and nausea (1)	N=32 (18 ap + plac, 14 ap + d-a)	1 in plac gr	6 wks	4
Sarcosine													
Tsai 2004	yes		+ (SANS)	+ (PANSS)	+ (PANSS subscale)	0 (HAM-D)	+ (PANSS subscale, BPRS)	0 EPS (SAS), akathisia (BAS), TD	No SAEs; tachycardia (2)	N=38 (17 ap + sar, 21 ap + plac)	2 (1 in each group)	6 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
								(AIMS)					
Lane 2005 (also reported under D-serine)	Risp	6 mg/ day or less	+ (SANS)	+ ((PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (PANSS subscale)	0 EPS (SAS), akathisia (BAS), TD (AIMS)	No SAEs; e.g. weight gain, palpitations, insomnia, fatigability, orthostatic dizziness, weight loss, tension, salivation	N=65 (23 Risp + plac, 21 Risp + d-s, 21 Risp + sar)	3 in plac gr, 2 in d-s gr, 3 in sar gr	6 wks	5
Lane 2006	Cloz		0 (PANSS)	0 (PANSS)	0 (PANSS subscale)	0 (PANSS subscale)	0 (PANSS subscale)	0 EPS (SAS), akathisia (BAS), TD (AIMS)	Insomnia (2)	N=20 (10 cloz + sar, 10 cloz + plac)	0	6 wks	4
Lane 2008	no		0 (PANSS)	0 (PANSS)			0 (QOL)		No SAEs; insomnia (6), weight gain (3), sedation (1), constipation (1), fatigability (1)	N=20 (11 *2g* sar, 9 *1g* sar)	3 in 1g gr, 1 in 2g gr	6 wks	4
Lane 2010 (also reported under D-serine)	yes		+ (PANSS, SANS)	+ (PANSS)	+ (PANSS subscale)	+ (PANSS subscale)	+ (QoL, GAF)	0 EPS (SAS), akathisia (BAS), TD (AIMS)	No SAEs; e.g. weight gain, insomnia, fatigability, sedation, palpitations	N=60 (20 ap + plac, 20 ap + sar, 20 ap + d-s)	1 in sar gr, 4 on d-s, 4 in plac gr	6 wks	5
NAC; N-acetylcysteine													
Berk 2008	yes		+ (PANNS)	0 (PANSS)	0 (digit span, word learning, trail making, verbal fluency)		+ (CGI) 0 (GAF, SOFAS)	0 TD (AIMS), EPS (SAS) + akathisia (BAS)	0	N = 140 (71 ap + plac, 69 ap + NAC)	56, not specified per group	24 wks, f.u. at 28 weeks	4
Lavoie 2008	yes				0 (auditory discriminati				n.r.	N=9 (2 d-o ; 5 ap + NAC/plac,	2, not specified	2x 2 wks	3

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
					on task, P300) + (MMN)					2 ap + plac/NAC)	per group		
Eastern Herbs													
Naidoo 1956 (reserpine)	no						+ (clinical improvement)		No SAEs; Nasal congestion, periorbital edema, diarrhea, epigastric pain, salivating, pseudo-Parkisonian state, severe headaches, deep pains in limbs	N=80 (20 plac (A), 20 serpasil (B), 20 plac + ect (C), 20 serpasil + ect (D))	n.r.	11 wks of plac or treatment, then treatment for all groups (A+B serpasil, C+D reserpine) not specified for how many weeks	3
Mahal 1976	Only in AP-group Chlor	1st month 200 mg, 2nd month 300 mg	+ / 0 (B better than plac and Tagara, no sign dif with chlor)	+ / 0 (B better than plac and Tagara, no sign dif with chlor)			0 (MPQ, SAE)		n.r.	N = 136 (108 ct: 27 tagara, 27 brahmyadiyoga (B), 27 plac, 27 chlor)	28 (not specified per group)	2 mnts	3
Mundewadi 2008 (ayurvedic medicine: Bacopa monnieri, nardostachys jatamansi)	Olan in control group	10 mg dd	+ (as effective as ap) (PANSS)	+ (as effective as ap) (PANSS)			+ (as effective as ap) (clinical improvement)	+ (less weight gain than ap)	No SAEs; vomiting and diarrhea (2)	N=200 (97 ayurvedic medicine, 103 ap)	12 in am gr, 15 in ap gr	78 wks	3
Chen 2008, 2009	Risp	max 8 mg/ day	0 (SANS, PANSS)	0 (PANSS)	+ (WCST)	+ (HAM-D)	+ (QoL, SDSS, lower use of AP)	0 TD (AIMS, RSESE)	No SAEs; e.g. tremor, insomnia, akathisia, somnolence, headache, weight gain, constipation	N=120 (60 WSKY, 60 plac)	2 in WSKY gr, 2 in plac gr	8 wks	5

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
Chen 2008	Risp		0 (PANSS)	0 (PANSS)	0 (WCST)	0 (HAM-D)	+ (SDSS)	0 TD (AIMS, RSESE)	No SAEs; e.g. tremor, akathisia, insomnia, somnolence, constipation, weight gain, sight dim	N=200 (100 risp + WSKY, 100 risp + plac)	2 in plac gr, 4 in WKSY gr	8 wks	4
Xiao 2011	Risp		0 (PANSS)	0 (PANSS)	0 (WMS, mWAIS)		0 (CGI)		No SAEs; e.g. abnormal ECG, tremor, akathisia, drowsiness	N=90 (44 risp + plac, 46 risp + sars)	5 in plac gr, 5 in sars gr	8 wks	5
B-vitamins													
Vitamin B1 (thiamin)													
Joshi 1980 (+B6+B12)	Chlor, Trif	150 mg dd., 15 mg dd.					0 (Behavior Scale) + less ECT's in vit gr		0	N = 60 (30 vitamin injection, 30 placebo injection)	1 not specified per group	4 wks, f.u. 1 yr	4
Sacks 1989 (also acetazolamide)	yes		+ (SAPS)	+ (SANS)					No SAEs; some increased urination	N=26, c-o (24 ct ; 13 ap + A+T/plac, 11ap + plac/A+T	2, not specified per group	2x 8 wks, 4 wks wo before and in between	4
Vitamin B3													
Kline 1967	Yes 5 of 20				O Free drawing test		0 BPRS; 0 Rockland; 0 Wittenborn		n.r.	N=20: 10 plac, 10 1 or 2 gr NAD	0	20 days	5
Meltzer 1969	Yes 5 of 10						0 IMPS 0 BDI		n.r.	N=10; 5 plac, 5 thioridazine; AND plac or 2gr NAD	1	9 weeks	3
Greenbaum 1970 (4-12 year olds)	n.r.				0 (WISC, SFBT)		0 (behaviour ratings)			N=57 (17 niac, 16 nm + tranquilizer, 24 plac)	0	6 months	3
Ramsay 1970	Pheno-thiazide						0 BPRS 0 MMPI			N=30; 10 nicotinic acid,	0	6 months	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
							0 HOD			10 nicotin-amide, 10 plac			
Ananth 1972	Chlor						+ (BPRS, less chlor in nic gr) - (more chlor in na gr, more hospital days in nic gr and na gr)		No SAEs; rash in nic gr (1) and in na gr (1)	N=30 (9 chlor + nic, 10 chlor + na, 11 chlor + plac)	6 ct, 3 in na gr, 2 in plac gr, 1 in nic gr	2 years	4
McGrath 1972	yes						0 (recovery rate)		n.r.	N=184 (132 na, 133 plac)	43 in na gr, 38 in plac gr	12 months	4
Ananth 1973 (also reported under Vitamin B6)	yes						+ (BPRS, NOSIE)		Abnormal liver function, leukopenia, weight loss, in nic gr (5,1,1), in nic+pyr gr (5,1,2), weight gain (1), hypotension (2) in nic+pyr gr	N=30 (10 nic + pyr, 10 nic + plac, 10 plac + pyr)	1 in pyr gr, 2 in nic+pyr gr, 1 in nic gr	48 wks	4
Wittenborn 1973	yes						0 (hospitalization, use of tranquilizers, WPRS, RNRS)		+ (hyperkeratosis)	N=140 (75 ct, 47 3000 mg niacin, 28 6 mg niacin)	65 not specified per group	24 mts	3
Deutsch 1977	yes						0 (BPRS, CG, NOSIEI)		14 different adverse effects, not mentioned	N=30 (10 ap + nic, 10 ap + nm, 10 ap + plac)	1 in nm gr, 5 in nic gr	48 wks	4
Petrie 1981 (also reported under Vitamin B6)	yes						+ (BPRS, nic gr and pyr gr) 0 (BPRS, nic+pyr gr) 0 (NOSIE)		Abnormal liver function tests, hypotension, weight loss, flushing of the skin,	N=30 (10 ap + nic + pyr, 10 ap + nic + plac, 10 ap + pyr + plac)	1 in pyr gr, 2 in nic+pyr gr, 1 in nic gr	48 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
									dermatitis				
Vitamin B6													
Ananth 1972,1973 (also reported under Vitamin B3)	yes						+ (BPRS, NOSIE)		Nausea and vomiting (1), dizziness (1), tachycardia (1), weight gain (1), flush-ing of skin (2), dermatitis (2)	N=30 (10 nic + pyr, 10 nic + plac, 10 plac + pyr)	1 in pyr gr, 2 in nic+pyr gr, 1 in nic gr	48 wks	4
Petrie 1981 (also reported under Vitamin B3)	yes						+ (BPRS, nic gr and pyr gr) 0 (BPRS, nic+pyr gr)		Abnormal liver function tests, hypotension, weight loss, flushing of the skin, dermatitis	N=30 (10 ap + nic+ pyr, 10 ap + nic + plac, 10 ap + pyr + plac)	1 in pyr gr, 2 in nic+pyr gr, 1 in nic gr	48 wks	4
Lerner 2001, 2002	yes		0 (PANSS)	0 (PANSS)			0 (CGI)	+ TD (ESRS)	0	N=15, c-o (8 ap+ vit B6/plac, 7 ap+ plac/ vit B6)	0	2x 4 wks, 1 wk wo in between	3
Lerner 2004	yes						+ (CGI, BPRS)	+ NIA (BAS)	0	N=20 (10 ap + vit B6, 10 ap + plac)	0	5 days	4
Miodownik 2006	yes						+ (BPRS, CGI; in B6 gr and mian gr)	+ NIA (BAS)	0	N=60 (23 vit B6, 20 mian, 17 plac)	0	5 days	4
Lerner 2007	yes							+ TD (ESRS)	No SAEs; acne (1), allergic reaction (1)	N=50, c-o (28 ap + vit B6/plac, 22 ap + plac/vit B6)	10 on vit B6, 4 on plac	26 wks (2x12 wks + 2 wks wo in between)	3
Vitamin B9 (methylfolate)													
Godfrey 1990	yes						+ (Clinical Rating Scale)		n.r.	N=17 (subgr of 41; 9 ap + vit B9, 8 ap + plac)	0	6 mts	3
Vitamin B11 (folic acid)													

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
Hill 2011	yes		0 (SANS) + effect of MTHFR gt)	0 (PANSS)	0 (e.g. WAIS, WCST)	0 (CDSS)	0 (GAF, QoL)		n.r.	N=38 (19 ap + vit B11, 19 ap + plac)	5 in B11 gr, 5 in plac gr	12 wks	4
Vitamin B6, B9 en B12													
Levine 2006	yes		+ (PANSS)	+ (PANSS)	+ (WCST) 0 (DS, RAVLT, CFD)			0 TD (AIMS)	n.r.	N=55, c-o (20 ap + vit/ plac, 22 ap + plac/ vit)	13 (2 not specified; 5 on plac, 6 on vits)	2 x 3 mts	3
Anti-oxidants													
Vitamin C													
Bhavani 1962	no				0 (e.g. recall, attention, imitation)		0 (motor functioning)		n.r.	N=31 (15 ascorbic-acid, 16 plac)	n.r.	10 days	4
Dakhale 2005	Olan, Quet, Zipr	10/ 200/ 40 mg/ day					+ (BPRS)	+ (reduce of serum MDA)	0	N=40 (20 vit C, 20 plac)	4 in plac gr, 1 in vit gr	8 wks	5
Vitamin E													
Elkashef 1990	yes						0 (BPRS)	+ EPS (AIMS)	No SAEs; mild diarrhea (1)	N=10, c-o (8 ct; 5 ap + vit E/ plac, 3 ap + plac/ vit E)	2, not specified per group	2 x 4 wks, 2 wks wo before	3
Schmidt 1991	yes							0 EPA (AIMS)	negligible	N=23 c-o (all 14 days vit E / 14 days plac)	2 in both groups	28 days	3
Egan 1992	yes							+ TD (AIMS) for those <5 years	0	N=21 c-o (all 21)	1	12 wks	3
Shriqui 1992	yes							0 EPS (AIMS, ESRS)	n.r.	N=27, c-o (1 gr ap + vit E/ plac, 1 gr ap + plac/ vit E)	0	2 x 6 wks, 2-3 wks wo in between	3
Adler 1993	yes							+ TD (AIMS)	0	N=29 (28 ct ; 16ap + vit E, 12 ap + plac)	3; 1 not specified per gr; 2 on vit E	8-12 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
Akhtar 1993	yes							+ TD (TDRS)	0	N=32 (17 ap + vit E, 15 ap + plac)	0	4 wks	4
Dabiri 1994	yes							+ TD (AIMS)	diarrhea	N=11	1 vit E	12 wks	3
Lam 1994	yes						0 (BPRS)	0 TD (AIMS)	n.r.	N=16, c-o (1 gr ap + vit E/ plac, 1 gr ap + plac/ vit E)	4, not specified per group	2x6 wks, 2 wks wo before and in between	3
Lohr 1996	yes						0 (BPRS)	+ TD (AIMS	n.r.	N=55 (35 ct, 17 ap + vit e, 18 ap + plac)	20	2 mts	4
Dorevitch 1997	yes							0 TD (AIMS, CPK levels)	n.r.	N = 10, c-o (1 gr ap + vit E/ plac, 1 gr ap + plac/ vit E)	n.r.	2x 8 wks, 4 wks wo in between	3
Dorevitch 1997	yes						0 (BPRS)	0 TD (AIMS)	0	N=40, c-o (1 gr ap + plac/ vit E, 1 gr ap + vit E/ plac)	2 on plac	2 x 8 wks, 4 wks wo in between	3
Adler 1999	Flu, Hal, Risp						0 (BPRS, GAF)	0 TD (AIMS), akathisia (BAS), EPS (SAS)	0	N=158 (73 ap + vit E, 85 ap + plac)	22 in vit E gr, 29 in plac gr	1 year	5
Salmasi 2009	Olan							0 (insulin resistance)	n.r.	N=36 (32 ct, 15 olan + vit E, 17 olan + plac)	4, not specified per group	8 wks	3
Ginkgo biloba													
Zhou 1999	Hal	0,25 mg · kg^{-1} · day^{-1}	0 (SANS)	+ (SAPS)			+ (SOD levels)	+ (less behavioural toxicity and symptoms of nervous system)	0	N=54 (27 hal + EGb, 27 hal + plac)	n.r.	12 wks	3
Zhang 2001	Hal	0,25 mg · kg^{-1} · day^{-1}	0 (SANS)	+ (SAPS)			+ (SOD levels)	+ (less behavioural toxicity and symptoms of	n.r.	N=82 (43 hal + Egb, 39 hal + plac)	n.r.	12 wks	3

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
								nervous system)					
Zhang 2001a, 2001b, 2006	Hal	0,25 mg · kg^{-1}· day^{-1}	0 (SANS)	+ (SAPS)			0 (BPRS)	+ (better immune function, less behavioural toxicity and symptoms of nervous system)	0	N=112 (56 hal + Egb, 53 hal + plac)	1 in Egb gr, 5 in plac gr	12 wks	4
Zhang 2011	yes		0 (PANSS)	0 (PANSS)	0 (CPT-37, Stroop)			+ TD (AIMS)	0	N = 157 (78 ap + Egb, 79 ap + plac)	4 in plac gr, 1 in Egb gr	12 wks, f.u. + 6 mnts	5
Melatonin													
Shamir 2001	yes							+ TD (AIMS)	0	N = 24, c-o (22 ct, 10 ap + plac/ mel, 12 ap + mel/ plac)	2, not specified per group	2x 6 wks, 4 weeks wo in between	4
Other substances													
Multi-vitamins													
Altman 1973	yes						0 (MIBS)		0	N=151 (75 vit, 76 plac) of which 81 with schizophrenia	6 in vit gr, 13 in plac gr	6 wks	4
Vaughan 1999	yes						0 (BSI, BDI)		0	N=22 (10 ap + vit E + diet treatment, 9 ap + plac + diet challenge)	1 in plac gr, 0 in vit E gr	5 months	4
Hormones													
Prange 1979 (Protilerin)	no						+ (BPRS)		0	N=12, c-o (6 pro/niacin, 6 niac/pro)	0	2x 15 days	4
Akhondzadeh, 2003 (estradiol)	Hal		0 (PANSS)	+ (PANSS)			+ (PANSS)		n.r.	N=32 (16 estr / 16 plac)	0	8 weeks	3
Strous 2003 (dehydroepiiandrosterone	yes		+ (PANSS, SANS)	0 (PANSS)		+ (HAM-D)	+ (PANSS subscale)		n.r.	N=30 (15 DHEA, 15 plac)	3 in plac gr	6 wks	4

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
[DHEA])							+ (HAM-A)						
Nachshoni, 2005 (dehydroepiiandrosterone [DHEA])	yes						0 (BPRS)	+ Pakinsonism (SHRS)	0	N=34 (18 DHEA, 16 pla)	3 in DHEA gr, 1 in plac gr	7 days	4
Ritsner 2006 (dehydroepiiandrosterone [DHEA])	yes		+ (PANNS)	+ (PANNS)	+ (subscales of the CANTAB)	+ (PANNS subscale)	0 (QoL)	0 TD (AIMS), EPS (ESRS)	0	N=62, c-o (1 gr DHEA / plac, 1 gr plac / DHEA)	7 not specified per group	2x 6 wks	4
Strous 2007 (dehydroepiiandrosterone [DHEA])	Ola		0 (SANS)		0 (neutcogniti ve battery)			+ akathisia (BAS), EPS (SAS)		N=40 (20 DHEA, 20 plac)	4 in DHEA gr, 5 in plac ge	12 wks	4
Ko 2008 (Testosterone)	yes		+ (PANNS)	0 (PANNS)		0 (CDSS)		0 (DIEPSS)	0	N=30 (15 plac, 15 testosterone)	2 in tes gr, 2 in plac gr; +5 in tes gr at fu, + 4 in plac gr at fu	1x4 wks, 2 wks fu	4
Ritsner 2010 (dehydroepiiandrosterone [DHEA] and pregnenolone [PREG])	yes		0 for all groups (PANSS)	+ for 30mg / PREG gr 0 for 200mg PREG / 400mg DHEA gr (PANSS)	0 for all groups (CANTAB)		0 for all groups (CGI, GAF)	+ for 30mg PREG / 400mg DHEA gr 0 for 200mg PREG gr on EPS (ESRS) 0 for all groups on akathisia (BAS)	0	N=58 (16 PREG 30mg , 10 PREG 200 mg, 16 DHEA 400 mg, 16 plac)	2 in 30mg PREG gr, 4 in 200 mg PREG gr, 3 in 400 mg DHEA gr, 5 in plac gr	8 wks	5
Kulkarni, 2008 (estradiol)	yes		0 (PANSS)	= (PANSS)	= (PANSS)		+ PANSS)		n.r.	N=102 (56 estr ; 46 plac)	5 estr gr; 10 plac gr	28 days	5
Kulkarni, 2011 (estradiol)	yes		0 (PANSS)	0 (PANSS)			+ (PANSS subscale)		0	N=53 (26 estradiol, 27 plac)	0	14 days	3
Inositol													

Study[1]	Also AP?	AP dosage	Effects of natural medicine[2]						Side effects of natural medicine[2]	N, design, description of treatment / control group	Drop-out	Duration of study (and follow-up, if applicable)	Jadad Score
			Negative sx	Positive sx	Cognition	Depression	General psychopatho-logy	Adverse side effects AP					
Levine 1994	yes		0 (PANNS)	0 (PANNS)					n.r.	N=14 (12 ct ; 7 ap + inositol/ plac, 5 ap + plac/ inositol)	2, not specified per group	2x 4 wks, no wo	3
Gamma-Hydroxybutyrate (GHB)													
Schulz 1981	n.r.						0 (BPRS)		0	N=7 (all patients plac / GHB / plac)	0	10-29 days	3
Levy 1983	Flu	5 mg / d					0 (BPRS, CGI)		No SAEs, 1 a-symptomatic bradycardia	N=11, c-o (1 gr GHB / chl hy, 1 grchl hy / GHB)	1 on plac	2x 3 wks	3
Des-Tyr-Gamma-endorphin													
Verhoeven 1979	yes			+ (psychotic symptoms rating scale)			+ (contact, e-motional res-ponsiveness)		0	N=6, c-o (3 ap +DTGe/plac, 3 ap+plac/DTGe)	0	2x 8 days, 6 wks fu	4

[1] Classified per agent, in order of year of publication

[2] Scoring of effects: + = positive effect, - = negative effect, 0 = no effect.

A, acetazolamide; AA, arachidonic acid; ABA, Alternative Neliefs Assessment; am, ayurvedic medicine; AP, antipsychotics; ari, aripriprazole; ARSNS, Andreasen's Rating Scale of Negative Symptoms; AT, Ayurvedic treatment; BAS, Barnes Akathisia Scale; BDI, Behaviour Disturbance Inventory; BMI, body mass index; BMT, bromocriptine; BSI, Brief Symptom Inventory; CANTAB, Cambridge Automated Neuropsychological Test Battery; CAT, catalase; CDSS, Calgary Depression Scale for Schizophrenia; CFD, Complex Figure Drawing; CGI, clinical global impression scale; chl hy, chloral hydrate; Cloz, Clozapine; CP, Chlorpromazin; CPK, serum creatine phosphokinase; CPRS, Comprehensive Psychopathological Rating Scale; c-o, CPT, Continuous Performance Test; c-o, cross-over; contr, control (group); crt, choice reaction time ; ct, completed treatment; d-a, d-alanine; d-b, double-blind; d-c, d-cycloserine; DHA, docosahexaenoic acid; DIEPSS, Drug-Induced Extrapyramidal Symptoms Scale; d-o, drop-out; DS, Digit Span; d-s, d-serine; DTGe, Des-Tyr-Gamma-endorphin; ECT, electroconvulsive therapy; E-E, ethyl-eicosapoentaeonate; E-EPA, ethyl-eicosapentaenoic acid; Egb, extract of gingko biloba; EPA, eicosapentaenoic acid; EPS. extrapyramidal symptoms; ESRS, Extrapyramidal Rating Scale; exp, experimental (group); FBS, fasting blood sugar; Flu, Fluphenazine; f-u, follow-up; GAS, galactorrhea amenorrhea syndrome; glyc, glycerine; GPX, glutathione peroxidase; gr, group; gt, genotype; Hal, Haloperidol; Ham-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; HOD, Hoffer-Osmond Diagnostic; HOMA-IR, homeostatic model assessment of insulin resistance; inj, injection; LUNSERS, Liverpool University Neuroleptic side Effects Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; MDA, malondiadehyde; mel, melatonine; mian, mianserin; MIBS, Inpatient behaviour form; MMN, mismatch negativity; MMPI, Minnesota multiphasic personality inventory; MMSE, mini-mental state examination; Mol, molindone; MPQ, multiphasic questionnaire; mts, months; mWAIS, Modifi8ed Chinese version of the Wechsler Adult Intelligence Scale; na, nicotinamide; NAC, N-Acetylcysteine; NAD, nicotinamide adenine dinucleotide; NIA, neuroleptic induced acathasia; niac, niacinamide; nic, nicotinic acid; NIP, neuroleptic induced Parkinsonism; NOSIE, Nurses Observation Scale for Inpatient Evaluation; NPT, neuro psychological test; n.r., not reported; Olan, Olanzapine; p-c, placebo controlled; PGD, Peony-Glycyrrhiza Decoction; plac, placebo; pro, protirelin; PRT-BT, Probability Reasoning Task – Bead Task; prv, post-randomization visit; PSYRATS, Psychotic Symptom Rating Scales; pyr, pyridoxine; Quet, Quetiapine; QoL. Quality of life; RAVLT, Rey Auditory Verbal Learning Test; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; Ris, Risperidone; RNRS, Rutgers Nurses's Rating Scale; RRSP, Rockland's Rating Scale for Psychotics; RSESE, Rating Scale for Extrapyramidal Side Effects; SAE, spiral after effect; SAEs, serious adverse events; SAPS, Scale for the Assessment of Positive Symptoms; sar, sarcosine; sars, sarsasapogenin; SAS, Simpson-Angus Scale; s-b, single-blind; SDSS, social disability screening schedule; SFBT, Sequin Form Biard Test; SHRS, St. Hans Rating Scale; SIRP, Sternberg's item recognition test; SOD, superoxide dismutase; SOFAS, Social and Occupational Functioning Assessment Scale; srt, simple reaction time; SOPS, Scale of Psychosis-risk Symptoms; SSTMSP, Sternberg Short Term Memory Scanning Paradigm; sx, symptoms; T, thiamine; TBARS, thiobarbituric acid reactive substances; TD, tardive dyskinesia; TDRS, Tardive Dyskenesia Rating Scale; tes, testosterone; Trif, Trifluperazine; vit, vitamin; vlmr, verbal learning and memory functions; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test; WISC, Wechsler Intelligense Scale for Children; wks, weeks; WMS, Wechsler Memory Scale; wo, washout; WPRS, Wittenborn Psychiatric Rating Scale; YGS, yi-gan san; Zipr, Ziprasidone;

When 'Also AP?' is answered with 'yes', then the subjects used different types of AP; when 1 AP is mentioned, then all used that one.

- Vitamin B3 can be administered in the form of Niacin, Nicotinic acid or Nicotinamide.
- Full NDMA (N-methyl D-aspartate agonisten): glycine, D-serine; partial: D-cycloserine (D-alanine is endogenous agonist).
- Glycine transporter inhibitor (Gly-T1): sarcosine, also called N-methylglycine.

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Chapter 6

Temporal dynamics of symptom and treatment variables in a lifestyle-oriented approach to anxiety disorder: a single-subject time-series analysis

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Abstract

Background:
Although there is increasing evidence for the positive effects of a healthy lifestyle on mental health, most studies only take into account a single lifestyle factor, ignore the possibility of bidirectional causality, and focus on average group results.

Methods:
In the present single-subject study we used time-series analysis to unravel the dynamic interplay between symptom and treatment variables in a multi-component treatment of anxiety disorder. Main treatment variables were two lifestyle factors (physical activity and relaxation).

Results:
The patient in this study recovered completely. Multivariate time-series analysis revealed an intricate pattern of dynamic relationships between symptom and treatment variables. Relaxation was predictive of symptom reduction but physical activity surprisingly worsened the symptoms. Changes in energy predicted changes in anxiety. Evidence for bidirectional causality was present as well, with changes in relaxation predicting changes in energy and vice versa, indicating a positive feedback loop.

Conclusions:
This type of research is useful for gaining insight into the causal mechanisms underlying the effects of a healthy lifestyle on mental health.

Introduction

There is increasing interest in, and evidence for, the beneficial effects of a healthy lifestyle, including diet, activity and relaxation, on mental health (Walsh, 2011). A strong relationship has been found, for example, between physical activity and mental health, in population-based as well as intervention studies (Morgan, 1997; Biddle et al., 2000; Penedo & Dahn, 2005; Pisinger et al., 2009). Most evidence for the beneficial effects of activity has been found in patients with depressive disorder (Craft & Landers, 1998; Lawlor & Hopker, 2001; Mead et al., 2009), although some effects in anxiety (O'Connor et al., 2000), and other psychiatric disorders (Gorczynsky & Faulkner, 2010) have been found as well. Relaxation practices like yoga, meditation, guided imagery, breathing, and progressive muscle relaxation have also been associated with improved psychological well-being, including reduced feelings of anxiety (Eppley et al., 1989; Bindeman et al., 1991; Beck et al., 1994; Conrad & Roth 2007; Grossman et al., 2007; Craigie et al., 2008; Lolak et al., 2008; Brown & Gerbarg, 2009; Chiesa & Seretti, 2010; Walsh, 2011).

An important limitation of this research is that different lifestyle behaviors are usually studied in isolation. There are to our knowledge no studies on multiple-component approaches of improving health-related behavior in psychiatric patients, and thus no studies that have investigated how different lifestyle behaviors interact in producing health gains. This may be important, as different health-related behaviors may reinforce or counteract each other. A second problem is that in most studies only unidirectional effects have been studied, i.e. how lifestyle behaviors affect mental health. The possibility of reverse causality, i.e. that psychological symptoms influence the readiness to engage in health-related behaviors, is rarely accounted for. Moreover, conventional studies generally show treatment effects at the group level, while at the individual level great differences in efficacy or effectiveness exist. Finally, little is known about the causal mechanisms by which lifestyle 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; Molenaar & Campbell, 2009).

The present study is an attempt to address the above issues. We investigate the temporal relationships between health-related behaviors and symptoms of psychological distress in a patient receiving a multi-component treatment for anxiety disorder. Our aim is to unravel the dynamic interplay between lifestyle behaviors and outcomes using a single-subject time-series approach. In this approach, multiple repeated measurements are assessed within a single individual and idiosyncratic series are analyzed by means of time-series analysis (Lütkepohl, 2006; Brandt & Williams, 2007). Capitalizing on the power of the multitude of repeated measurements, such studies can give a detailed and person-tailored account of the dynamic relationships between several variables and the temporal order and reciprocity of their effects, therewith greatly enhancing the potential to draw causal inferences (Hilliard, 1993; Molenaar, 2004; Barlow & Nock, 2009).

Methods

Participant
The participant (called "Alex" in this paper) was a 56-year-old man with a 25-year history of recurrent episodes of anxiety, well controlled by 40 mg of paroxetine (a selective serotonin reuptake inhibitor; SSRI), at the cost of substantial side effects (impotence, 10 kg weight gain and heavy sweating). Because of these side effects, Alex had tapered his use of paroxetine successfully in 2006 with the aid of his therapist (RH, the first author). In the fall of 2008 he was readmitted to our outpatient center[1], because of a relapse of anxiety after accepting a job for the first time in many years. He had been unemployed for 2 years because of his symptoms and because his wife had died of breast cancer, after which he had to take full parental responsibility for his 4 daughters aged 10 to 18. Just before his readmission he was told that his oldest daughter carries the same breast cancer gene as his wife. He experienced a general feeling of anxiety and fear, and mild depressive symptoms but no specific phobias or panic attacks. He also had many physical symptoms like fatigue, low energy and nausea. The clinical diagnosis did not fulfill the criteria for any specific anxiety disorder. Anxiety Disorder NOS and cluster C personality traits (DSM-IV; American Psychiatric Association, 2000) were diagnosed by RH.

Study design
The study had a naturalistic design; the treatment followed the regular course of treatment as given at the center. Alex recorded symptom and treatment variables on a daily basis by means of a self-report registration form. These recordings were part of the lifestyle intervention. Daily completion of the registration form started as soon as the treatment started, on October 23, 2008, after the intake interview. Alex continued his recordings until June 15, 2009 resulting in a series of 236 assessment points. After termination of the therapy Alex gave his informed consent for the use of his data for research and publication.

Treatment
The treatment was explicitly multifactorial. A biopsychosocial approach was adopted, in which lifestyle interventions and psychiatric counseling were combined with selected psychotropic medication or nutritional supplements (Hoenders et al., 2010). The treatment started with lifestyle interventions targeting relaxation and physical activity. After identifying the most prominent symptoms (low energy and anxiety), Alex was instructed to score the intensity of these symptoms daily, together with the time spent on relaxation practices and physical activity. This was done because results of behavioral interventions are known to improve when patients keep track of their own behaviors and get feedback on them from their therapist. Daily self-monitoring enhances self-observation and control, which in turn may foster responsibility and motivation for treatment (Quenter et al., 2002). Alex did not want to start again with regular medication because of the side effects. Therefore, RH suggested inositol, a naturally occurring compound that is a member of the B-vitamin family. There is evidence for its effectiveness in anxiety-related disorders and depression (Belmaker & Levine, 2008). The effective dosage is 12-18 g (Settle, 2007). In the second half of the study period Alex switched to paroxetine again, for reasons that will be addressed in the Results section. Paroxetine is registered for

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treating depression and anxiety-related disorders. The recommended dosage of paroxetine is 20-60 mg.

During the entire study period, Alex and RH had regular therapy contacts. They had 17 contacts in total, varying in duration from 5 to 50 minutes (mean = 33 min). During these contacts Alex and RH discussed his registration and RH advised and commented on them, reinforcing healthy lifestyle changes. He further employed an eclectic supportive psychotherapeutic approach, focusing on unconditional positive regard, adjusting to Alex's needs and preferences and helping him to regain a sense of control. RH consistently endorsed Alex's initiatives and decisions regarding his own treatment (for instance his initiative to adjust RH's general lifestyle advice to his personal situation and his wish to be medicated with 'natural medicines'), to strengthen the therapeutic relationship and Alex's sense of self-management.

Assessment

The study variables were assessed daily by means of a registration form. The form consisted of 7 columns, two in which Alex recorded his daily levels of energy and anxiety (range 0-10), two for registering the type of relaxation practices and physical activity, and two for the time he spent on it (in minutes). In the seventh column Alex could mark special events. The Energy score refers to the patient's morning energy level, because the morning was the time of day Alex could estimate this level most accurately. The Anxiety score refers to the average anxiety level experienced during the day. The Relaxation score denotes the time spent on relaxation-related techniques like yoga and mediation. The Activity score denotes the time spent on physical activities including walking, gardening and household activities.

Statistical analysis

The statistical analyses were done by one of the authors (EB), who was blinded to treatment outcomes. Univariate time series were investigated using time-series regression analysis, to examine trends over time (Ostrom, 1990). Time-series regression accounts for the fact that repeated observations tend to be serially correlated (autocorrelation) by fitting autoregressive moving average (ARMA) models to the residuals. To investigate the dynamic relationships between the different variables, we used Vector Auto Regressive modeling (VAR) (Lütkepohl, 2006; Brandt & Williams, 2007). VAR was originally developed by Sims (1980) in econometrics and since then has also been used in fields like meteorology, sociology, political science, and neuroimaging. In the field of psychiatry, VAR has only been used occasionally (e.g., Dugas et al., 2009). An attractive feature of VAR is its ability to investigate bidirectional influences between variables without having to make a priori assumptions about the direction of the effects. By separating the dynamic part of the model (the relationships between the lagged values of the variables) from the simultaneous part (the relationships between the contemporaneous values), the model allows to make inferences about the temporal order of the effects and thus about causality (Brandt & Williams, 2007). A further advantage is that VAR allows for feedback effects and for indirect links between variables, i.e. that the effect of one variable on another runs via a third variable. This makes the VAR approach very suitable for studying mechanisms of change.

A VAR model is a multivariate autoregressive model that consists of a set of unrestricted regression equations for a system of two or more variables (Brandt & Williams, 2007). All variables in the system are treated as endogenous, which means

that they can be both determinant and outcome. Each of the endogenous variables is regressed on its own lagged values and the lagged values of the other variables. The error terms, called innovations or shocks, should be serially uncorrelated but can be contemporaneously correlated. In VAR, the coefficients in the regression equation cannot be interpreted individually, because they are part of a system in which all elements are dynamically related to each other. Therefore, VAR is usually accompanied by the techniques of Granger causality testing, impulse response analysis and forecast error variance decomposition, which give an indication of the system's dynamic behavior (Brandt & Williams, 2007).

In the present study, a 4-variable VAR was used, modeling the temporal dynamics of Energy, Anxiety, Relaxation and Activity. To account for the potential effects of inositol and paroxetine, we added two control variables denoting the dosages of these drugs to the model. These control variables were considered exogenous to the system (which means that they may influence the system but cannot themselves be influenced by the system). A variable denoting the treatment contacts (0/1) was also included as an exogenous variable, but as it did not contribute significantly to the model it was removed from the final model. After estimation of the VAR, we examined whether the coefficients of some parameters could be constrained (set to 0; Lütkepohl, 2006). The VAR was re-estimated after placing each constraint. Parameters with the lowest t-values were constraint first. The procedure was continued until a p-value of 0.300 was reached. We checked whether the final VAR model was correctly specified using diagnostic tests on stability and residual autocorrelation (Lütkepohl, 2006). A two-tailed alpha level of 0.05 was used to determine statistical significance. Bootstrapped 95% confidence intervals were used for the error bands of the impulse response functions (Lütkepohl, 2006). Analyses were performed in STATA 11.

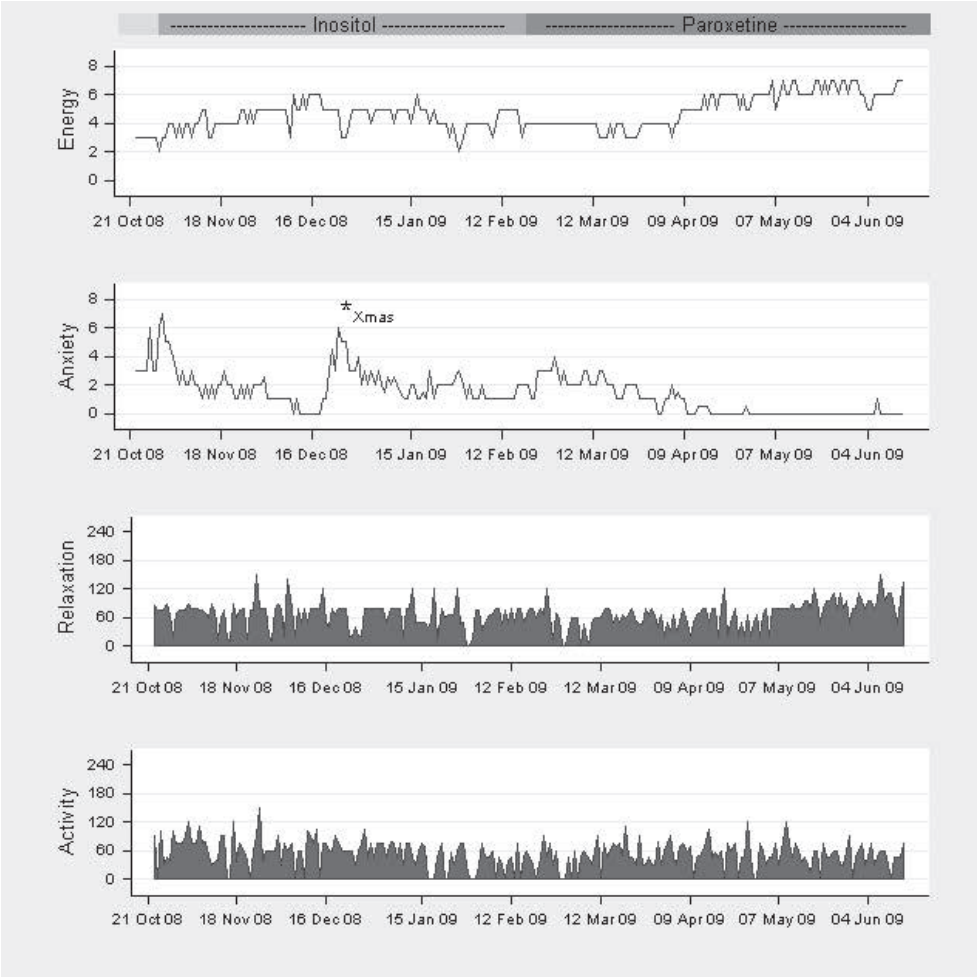
Results

Figure 1 shows the time series of daily energy and anxiety levels, and the time spent on relaxation practices and physical activity. Alex completed the registration form every single day, yielding a unique series of 236 consecutive daily observations with no missing values. He engaged in relaxation practices and physical activities almost every day (see Figure 1). The relaxation practices he recorded most often were yoga and meditation. Occasionally, he recorded massage and singing in a Russian choir. The physical activities he recorded were walking, gardening, housekeeping, and swimming. Walking was the activity he registered most often. The average daily time spent on Relaxation during the study period was 66 minutes (SD = 28, range 0-150). The average time spent on Activity was 52 minutes (SD = 30, range 0-150). Energy scores ranged from 2 to 7 (mean = 4.72, SD = 1.15). Anxiety scores were between 0 and 7 (mean = 1.42, SD = 1.36).

After a baseline phase of 8 days Alex started to use 2 g inositol, increasing the dosage to 4 g after another 8 days. After 90 days, he lowered the dosage to 2 g and stopped inositol intake two weeks thereafter. Alex did not come near the supposed efficacy threshold (10-12 g) for inositol at any moment during the study period. He did not suffer from any side effects but decided to stop because he regarded the effect, though present, as too slow and too weak, and now felt more confident to try paroxetine again because of previous success. The prospect of suffering the side effect of impotence was less problematic for him at this time because his girlfriend

had ended their relationship and he did not feel like engaging a new one in the near future. Alex started with 10 mg paroxetine 2 days after he stopped using inositol, gradually increasing the dosage to 40 mg in 4.5 weeks. He continued to take 40 mg paroxetine until the end of the study period.

Figure 1. Daily ratings of Energy and Anxiety (range 0-10), and Relaxation and Activity (minutes) from October 23, 2008 until June 15, 2009 (236 days). The bar at the top of the graph shows the period in which the participant used inositol and paroxetine.



On Christmas Day, Alex started to add alprazolam to his medication, at his own initiative. Alprazolam is a benzodiazepine that is used as an anxiolytic. Alex used this drug before and had some leftover. He discussed this initiative with his therapist, who accepted it because this medicine is appropriate for short-term use in anxiety.

Moreover, endorsing Alex's initiatives was in line with the supportive treatment approach and the intention to help Alex regaining a sense of self-determination and control. During the next 3 months, Alex took 1 to 3 tablets of 0.25 mg alprazolam on days he felt the need to do so. He recorded his use of the drug on the registration form. He used alprazolam on 38 days in total. Most often he used 1 tablet; sometimes he used 2 or 3 tablets. Since an effect on Energy and Anxiety can be expected from taking this drug, a variable denoting the number of alprazolam tablets was added to the VAR model as a control variable. We also included the first lag of this variable to account for possible lagged anxiolitic effects.

Special events
According to the registration form, the days around Christmas had been very burdening, leading to a sharp increase in anxiety symptoms (see Figure 1). Alex told his therapist that he had had a major crisis during these days as a result of a coincidence of stressful events: getting back to work, worries concerning his daughters, and the Christmas period with its many social happenings bringing back memories of his deceased wife. To control for possible confounding effects due to this unusual time of the year, we included a dummy variable denoting the Christmas period (coded '1' for the 10 days around Christmas and '0' otherwise) as an exogenous variable to the VAR model.

Course of symptom and treatment variables
We first examined overall trends in the four time series over the whole study period. As can be seen in Figure 1, the Energy scores showed a gradually increasing trend over time, while the Anxiety scores gradually decreased, the Christmas period being a major exception. We examined whether these trends were significant using time-series regression analysis, modeling a linear trend. As the Energy and Anxiety series showed heteroscedasticity (nonstationary variances), we used the natural logs of these variables to stabilize the variances (Brandt & Williams, 2007). The linear trend was significant in the models for Energy (B = 0.002, p = 0.005), Anxiety (B = -0.006, p = 0.000) and Activity (B = -0.071, p = 0.013). Thus, Alex showed a significant increase in Energy and a significant decrease in Anxiety over time, while his Activity levels gradually diminished during the study period. This overall pattern of symptom relief was in line with RH's clinical impression and Alex's own experience of gradual recovery.

Estimation of the VAR
We determined how many time lags were needed in the VAR model (a "lag" denotes the time interval between a value and a previous value). In VAR, the optimal lag length can be found using lag-length selection criteria[2] (Lütkepohl, 2006). Most of these criteria suggested an optimum lag length of 2, some suggested including 1 lag. We tested both a 1- and a 2-lag VAR, but as the former showed considerable residual autocorrelation, we proceeded with the 2-lag model.

Next, the VAR with 2 lags was estimated. Table 1 presents the final VAR model in which the 4 endogenous variables (Energy, Anxiety, Relaxation, Activity) were modeled as a function of their own previous values (lags 1 and 2), the previous values of the other endogenous variables, and the control variables. As can be seen

[2] Likelihood Ratio test, Final Prediction Error, Akaike Information Criterion; Hannan-Quinn Information Criterion, and Schwarz Bayesian Information Criterion.

in the table, both the Energy and Anxiety series showed important positive autocorrelation: the first and second lags of these variables significantly predicted their own current values. Some positive autocorrelation was also detected in the Relaxation series. The Activity series did not show significant autocorrelation. Besides these autoregressive effects the variables showed some lagged correlations with each other. The second lag of Energy was related to current Anxiety scores: higher levels of Energy were followed by lower levels of Anxiety two days later. A trend for the reverse effect was also present, with increases in Anxiety being related to decreases in Energy the next day. Lagged values of Relaxation were positively related to Energy and negatively to Anxiety; the more time Alex engaged in Relaxation, the higher his Energy and the lower his Anxiety levels the next day. A reverse effect from Energy to Relaxation was present as well: higher Energy levels were followed by more time spent on Relaxation the next day. Lagged values of Activity were also associated with Energy and Anxiety. The nature of these relationships, however, was contrary to what we had expected; higher levels of Activity were related to *lower* Energy and *higher* Anxiety levels the next day.

Table 1. VAR estimates for the 2-lag model

	Dependent Variables			
	Energy	*Anxiety*	*Relaxation*	*Activity*
Variable	*Coefficient*	*Coefficient*	*Coefficient*	*Coefficient*
Energy (lag 1)	0.426***	0	0.455***	0
Energy(lag 2)	0.215***	-0.226*	0	0
Anxiety(lag 1)	-0.049˜	0.433***	0	0
Anxiety(lag 2)	0	0.240***	0	0
Relaxation(lag 1)	0.035*	-0.060˜	0.154*	0
Relaxation(lag 2)	0	0	0	0
Activity(lag 1)	-0.038*	0.064*	0	0.067
Activity(lag 2)	0	0	0	0
Control variables				
Inositol	0.019*	-0.048**	0	0
Paroxetine	0.003*	-0.009***	0	0
Alprazolam	-0.044*	0.142***	-0.129*	-0.132*
Alprazolam(lag 1)	0.022	-0.111***	0	0
Christmas	0.053	0.281***	0	0.235
R^2	0.72	0.85	0.14	0.04

Note. Energy and Anxiety are natural log-transformed variables. Relaxation and Activity are scaled in hours. Coefficients denoted with 0 are constraint parameters. Control variables are exogenous to the system. Number of observations = 234. ˜p < 0.10, *p < 0.05, **p < 0.01, ***p < 0.001.

Inositol and paroxetine were significantly related to Energy and Anxiety as well. Higher dosages of inositol and paroxetine were associated with more Energy and less Anxiety. Alprazolam was related to all 4 endogenous variables. More alprazolam tablets were taken on days with less Energy and more Anxiety, and taking this drug went along with reduced levels of Relaxation and Activity. The presumed anxiolitic effect of this benzodiazepine could be observed the day after; the first lag of alprazolam was negatively related to Anxiety. Finally, a strong relationship was found between the Christmas period and Anxiety.

Granger causality

In time-series analysis, the temporal ordering of events can be used to empirically distinguish between leading and lagging variables. This distinction is the basis of a definition of causality called 'Granger causality' (Granger, 1969). A variable X 'Granger causes' Y if past values of X improve the prediction of Y (beyond past values of Y and other variables in the system) (Lütkepohl, 2006). We performed Granger tests to investigate whether there was Granger causality present in our system. Table 2 shows the results of these tests. The table shows that the relationship between Relaxation and Energy was bidirectional: past Relaxation levels predicted current Energy scores (p = 0.035), but also the reverse was true (p = 0.002). Past Relaxation levels also tended to predict current Anxiety scores (p = 0.062). Past Energy levels predicted current Anxiety scores (p = 0.039), and a trend for the reverse effect, from Anxiety to Energy, was present as well (p = 0.072). Activity influenced both Energy and Anxiety (p = 0.011 and 0.031), but was not itself affected by any of the other variables. Thus, Activity was exogenous to the system.

Table 2. Granger causality tests

Hypothesis	χ^2	p
Relaxation → Energy	4.46	0.035
Activity → Energy	6.43	0.011
Anxiety → Energy	3.25	0.072
Energy → Anxiety	4.27	0.039
Activity → Anxiety	4.65	0.031
Relaxation → Anxiety	3.49	0.062
Energy → Relaxation	9.19	0.002
Anxiety → Relaxation	-	
Activity → Relaxation	-	
Energy → Activity	-	
Anxiety → Activity	-	
Relaxation → Activity	-	

Note. Tests denoted with (-) were not performed because the parameters involved were constrained. A significant χ^2-value implies that the first variable "Granger causes" the second variable. Thus, the first variable is considered to have causal impact on the second variable (whether the impact is positive or negative cannot be derived from this table, but becomes clear from the sign of the estimates in Table 1 and the form the impulse response functions below).

Contemporaneous correlations

We subsequently calculated the contemporaneous correlations between the endogenous variables, using the residuals of the VAR model (Brandt & Williams, 2007). These correlations represent the immediate relationships between the variables, i.e. on the measurement days itself. Table 3 shows that the highest contemporaneous correlation was between Energy and Anxiety; these variables were negatively correlated with each other (r = -0.338). The other correlations were positive but small.

Table 3. Contemporaneous correlations

	Energy	Anxiety	Relaxation	Activity
Energy	-			
Anxiety	-0.338	-		
Relaxation	0.109	0.059	-	
Activity	0.077	0.116	0.120	-

Impulse Response Functions

The regression coefficients of a VAR can only be interpreted as part of a system of variables that are dynamically related to each other. Impulse Response Functions (IRFs) allow tracing out the dynamic impacts of changes in each of the endogenous variables over time. They do so by visualizing the impact of an isolated shock in one of the variables to the other variables, thus showing how these innovations are propagated through the system. IRFs only take into account the time-lagged relationships between the endogenous variables. Orthogonalized Impulse Response Functions (OIRFs) are variants of IRFs that take into account the contemporaneous correlations between the variables as well (see Brandt & Williams, 2007). OIRFs assume that a specific ordering is chosen for the direction of the contemporaneous relationships. If no theory is available guiding this choice, the results of alternative orderings can be presented. The critical point in VAR is that the decision about this ordering can be made explicit and can be evaluated after accounting for the dynamics in the data (Brandt & Williams, 2007). In the present study, we know that the Energy scores refer to Alex's morning energy levels and the Anxiety scores to his average anxiety level during the day. We further know that Alex did his relaxation practices generally at earlier times of the day than his activities. Thus, a reasonable ordering for the innovations in the variables within the same day is that changes in Energy precede changes in Anxiety, which precede changes in Relaxation, which precede changes in Activity. This is the ordering of our first choice (Order 1: Energy–Anxiety–Relaxation–Activity). We investigated alternative orderings as well.

Figure 2 shows the OIRFs for Order 1. The upper row shows the impact of a shock in Energy. The first graph of this row shows the response of Energy to its own shock. This response is positive and persists over many days, slowly decaying to 0 after about 10 days. The same pattern of strong persistence can be seen in the response of Anxiety to the Energy shock (2nd graph of 1st row). We see a significant direct decrease in Anxiety that slowly diminishes during the following days. The next two graphs show that a shock in Energy also results in a direct increase in Relaxation and Activity. This effect is not significant for Activity, but becomes significant after 1 day for Relaxation. The latter effect decays slowly to 0 after 1 week.

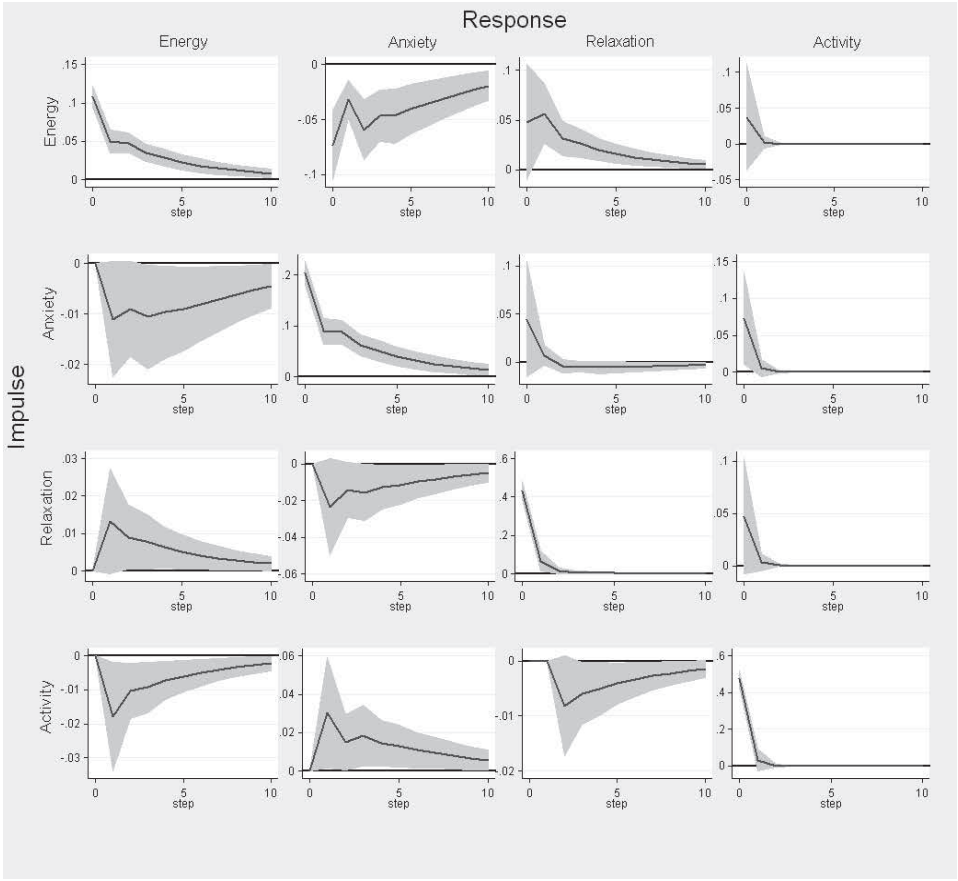
The second row shows the impact of a shock in Anxiety. An increase in Anxiety is followed by a decrease in Energy the next day, which becomes significant after 3 days and persists over several days. Strong persistence can also be seen in the response of Anxiety to a shock to itself. We further see that the Anxiety shock has a positive impact on Relaxation and Activity, but this effect is short in duration and only significant for Activity. Thus, on anxious days, the participant spent more time than average on physical activities.

The third row shows the impact of a shock in Relaxation. The responses of Energy and Anxiety to this shock are initially 0, which is a natural result of the chosen ordering in which changes in Relaxation follow after changes in Energy and Anxiety within the same day. The impact of the shock in Relaxation becomes visible after 1

day, when an increase in Energy and a decrease in Anxiety can be observed. These effects become significant later, as the confidence intervals become smaller. Both effects persist during the next days, slowly dying out after about 10 days. The response of Relaxation to a shock to itself is short in duration and disappears after 2 days. The response of Activity to the Relaxation shock is not significant.

The lowest row shows the impact of a shock in Activity. An innovation in Activity leads to a decrease in Energy and an increase in Anxiety the next day. Also these effects gradually taper off to 0 after several days. The Activity shock further leads to a delayed decrease in Relaxation. This must be an indirect effect, as the Activity parameters in the VAR equation for Relaxation were both set to 0 because they did not contribute significantly to the model. Presumably, this effect runs via reductions in Energy. Finally, there is no persistence in the response of Activity to its own shock after the first day.

Figure 2. Orthogonalized Impulse Response Functions for a 4-variable VAR with 95% bootstrapped error bands. Responses are considered significant if their error bands do not include 0. Energy and Anxiety are natural log-transformed variables. Relaxation and Activity are scaled in hours. Order 1: Energy–Anxiety–Relaxation–Activity. Responses are plotted over a 10-day horizon.



Cumulative Impulse Response Functions
The accumulated impact of a shock over time is calculated by computing Cumulative Orthogonalized Impulse Response Functions (COIRFs). The results showed that an isolated one-time shock of 1 SD in the natural logs of Energy (corresponding to a 10% increase in Energy) results in a total reduction in Anxiety of 44% over 10 days. The same Energy shock leads to a total increase in Relaxation of about ¼ hour over that period. The response of Activity to the Energy shock is negligible. A shock of 1 SD in Relaxation (about ½ an hour) leads to a total increase in Energy of 6% and a total decrease in Anxiety of 11% over 10 days. A similar shock in Activity on the other hand results in a total *decrease* in Energy of 7% and a total *increase* in Anxiety of 13% over the same period.

Alternative orderings
We also considered OIRFs for alternative orderings of the contemporaneous correlations. The results appeared to be rather robust to different orderings. The main differences resulted from converting Energy and Anxiety in the ordering, which is not surprising because these two variables showed the largest contemporaneous correlation. However, these differences did not change the results in a fundamental way.

Discussion

This study aimed to unravel the dynamic relationships between psychological symptoms and the health-related behaviors intended to improve these symptoms. These relationships turned out to be characterized by bidirectionality, lagged influences, indirect effects, and feedback loops, both between symptoms and behaviors as well as among them. The present time-series design with its many data points enabled us to disentangle these complex effects. These would have gone unnoticed in conventional group studies, as the small number of measurements and the aggregation of data across individuals in such studies obscures relevant information on the dynamic interdependencies between variables (Hilliard, 1993; Molenaar & Campbell, 2009; Dugas et al., 2009).

The results showed that this patient's symptoms and behavior were interrelated in an intricate way. One important finding was that energy and relaxation mutually reinforced each other. Changes in relaxation tend to be followed by changes in energy, but also the other way around. Furthermore, both energy and relaxation were predictive of anxiety. Anxiety in turn was predictive of energy, particularly in the longer run. This suggests an intricate system of indirect effects and positive feedback loops, which may form a target for initiating a positive spiral. Once initiated, such a spiral may bring about a cascade of small but relevant increments in healthy behaviors and reductions of symptoms. It is precisely this potential cascade effect that makes the results meaningful. Although the isolated effects of changes in individual variables may be small, the eventual effects can be large because of the way these changes propagate through the system and mutually reinforce each other. Moreover, in daily life changes are often not isolated and once only but occur in concert and more frequently.

The effect of relaxation on anxiety seemed to be a delayed one. The present-day correlation between relaxation and anxiety was low and the effect after 1

day was not yet significant. The OIRF showed a significant favorable effect of relaxation on anxiety only after a few days. This suggests that the direct effects of relaxation on anxiety are small in this patient, but that the indirect effects, presumably via increments in energy, are larger. A more immediate connection seemed to exist between energy and anxiety. The contemporaneous correlation between these symptoms was moderately large. Furthermore, past energy levels influenced current anxiety scores and also a trend for the reverse effect was present. So, energy and anxiety seemed to mutually reinforce each other.

A striking result was that activity seemed to *worsen* the patient's symptoms. Increases in activity were followed by decreases in energy and increases in anxiety. The results further showed that activity had a negative effect on relaxation. These findings could possibly have large implications for everyone promoting lifestyle behavior for (mental) health and assuming that all 'healthy behavior' is healthy for anyone. This might not be the case. In this patient exercise was not beneficial, at least not in the short run. Maybe Alex did his activities in the wrong way, for example by not respecting his limits. That might have stirred up an already overactive stress response system. In several mental disorders including anxiety, the stress response systems (the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS)) are hyperactive (Wolkowitz, 2001; Mantella et al., 2008). Prolonged or excessive activation of these systems can lead to excessive anxiety and fatigue (McEwen, 2000; Wolkowitz, 2001; Heim et al., 2000). Anxiety and fatigue (lack of energy) were Alex's two main problems. Exercise represents a physical stressor that activates the stress response systems (McEwen, 2008; Mastorakos, 2005). Whereas sustained physical conditioning is associated with a decreased stress response to exercise, in untrained individuals or when applied inappropriately the response is relatively high (Howlett, 1987; Mastorakos, 2005).

Interestingly, relaxation practices such as yoga and meditation are known to do the opposite. They down-regulate the stress response systems (Astin, 1997; Brown & Gerbarg, 2009; Chiesa & Serreti, 2010), stimulate a relaxation response by increasing parasympathetic nervous system activity (Hoffman et al., 1982; Innes et al., 2005; Benson, 2009), and improve subjective measures of fatigue (Brown & Gerbarg, 2009). Possibly, in some circumstances or in some type of individuals, relaxation practices are more beneficial than exercise. Similar evidence has been reported by some other authors (Ross & Thomas, 2010; Streeter et al., 2010). By down-regulating the stress response systems, relaxation practices may create a window of opportunity for dynamic interactions to instigate a positive feedback loop that advances recovery.

Inositol as well as paroxetine had positive effects, decreasing anxiety and increasing energy. The design, however, did not allow drawing any conclusions about the effectiveness of these drugs, as there was no good control (baseline period too short, no predefined intake schedule, and too little variation in dose). There are some strong experimental designs for testing the effectiveness of treatments in single subjects (e.g., Guyatt et al., 1986; Ottenbacher, 2001), but these were not applied here.

According to RH's clinical impression, another important factor in Alex's recovery was the promotion of his sense of control. Yoga and meditation are thought to be beneficial not only because of their relaxing effects, but also because they cultivate feelings of self-regulation and control (Astin, 1997; Shapiro et al., 2006). Further, during the treatment sessions RH consistently endorsed Alex's initiatives and decisions regarding his own treatment, which seemed to have strengthened the

therapeutic relationship and Alex's self-efficacy. Research has shown that treatment is most effective when patients are actively involved in treatment decisions (e.g., Nikles et al., 2005; Ryan & Deci, 2008) and when therapists and interventions are matched to the patient's worldview, preferences, and motives (Prochaska et al., 1992; Rothwell et al., 2007). Also evidence-based medicine (EBM) defines patient preference as one of three pillars in decision making (Sackett et al., 2000).

The most important limitation of this study is that the results cannot be generalized to a larger patient population because we used a single-subject design. Broader generalization can be established by systematic replication, gradually expanding the population to patients with different profiles (Hilliard, 1993; Ottenbacher, 2001). It should be noted however that generalization of group-averaged results to individuals, as is implicitly done in nomothetic research designs, is often not justified (Molenaar, 2004). The study has also several strong features, including its naturalistic design, the high-intensity data set, and the innovative analytic techniques, which allowed us to catch sight of the intricate dynamic processes involved in psychophysiology and behavior. We feel this kind of research may be useful for improving our understanding of the complex mechanisms underlying the effects of a healthy lifestyle on mental health and individual differences therein, and may prove valuable for identifying the critical elements of the psychotherapeutic process.

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Chapter 7

Pitfalls in the assessment, analysis, and interpretation of routine outcome monitoring (ROM) data; results from an outpatient clinic for integrative mental health

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Abstract

There is considerable debate about routine outcome monitoring (ROM) for scientific or benchmarking purposes. We discuss pitfalls associated with the assessment, analysis, and interpretation of ROM data, using data of 376 patients. 206 patients (55%) completed one or more follow-up measurements. Mixed-model analysis showed significant improvement in symptomatology, quality of life, and autonomy, and differential improvement for different subgroups. Effect sizes were small to large, depending on the outcome measure and subgroup. Subtle variations in analytic strategies influenced effect sizes substantially. We illustrate how problems inherent to design and analysis of ROM data prevent drawing conclusions about (comparative) treatment effectiveness.

Background

Routine outcome monitoring (ROM) is a method to assess the effectiveness of treatments by systematically collecting outcome data in everyday clinical practice. ROM was introduced to improve treatment results (Carlier et al., 2012), learn from patient experience, and assess treatment quality to justify costs of mental health care (Bruinsma et al., 2012; Macdonald, 2009). Scientific interest for ROM grew with an increasing awareness that efficacy-focused randomized clinical trials (RCTs) do not adequately describe patient care (Gilbody et al., 2002). ROM is on the rise because of exploding costs of health care, and -in the Netherlands particularly- because of an increasing influence of insurance companies. These companies emphasize more transparency regarding cost-effectiveness and patient satisfaction. ROM is considered a means to this end, especially because it can be used for benchmarking results of all mental health institutions, so that therapies, therapists, departments or even facilities can be compared (Nugter & Buwalda, 2012).

However, ROM does not come without problems. First, ROM data collection and analysis is expensive and labour intensive, while (cost-)effectiveness is unclear (Carlier et al., 2012; Slade et al., 2006). Further, non-response percentages are typically high and seemingly ineradicable. Despite huge efforts and a motivated staff, De Beurs et al. (2011) reported a 50% reduction of the sample on *each* successive assessment. In a study by Stiles et al. (2006), post-treatment data were available for only 33% of the patients that had provided pre-treatment data. These percentages might indicate attrition bias, e.g. when patients who did not improve do not complete the ROM measurement; and selection bias, e.g. when therapists (unconsciously) include patients that tend to improve easily.

Another problem is that the use of different outcome measures can lead to different results (detection bias), e.g. because some instruments are more responsive to change than others (De Beurs et al., 2012). Further, there is the risk of reporter bias: therapists may report more favorably about their own patients than an objective observer would, and patients may under-report their symptoms because they don't want to disappoint their therapist or over-report them because they want to stay in therapy (Bilsker & Goldner, 2002). Not all authors, however, have found these suggested biases (e.g. MacDonald & Trauer, 2010).

In the analysis process a number of problems arise as well. First, different statistical techniques can lead to different outcomes (Burgess et al., 2009). Secondly, differences in casemix can lead to confounding and make it seemingly impossible to compare the effects of different therapists or institutions (Clark et al., 2008; Gilbody et al., 2002; Holloway, 2002). Third, because of the lack of a control group it remains uncertain whether the observed effects can be attributed to the treatment (Clark et al., 2008; Happell, 2008). Thus, there is considerable risk that ROM results are misinterpreted and conclusions are drawn that are not warranted (Clark et al., 2008; Van Os et al., 2012).

In view of these problems, there is considerable debate on whether the use of ROM is feasible and valid (Bruinsma et al., 2012; Clark et al., 2008; Van Os et al., 2012). This debate focuses on the use of group-level ROM data for effectiveness studies and benchmarking, which should be distinguished from the use of individual-patient ROM data by patients and clinicians for optimizing the individual treatment regimen (Bickman et al., 2011; Hawkins et al., 2004; Hysong, 2009). We will illustrate these problems using ROM data from the Center for Integrative Psychiatry (CIP), a department of Lentis, a mental health care institution in the north of the Netherlands.

We present the first results of ROM data collected at the CIP since 2008 and discuss the problems and pitfalls in the analysis and interpretation of such data. Specifically, we present a regular analysis of the presumed treatment effect and effect sizes, an example illustrating the use of ROM data for comparing groups, some examples showing consequences of different procedures for data processing and analysis, and discuss the implications for interpretation. This paper does not discuss the use of ROM for optimizing the individual treatment regimen.

Methods

Participants and procedure

The CIP is a small department of Lentis, a publicly funded large community mental health care institution. The CIP provides outpatient psychiatric care to about 500 adult outpatients, suffering from a large variety of psychiatric disorders, although mood disorders are most prevalent. Patients with severe addiction disorders, neurological problems, mental retardation, or requiring highly specialized psychiatric inpatient treatment are not admitted. About 40% of patients are referred to the CIP by family doctors and 60% by other outpatient psychiatric treatment centers. Reasons for referral are psychiatric disorders that are too complex or severe for family doctors or general outpatient treatment centers, or a wish for integrative psychiatric treatment (e.g. refusal of chemical drugs, wish for natural medicines, interest in mindfulness-based cognitive therapy (MBCT)).

Since September 2008, all patients admitted to the CIP are asked to participate in ROM. At that time, implementation of ROM by mental health services in our country was still optional, but in recent years it has become mandatory (i.e. coupled to funding from insurance companies). Completion by patients is voluntary, although ROM is presented as part of the standard intake procedure. An introductory letter explaining the goals of ROM is sent together with an invitation for the clinical intake. Patients complete the pre-treatment ROM questionnaires at the CIP, just before the intake. Reassessments are done every 6 months during treatment, at the end of treatment, and 6 months after the end of treatment. The completed questionnaires are returned in a postage paid envelope provided by the CIP. Data are collected and processed by independent research assistants. Patients are informed that ROM is part of the general policy of the CIP to monitor treatment outcome and learn from patient experience, that their data are only accessible for their therapists, and that anonymous data will be used for research purposes. If patients object to such use, their data are removed (this almost never happens). The Medical Ethical Committee in the Netherlands has agreed with this policy. Diagnosis and classification according to DSM-IV-R criteria is made by clinicians (psychiatrists or senior psychologists) during the intake interview.

Treatment

At the CIP, patients are treated with conventional therapies (medication, cognitive behavioral therapy, EMDR, and counselling by specialized nurses), lifestyle training (diet, exercise, relaxation, communication, and heart rate variability training), MBCT, and a selection of evidence-based complementary medicines such as St. John's wort, omega-3 fatty acids, s-adenosyl methionine (SAMe) and methylfolate. The CIP follows the principle of stepped care and uses a protocol with an algorithm to guide clinical decision making (Hoenders et al., 2011). Reaffirming the importance of the

therapeutic relationship (including shared decision making and emphasis on patient preference) is one of its main features (Consortium of Academic Health Centers for Integrative Medicine [CAHCIM], 2004).

Measures

Besides demographic and disease characteristics collected at baseline, ROM consists of questionnaires for the assessment of psychological symptoms, quality of life, autonomy, social optimism, and client satisfaction. This set of ROM questionnaires is the standard for ROM in several mental health institutions in the Netherlands (Huijbrechts et al., 2009).

Psychological Symptoms. Psychological Symptoms are assessed by means of the SSL (Short Symptom List; Dutch: Korte Klachten Lijst). The SSL is a self-report questionnaire with 13 items about the degree to which respondents suffer from common psychological symptoms, such as anxiety, depression, sleeping problems, and addiction (Lange & Appelo, 2007; Lange et al., 2000). Scores for each item can range from 0 (not at all) to 4 (very much). Total range for the SSL sum score may thus vary from 0 to 52. The reliability and validity of the SSL are satisfactory to good (Lange et al., 2007; Lange et al., 2000). The SSL is a proper short alternative for the SCL-90; total scores on these measures are highly correlated (Lange et al., 2007).

Quality of Life. The first three questions used for measuring quality of life are based on the Sheehan Disability Scale (SDS) (Sheehan et al., 1996). Respondents are asked to rate to what extent their psychological problems have a negative effect on their social functioning, their ability to work, and their relationship with people close to them. The questions are answered on a scale ranging from 0 “no effect” to 10 “extreme effect”. The fourth question for measuring quality of life is the Happiness Index (Abdel-Khalek, 2006; Veenhoven, 2002). Respondents are asked to rate their happiness in the previous month on a scale ranging from 0 “very unhappy” to 10 “very happy”. Both the SDS (Rush et al., 2000) and The Happiness Index (Abdel-Khalek, 2006; Veenhoven, 2002) have been tested and validated, showing satisfactory psychometric features. The summary measure for Quality of Life is calculated by reverse-coding the first 3 items and then dividing the sum of all 4 items by the number of the available items (Huijbrechts et al., 2009).

Autonomy and Social Optimism. Autonomy and Social Optimism are assessed with the Positive Outcomes List (POL; in Dutch: ‘Positieve Uitkomsten Lijst’). The POL is a short Dutch self-report questionnaire consisting of 10 items, that is developed to measure resilience based on the perceived level of autonomy and social optimism. Items are rated on a 4-point scale, ranging from 1 “not at all” to 4 “yes, completely”. The Autonomy subscale (7 items) assesses feelings of autonomy, control, and independence. The Social Optimism subscale (3 items) measures to what extent respondents are satisfied with and have confidence in their social relationships. The psychometric properties of the POL are satisfactory (Appelo & Harkema-Schouten, 2003).

Patient satisfaction. At the first measurement patients are asked to rate their satisfaction with the CIP on a scale ranging from 1 to 10. At follow-up measurements patients answer the same question and also rate their satisfaction with their main therapist and the result of the treatment received at the CIP, on a scale ranging from 1 to 10. The fourth question is whether patients would recommend the CIP to others with mental health problems, in five categories, ranging from “yes definitely” to “no absolutely not”. These questions are not part of an established questionnaire, but are composed by a large mental health organisation in the Netherlands (PsyQ) and in

use for ROM since 2008. Internal consistency of these four questions (Cronbach's alpha) is good (.82) (Huijbrechts et al., 2009).

Statistical analysis

The label of all follow-up measurements (i.e. 'during treatment', 'post-treatment', and '6-months post-treatment') was inspected and corrected if necessary, using the date of intake and discharge from the center as reference points. Measurements within 3 months of the discharge date were labelled 'post-treatment'; measurements outside that window were labelled either 'during treatment' or '6-month post-treatment', depending on the date of completion. This was done to ensure that labels most optimally reflected the intended measurement moment[1]. Such a re-labelling procedure is often used in mental health institutions in the Netherlands. At a total of 357 follow-up measurements, 41 measurements were relabelled (11%).

Patients included in the analyses were those who completed the pre-treatment assessment and at least 1 follow-up assessment ('completers'). Differences in baseline characteristics between completers and non-completers were tested using X^2-tests and independent samples t-tests. Linear mixed models (with intention-to-treat) were used to examine change over time in the outcome measures. These models have the advantage that all available data can be used and time effects can be modelled with great flexibility. A categorical variable denoting the specific measurement points (pre-treatment; during treatment, post-treatment, and 6-months post-treatment) was used as the predictor, with pre-treatment as the reference category. All measurements during treatment were collapsed in these analyses. In a secondary analysis, we used a model with a continuous variable denoting the real time of the measurements (i.e. time since intake) as a predictor. A random intercept was used in all linear mixed models to account for the nesting of measurements within subjects. A random slope term was modeled as well, but removed from the models when not significant. To investigate differences in outcome among different subgroups, we focused on the post-treatment measurement, using a covariance analysis approach (Vickers & Altman, 2001). We used a linear regression model with post-treatment scores as the dependent variable and the subgroup variable as the predictor, adjusting for baseline scores. Differences in baseline characteristics between the subgroups were tested with X^2-tests and independent samples t-tests. To investigate associations between disease characteristics and outcome, we used linear mixed models with the disease characteristic as the predictor and outcome at all assessment waves as the dependent variable, adjusting for baseline scores on the outcome measures. Distributions of some of the variables showed deviations from normality, especially at later measurement waves. For this reason, we used bootstrapped confidence intervals in all analyses, and show medians and interquartile ranges (IQR) as descriptive statistics for skewed variables. Analyses were done using IBM SPSS Statistics 20. A two-tailed alpha level of 0.05 was used to determine statistical significance.

Results

In total, 850 new patients were referred to the CIP between October 2008 and September 2011. We excluded patients who received no treatment after the diagnostic interview (second opinions, consultations, mismatch; n = 164) from the analyses. We also excluded patients who received their main treatment in other departments of the Lentis institute and came to the CIP only to receive MBCT (n = 139). The remaining patients (n = 547) could be divided into 3 subgroups: (1) treatment at the CIP only ('CIP only', n = 218); (2) treatment at the CIP and other Lentis departments concurrently ('CIP and other treatment', n = 253); and (3) participation in a MBCT group course only ('MBCT', n = 76; we distinguished the latter subgroup because these patients might be different from those who received individual treatment (e.g. drugs, lifestyle training, complementary medicines and or psychotherapy) and also the effect of self-help training such as MBCT might be different than the effect of individual treatments). Of these 547 patients eligible for ROM, 376 patients (69%) completed the baseline measurement; this is the sample described in the present study. Of these, 206 (55%) completed one or more follow-up measurements (including 87 (23%) at the end of treatment). These 206 patients are the subjects included in the mixed-model analyses.

Baseline characteristics

Demographic and clinical characteristics of the study sample (n = 376) are shown in Table 1. The sample consisted of 115 men and 261 women. Mean age was 41.3 years (SD = 12.8). Fifty percent had a high educational level. Median illness duration was 11 years (IQR = 15). Median treatment duration of the patients whose treatment was finished at the time of analysis was 288 days (IQR = 356; n = 245). Median treatment duration of all patients, including those who were still in treatment, was 388 days (IQR = 357). The latter group also included a number of patients who receive low-intensity maintenance treatment for medication control (e.g., patients with bipolar disorder). Baseline scores on the outcome measures are shown at the bottom of Table 1. The outcome measures showed moderate correlations among each other in the expected direction: Symptoms were negatively related to Quality of Life (r = -.472), Autonomy (r = -.544) and Social Optimism (r = -.388). Quality of Life was positively related to Autonomy (r = .547) and Social Optimism (r = .439). Autonomy was positively related to Social Optimism (r = .525) (all p-values < .001).

Primary DSM-IV diagnoses on axis I and axis II are shown in Table 2 (co-morbidity as defined by a second or third diagnosis on axis I or II is not shown as these data were not available). The sample was highly heterogeneous as regards diagnosis. Mood and anxiety disorders were most prevalent on axis I. Most prevalent diagnoses on axis II were borderline and type C personality disorders (avoidant, dependent and obsessive-compulsive disorder).

Table 1. Demographic and clinical characteristics of the baseline sample (n=376)

Female (n, %)	261	69%
Age, years (mean, SD)	41.3	12.8
Having a partner (n, %)	200	55%
Living situation (n, %)		
Alone	142	39%
With partner and/or children	179	49%
Other	43	12%
Educational level (n, %)		
Low	62	17%
Middle	120	33%
High	182	50%
Illness duration, years (median, IQR)	11	15
Treatment duration, days (median, IQR)[1]	288	356
Medication and supplements (n, %)[2]		
Antidepressants	79	35%
Sedatives	34	15%
Antipsychotics	23	10%
Mood stabilizers	10	4%
Stimulants	1	0.4%
Food supplements	27	12%
Complementary medicines	20	9%
Somatic medicines	20	9%
No medication or supplements	97	43%
Symptoms (mean, SD)	17.3	7.9
Quality of Life (mean, SD)	4.6	2.0
Autonomy (mean, SD)	18.1	3.9
Social Optimism (mean, SD)	8.7	1.9

SD = standard deviation, IQR = interquartile range

[1] For those who finished treatment at the time of analysis
[2] Medication use at baseline (before intake). These data were available for only 225 patients as this questionnaire was not assessed during the first study years. Patients can use more than one type of medication/supplement.

Table 2. DSM-IV Classification in the baseline sample (n=376)

	n	%
Primary diagnosis		
Axis I only	248	66
Axis II only	5	1
Both Axis I and Axis II	123	33
Diagnosis axis I		
Depressive disorder[1]	93	25
Adjustment disorder	40	11
Anxiety disorder[2]	57	15
Relationship problems	38	10
Bipolar disorder[3]	40	11
Other[4]	103	27
No or deferred diagnosis on Axis I	5	1
Diagnosis axis II		
(Traits of) personality disorder (total)	128	34
Cluster A[5]	2	1
Cluster B[6]	34	9
Cluster C[7]	68	18
Not otherwise specified	24	6
No or deferred diagnosis on Axis II	248	66

[1] recurrent (77); single episode (13); NAO (3)
[2] panic disorder (13); post-traumatic stress disorder (11); generalized anxiety disorder (10); obsessive-compulsive disorder (3); phobia NAO (1); social phobia (2); NAO (17)
[3] bipolar I (26); bipolar II (11); NAO (3)
[4] dysthymic disorder (22); attention deficit hyperactivity disorder (13); identity problem (13); somatoform disorder (8); psychotic disorder (7); developmental disorder (7); substance abuse (5); eating disorder (5); bereavement (5); dissociative disorder (3); sleeping disorder (3); job-related problem (3); mood disorder NAO (2); mood disorder based on physical disease (1); psychiatric problem based on physical disease (2); separation anxiety (1); religious problem (1); cognitive disorder NAO (1) and life stage problem (1)
[5] schizoid (1), schizotypical (1)
[6] borderline (29), narcissistic (4), antisocial (1)
[7] avoidant (22), dependent (25), obsessive-compulsive (21)

Drop-out analysis
Follow-up measurements were missing or invalid for 170 of the 376 patients with a baseline ROM assessment (45%). Drop-out analysis showed that non-completers were younger than completers (mean age 38.7 vs. 43.5 years; t = -3.68, df = 374, p < 0.001); had a lower level of education (X^2 = 8.81, df = 2, p = 0.012); and a lower baseline score on the Social Optimism scale (8.3 vs. 9.0; t = -3.23, df = 347, p = 0.003). Further, 57 (50.9%) of non-completers used no medication at the start of treatment, against 40 (35.4%) of completers (X^2 = 5.51, df=1, p=0.019). No differences in gender, having a partner, living situation, or illness duration were found between non-completers and completers.

Patient satisfaction
Results for patient satisfaction were very similar at the different assessment points, so we pooled the results over all follow-up assessments (total observations = 349). Patients' satisfaction with the treatment center was good (median = 8; range 1 to 10). Also satisfaction with the main therapist was good (median = 8; range 1 to 10). Patients were also rather satisfied with the results of the treatment (median = 7; range 1 to 10). The question whether the respondent would recommend the CIP to someone who has problems or complaints was answered with "Yes, for sure" in 52.9% of the cases, with "Yes, probably" in 34.0%, with "I doubt" in 9.3%, and with "No, probably not" in 3.5% of the cases. The answer "No, absolutely not" was recorded only once (0.3% of the cases).

'Treatment' effect
In ROM studies, the presumed treatment effect is typically assessed by investigating change over time. Figure 1 shows the changes in the scores on the outcome measures over the different assessment points. All assessments done during treatment were pooled in these graphs ('dur'). The mixed-model analyses showed that these changes were significant for all outcomes and all assessments points, except for the subscale Social Optimism (Table 3).

Figure 1. Change in scores on the outcome measures over the ROM study period.
pre = pre-treatment; dur = during treatment; post = post-treatment; fu = 6-months follow-up.
**** p<0.005; *** p<0.001. Error bars: 95% confidence intervals.**

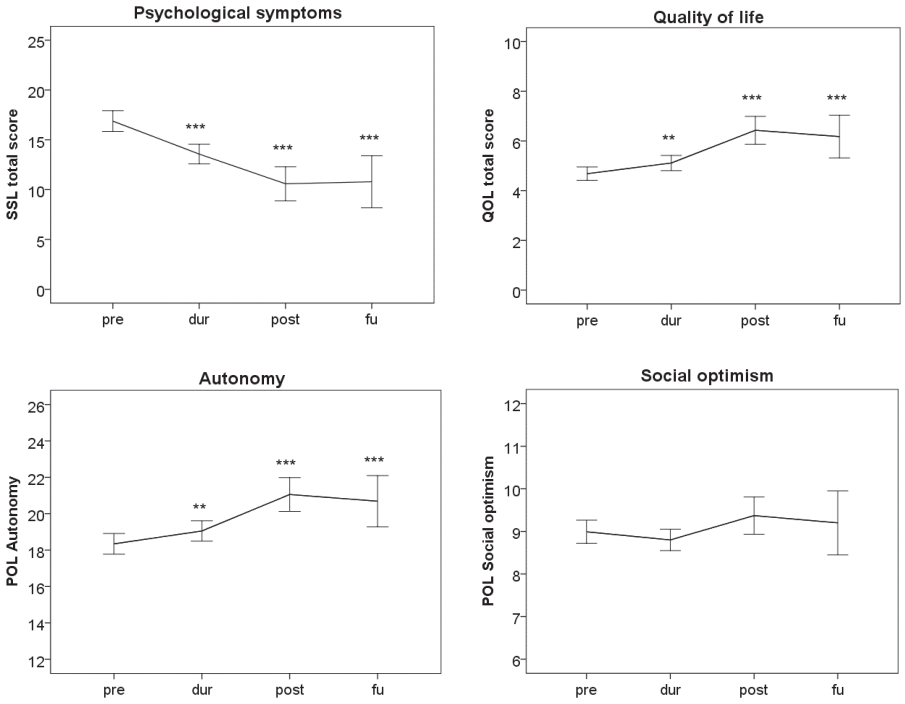

Table 3. Results of the mixed-model analyses (n=206)

Outcome measure	Assessment	B	95% boot-strapped CI		p
			lower	upper	
Symptoms	Pre-treatment	ref			
	During treatment	-4.19	-5.33	-3.04	<0.001
	Post-treatment	-5.74	-7.43	-4.05	<0.001
	6 months post-treatment	-5.58	-7.56	-3.59	<0.001
Quality of Life	Pre-treatment	ref			
	During treatment	0.58	0.22	0.95	0.002
	Post-treatment	1.68	1.14	2.21	<0.001
	6 months post-treatment	1.41	0.78	2.04	<0.001
Autonomy	Pre-treatment	ref			
	During treatment	0.90	0.28	1.51	0.004
	Post-treatment	2.49	1.61	3.38	<0.001
	6 months post-treatment	2.04	0.89	3.19	<0.001
Social Optimism	Pre-treatment	ref			
	During treatment	-0.08	-0.35	0.20	0.588
	Post-treatment	0.19	-0.19	0.58	0.322
	6 months post-treatment	-0.01	-0.56	0.53	0.963

Effect sizes

Effect size measures, such as Cohen's d, are often used in ROM studies, as they seem practical for comparison given their standardized nature. We calculated within-group effect sizes by dividing the estimated mean difference between the pre- and post-treatment scores on the outcome measures by the standard deviation of the pre-treatment scores. Table 4 shows the effect sizes for the entire ROM sample as well as for the three different subgroups in the sample. Effect sizes for the Social Optimism subscale were very small, in all groups. Effect sizes for the other outcome measures were moderate to large, ranging from 0.62 to 0.86 in the entire sample. Effect sizes were highest in the 'CIP only' group, somewhat lower in the 'MBCT' group, and lowest in the 'CIP and other treatment group'.

Table 4 Effect sizes for pre- to post-treatment difference in the outcome measures

Outcome measure	Cohen's d					
	CIP only (n=86)	CIP and other treatment (n=89)	MBCT (n=31)	All (n=206)	All; without pre-processing (n=598)	All; baseline score above threshold[1] (n=153)
Symptoms	1.30 (1.01–1.58)	0.44 (0.22–0.66)	0.66 (0.27–1.05)	0.77 (0.61–0.92)	0.78 (0.69–0.87)	1.18 (0.97–1.39)
Quality of Life	1.42 (1.12–1.72)	0.61 (0.38–0.83)	0.59 (0.20–0.96)	0.86 (0.70–1.02)	0.97 (0.88–1.07)	1.04 (0.84–1.23)
Autonomy	0.93 (0.67–1.18)	0.38 (0.16–0.60)	0.76 (0.36–1.16)	0.62 (0.48–0.77)	0.58 (0.49–0.67)	0.75 (0.57–0.92)
Social Optimism	0.15 (-0.06–0.36)	0.04 (-0.17–0.25)	0.20 (-0.15–0.56)	0.10 (-0.04–0.24)	0.21 (0.13–0.30)	0.15 (-0.01–0.31)

[1] Threshold for baseline symptom severity: SSL score > 11.

Between parentheses the 95% confidence intervals for the effect sizes.

The use of ROM data for comparing groups

When ROM data are used for benchmarking, outcomes of different departments or institutions are compared. To illustrate the difficulties arising at this point, we compared the results of the 'CIP only' group (n=86) and the 'CIP and other treatment' group (n=89). We tested the differences in improvement from pre- to post-treatment between the two groups using a linear regression model with post-treatment scores as dependent variable and Group as predictor, adjusting for baseline scores. Post-treatment measurements were available for 61 of these participants (29 'CIP only'; 32 'CIP and other treatment'). Although this is only a small group, we do show these results, because effect sizes are usually based on post-treatment data and low post-treatment response percentages are the rule rather than the exception in ROM studies. According to these analyses, the difference between the groups was significant for Symptoms (B = 5.91, 95% CI = 1.74 to 10.07, p = 0.007). Thus, the 'CIP only' group had significantly fewer symptoms at post-treatment than the 'CIP and other treatment' group when differences in baseline severity were adjusted for. For the other outcome measures, the difference between the groups was not significant (Quality of Life: B = -1.14, 95% CI = -2.50 to 0.16, p = 0.100; Autonomy: B = -1.38, 95% CI = -3.67 to 0.53, p = 0.193; Social Optimism: B = -0.39, 95% CI = -1.26 to 0.54, p = 0.406).

A critical problem in the comparison of groups is that differences in outcome can be confounded by differences in baseline characteristics and/or treatment duration. Commonly, researchers try to account for such differences by statistical adjustment for such confounders, if these are available. In our example, the 'CIP only' group was significantly higher educated than the 'CIP and other treatment'

group (X^2 = 9.97, df = 2, p = 0.007), and was living less often together with partner and children (X^2 = 6.60, df = 2, p = 0.037). When we adjusted for these two variables in the mixed models, the baseline-adjusted group difference on the post-treatment Symptom scores remained significant and the estimated difference became somewhat larger (B = 6.85, 95% CI = 2.55 to 11.30, p = 0.006). Obviously, we could only adjust for the patient and treatment characteristics that we measured. These are usually limited in ROM studies. We thus remain ignorant as regards the influence of other potential confounders (Brookhart et al., 2010).

A related problem associated with the use of ROM data for benchmarking purposes is that patients treated in different health care settings may differ in the complexity of their problems. One aspect of this complexity may be illness duration; the literature shows that a recent disease onset is often related to a better outcome (Carter et al., 2003; Clark et al., 2008; Mynors-Wallis & Gath, 1997). We therefore examined whether illness duration was related to outcome in our sample, using a mixed model with illness duration as the predictor, adjusting for baseline scores. Illness duration was significantly predictive of a worse outcome for all outcome measures: Symptoms, B = 0.12, 95% CI = 0.06 to 0.17, p < 0.001; Quality of Life, B = -0.033, 95% CI = -0.052 to -0.015, p = 0.002; Autonomy, B = -0.046, 95% CI = -0.076 to -0.016, p < 0.001; Social Optimism, B = -0.012, 95% CI = -0.026 to -0.001, p = 0.049. Another aspect of disease complexity is the presence of a comorbid personality disorder (Grilo et al., 2010; Massion et al., 2002; Van Noorden et al., 2012). We investigated whether patients having a diagnosis at both axis I and II had a worse outcome than patients who had a disorder at only one axis (most often axis I). This appeared to be true for all outcome measures: having a disorder at both axis I and II was related to higher baseline-adjusted follow-up scores for Symptoms (B = 2.55, 95% CI = 1.32 to 3.83, p < 0.001) and lower scores for Quality of Life (B = -1.06, 95% CI = -1.51 to -0.63, p < 0.001); Autonomy (B = -1.32, 95% CI = -2.00 to -0.65, p < 0.001); and Social Optimism (B = -0.60, 95% CI = -0.87 to -0.27, p < 0.001). So, disease complexity as indexed by longer illness duration and/or a diagnosis at both axis I and II was indeed related to a worse outcome in our sample.

Differences in procedures for data processing and analysis

Because several choices are made during pre-processing and analysis of ROM data, we examined the consequences of some of these choices. First, we compared what the results would look like when no pre-processing was done at all (e.g., no adjustment of assessment labels, no exclusion of patients not eligible for ROM, et cetera). So, we repeated our mixed-model analyses on treatment outcome, but now in the raw data set. The only pre-processing step performed in this data set was a data entry check, in which data entry errors were corrected. The resulting file was similar to the one we sent to the “Stichting Benchmark Geestelijke Gezondheidszorg (SBG)”, the overarching association involved in benchmarking activities in Dutch mental health care. The information required for most preprocessing steps is not available for the SBG, since it is stored in a different database than the ROM data (e.g. information on actual discharge date, second opinions, concurrent treatment at other centers). We spent many days to retrieve this information and to perform the required preprocessing steps. So it is unlikely that all these steps will be done when analyses are done by a nation-wide benchmark institution. The sixth column of Table 4 shows the results from the non-pre-processed data set. The effect sizes were rather similar as those from the pre-processed data set (fifth column), except for

Quality of Life and Social Optimism: higher effect sizes were found when no pre-processing was done.

Next, we examined the results when patients with low baseline symptom severity were excluded from the analyses. We did this because we observed this practice in studies from leading ROM authors in the Netherlands (Van der Lem et al., 2012; Van Noorden et al., 2012). We used a threshold of >11 on the SSL, excluding all patients with 'low' and 'very low' symptom severity according to norm scores (Huijbrechts et al., 2009). As could be expected, this resulted in higher effect sizes on all outcome measures. The last column of Table 4 shows these results.

We also examined changes in symptoms over time by means of a model with 'real time' as independent variable, i.e., the time passed since the intake date. Using this model, we found a change of -3.61 points on the Symptoms scale per year (95%CI -4.48 to -2.90, p = 0.001). This analysis shows a discrepancy with the results from the original model. In the original model, the estimated change from pre- to post-treatment on the Symptoms scale was -5.74 (Table 3). Mean time since intake for the post-treatment assessment was 0.95 years for this sample, which is almost a year. The model with real time, however, showed a rate of change of -3.61 per year, which is thus substantially lower than the estimate from the original model. This discrepancy can partly be explained by the fact that outcomes assessed at post-treatment are generally low 'by definition', since patients are usually discharged from the center only when they show sufficient symptom reduction. This also points to the potential problem of circularity when outcome measures are used simultaneously for scientific or benchmark purposes and for treatment feedback by the clinician.

Discussion

We analyzed the data of three years ROM in our outpatient clinic for integrative mental health care. Patients were highly heterogeneous in diagnosis and many of them had a co-morbid personality disorder. The median illness duration was more than 11 years. Long illness duration and the presence of a co-morbid personality disorder were related to worse outcome. Follow-up data were missing for 45% of the baseline sample. The results showed a significant decrease in symptoms and a significant increase in quality of life and perceived autonomy. No significant improvement was observed in social optimism. Patient satisfaction was high, which seems in accordance with Integrative Medicine's aim of reaffirming the importance of the therapeutic relationship (CAHCIM, 2004). Patients treated only at the CIP did better than those who were also treated in other Lentis departments. Although the effects of treatment at the CIP seem positive in this sample we have concerns about the numerous ways in which the data can be confounded, biased, or misinterpreted. Below we discuss some of the pitfalls and challenges in the assessment, analysis, and interpretation of ROM data, based on our own results.

'Treatment' effect

For a number of reasons, we do not know whether the observed changes really reflect the effect of the treatment at the CIP. First, many patients also received other treatments in other departments, before, after, or during the CIP treatment. Some for a long time, some shortly, some stopped CIP treatment completely, others stopped for a while and continued again. The most consistent feature we encountered when analyzing the data was the lack of consistency. Another reason is that loss to follow-

up was high. This is often the case in ROM studies, and it presents a problem as it may distort results substantially (Bilsker & Goldner, 2002; Clark et al., 2008; De Beurs et al., 2011; Stiles et al., 2006). If non-completers are the ones who benefit least from treatment or the ones who are most dissatisfied, then the results will be overly optimistic. A number of studies have shown that this is often the case (Clark et al., 2008; Stiles et al., 2003). However, Young et al. (2000) found that non-completers performed *better* on some outcome scales. In the present study non-completers also differed from completers in many respects. Thus, probably our (and most) ROM results do not reflect the real effects of treatment. We doubt whether response percentages will increase to acceptable levels in the future, given the fact that early ROM countries like the United States of America and the United Kingdom are still confronted with this problem (Clark et al., 2008; Stiles et al., 2003; Stiles et al., 2006). Australia seems to be an exception, showing an increase in response percentages in recent years (Burgess et al., 2012). One reason for this may be the huge investments from the Australian government in the implementation of ROM. Another important difference is that the core ROM instruments in Australia are collected and rated by clinicians. The ROM instruments used by the CIP are self-report measures rated by the patients, and also the data collection itself is not performed by clinicians. This is done to avoid reporter and selection bias, and to reduce administrative burden for those whose job is to provide care. Of note, response percentages in Australia are high especially for clinican-rated instruments, but actually rather low for consumer-rated instruments (AMHOCN, 2013).

Another concern is that ROM measures are usually very general, because they have to be used in a broad range of settings. Therefore, they may not be equally fit to detect symptoms or improvements in all patient populations, or fail to capture the subtlety of a multifaceted outcome (Ashworth et al., 2009; Gilbody et al., 2002; Happell, 2008; Lakeman, 2004). For example, relationship problems are a frequent reason for referral to the CIP, but the SSL only has 1 item to assess such problems. Patients with these problems may thus score very low on this questionnaire at baseline, despite having serious mental problems. A related concern is that some questionnaires are more sensitive to detect change than others (Ashworth et al., 2009; De Beurs et al., 2012). The SSL for instance has been found to have only moderate sensitivity to change compared to other symptom measures (De Beurs et al., 2012). Further, some patients in our sample with severe mental disorders (bipolar disorder, schizophrenia) remain in treatment for a very long time, for relapse prevention. Even when this approach is successful, it will not show in ROM data, because the outcome measures are not designed to measure such results. Finally, a more general problem is the lack of a control group, as a results of which the effects may also be caused by spontaneous recovery, regression to the mean, positive expectancy, or external events. The above described problems do not exclusively apply to the present study, but are encountered in most ROM studies, and are inherent to the design.

Effect sizes

The effect sizes in our study were moderate to large, especially in the ‘CIP only’ group. Effect sizes are standardized measures of effects, allowing for comparison of results from different measurement instruments. Therefore, they will be attractive for policy makers and insurance companies that want to compare institutions in an easy way for cutting costs. But the results may be misleading. One reason is that differences in effect sizes may be due to several other factors than differences in

treatment quality. Differential sensitivity of questionnaires can be one such difference; in a ROM study of Dutch psychiatric outpatients that used the same symptom scale as we did (SSL), an effect size of 0.52 was found (De Beurs et al., 2012), while the effect size on the symptoms scale of the OQ-45 in the same study was 0.63. Also, differences in casemix may play a role; for example, patients visiting integrative health care centers may be different from patients visiting conventional centers. We found four other ROM studies done in centers for integrative medicine (Greenson et al., 2008; Myklebust et al., 2008; Scherwitz et al., 2004; Smeeding et al., 2010), with effect sizes ranging from 0.00 to 1.20 depending on the outcome measure. However, a proper comparison is still not possible because of differences in outcome measures, medical conditions (mental, somatic, or both), demographic and disease characteristics (e.g. illness duration and baseline severity), alternative treatment (e.g. some centers used alternative therapies like homeopathy, acupuncture and anthroposophical medicine whereas we did not), time of assessment (e.g. 3 months vs 6 or 12 months), type of assessment (e.g. self-report vs. telephone interview), type of referral (self-referred or not), and reason for admission (e.g. improving health vs. treatment of a disorder).

Another problem with the use of effect sizes is that they may suggest substantial differences that in fact are not statistically significant. Presenting confidence intervals around the effect sizes may alleviate this problem to some degree, but still the figures may be misleading. For instance, we found a large difference in effect size between the 'CIP only' group and the 'CIP and other treatment' group in quality of life (effect sizes 1.42 vs. 0.61). However, this difference was not significant when analyzed properly using covariance analysis. Effect sizes are based on difference scores and disregard the absolute level of the scores at baseline. The underlying assumption is that a drop on a certain scale from 30 to 20 is as relevant as a drop from 20 to 10. This is not necessarily true (Delespaul, 2010; Iezzoni, 1996): for example, how to compare a decrease from 20 to 15 on a symptom scale in a group of patients with a long history of severe psychopathology accomplished in 3 years by medication and cognitive behavioral therapy, versus a decrease from 18 to 14 in a group of young patients with no history of mental health problems accomplished in 2 months by participating in a MBCT course? For the same reason, effect sizes do not adjust for regression to the mean, while a proper covariance analysis does (Vickers, 2001). Another way of assessing effects is to calculate figures on reliable and/or significant change, which can be especially useful to show individual differences in effects. However, these are subject to the same problems as mentioned above, as they are also based on difference scores.

The use of ROM data for comparing groups

The main problem with the use of ROM data for benchmarking purposes is 'pitting apples against oranges'; different departments / institutions may differ in many respects, including patient characteristics, baseline severity, type of treatments, length and intensity of treatments, co-morbidity, additional treatments, ROM instruments and procedures, and so on. These potential differences are too many to adequately control for, making comparisons between departments / institutions meaningless (Clark et al., 2008; Gilbody et al., 2002; Holloway, 2002; Van Os et al., 2012). For instance, when looking superficially at our results one could think that it is better for patients to receive treatment at the CIP only, because these patients improved more than patients who received treatment at other departments as well. However, probably the 'CIP and other treatment' patients differed from the 'CIP only'

patients in many respects (that might be the very reason why they are still being treated in another department as well). They might be more complex, more vulnerable, have a lower socio-economic status, a smaller social network, a longer illness history, more co-morbid disorders, et cetera (confounding by casemix). To be able to adjust for all these differences would imply having access to all (medical) data files, if these parameters have been measured at all, which is usually not the case in ROM (Brookhart et al., 2010; Höfler, 2005). Even if one is able to adjust for all baseline differences, the problem is not solved, because adjusting for one variable can introduce an imbalance in other variables (Bosco et al., 2010; Brookhart et al., 2010; Shrier & Platt, 2008). For these reasons, if patients of some department show only modest improvement in comparison with another department, this does not necessarily imply that this department is inferior. In one of the first large ROM assessments in the USA, patients who were treated appeared to be *worse* off than those not treated (Gilbody et al., 2002). In one subgroup it was possible to correct for a lot of baseline differences. In that analysis patients who were treated were *better* off. A similar reversal of outcome results has been found in other studies as well (Brookhart et al., 2010).

Differences in procedures for data processing and analysis
Choices in how to analyze the data can have a large influence on the results. For example, some authors exclude patients for which the time between baseline and next measurement was too short or too long; e.g. Van der Lem et al. (2012) excluded 169 patients because of these reasons. Some authors also exclude all patients with too low baseline severity (Van der Lem et al., 2012; Van Noorden et al., 2012). Our study showed that this procedure leads to much higher effect sizes. Further, we (and many others) did a number of pre-processing steps to prepare our data for analysis. What are the effects of all these actions? We chose to use a linear mixed-model to analyze our data, others may use different models. Some authors focus on pre- to post-treatment differences, others may use another end point or real time in their analysis. Our study showed that such choices can lead to substantial differences in results. Also Burgess et al. (2009) showed that choices in the way data are analyzed can lead to considerable differences in results (e.g. significant improvement in 38% versus 67% or even 73% of inpatient treatments).

Other concerns
Some institutions (not the CIP) ask their clinicians to check whether patients have completed ROM, and if not, to have them do it during their visit. This may lead to socially desirable responses in patients and selection and attrition bias due to clinicians (e.g., one might be tempted to show more effort in getting ROM data from patients that improve a lot). Another problem is confounding by indication; this may obscure the influence of disease complexity because complex patients are often referred to the most experienced clinicians / institutions (Bosco et al., 2010). There are also ethical concerns. The present ROM system functions in a way that inaccurate data collection could be rewarded as it increasingly guides funding and decision making (Bilsker & Goldner, 2002). This could lead to ‘gaming’ effects, like avoiding to include complex patients who will probably not improve easily (selection bias), putting more effort in obtaining follow-up data of patients with positive outcomes (attrition bias), and reporting higher than justified scores at referral and lower than justified at discharge (reporter bias/provider bias) (Bevan & Hood, 2006; Bilsker & Goldner, 2002). Such effects may be subtle and occur often unconsciously,

and are inherent to provider-based outcome measurement (cf. butchers inspecting their own meat).

Practical challenges
ROM requires a lot of time, effort and money. Moreover, patients may get burdened by too many assessments, some of which are only for administrative reasons. For instance, in the Netherlands response percentages for ROM are not calculated on the basis of the number of patients but on the number of treatments as indexed by the financial system (DTC; diagnosis treatment combination; in Dutch DBC), which has a maximum treatment duration of one year. Therefore, patients have to fill out an 'end of treatment' ROM every year, even when the treatment continues or when they just had had a ROM assessment. This seems odd and in contrast with common sense and daily practice. Moreover, when a patient is treated in different departments he or she will be asked to complete ROM questionnaires every 6 months for each department. This places an unreasonable burden on patients and may also undermine their willingness to fill out the questionnaires properly.

Conclusion

ROM of treatments at the CIP showed that, on average, patients' symptoms decreased and their quality of life and autonomy improved significantly during treatment. It is, however, not at all clear what conclusions can be drawn from these results as regards the effectiveness of treatments provided by the CIP. The lack of a control group and potential selection, attrition, and detection biases preclude conclusions about the real treatment effect, while confounding by casemix, differences in type, number, length, and intensity of treatments, and differences in measurement instruments and procedures for collecting and analyzing the data preclude proper comparisons between different departments or institutions. ROM may be useful as a clinical tool for individual-patient feedback, and for assessing unmet needs and improving communication between patient and practitioner. We think, however, it is less suitable for scientific and benchmarking purposes. As an alternative we suggest the use of selective well-designed effectiveness studies performed by an independent research facility, undertaken at random instead of routinely (Bilsker & Goldner, 2002). This would reduce costs, ensure independency, and increase reliability and validity of outcome evaluations.

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Endnotes

[1] In practice ROM measurements are not always completed at the intended moment; for example because the discharge of a patient is not reported timely to the ROM staff member or a respondent is slow in his or her response.

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Discussion

This thesis is about the conceptual foundation, implementation and effectiveness of integrative psychiatry. We will now discuss these three parts separately. After that we discuss and respond to criticism on integrative psychiatry, make a plea for an integrative research focus and do suggestions for future research.

Part I: conceptual foundation

As integrative medicine is a new concept in health care, we explored its conceptual foundation in the first part of this thesis and identified the main concerns in conventional medicine for which integrative medicine may provide some solutions (cf. Introduction). We argued that integration is not only a current tendency in medicine, but also a trend fitting the contemporary spirit of the age, in which integration seems to be the most common focus. It can be observed in religion, philosophy, spirituality and psychotherapy as well (chapter 1). We then compared conventional and alternative medicine as regards their perspective, paradigm, organization, scientific method and procedures. We showed that theoretically, conventional and complementary / alternative medicine are categorically opposed to each other in many respects. In practice, they seem to differ only gradually. However, in one aspect they seem to differ categorically both in theory and practice, namely in the commonly used theoretical models (mechanism / reductionism versus vitalism / holism). This aspect is therefore the main reason for heated debates. We nevertheless think these differences can be bridged using an integrative model that accommodates both (chapter 2). These two studies provide a conceptual basis for integrative medicine and the integration of non-conventional medicines in mental health care. Although these studies were based on literature searches, they were not performed in a systematic way, so they can be subject to bias.

There are different views on the integration of conventional and complementary / alternative medicine: if and how it could or should take place. Parker (2007) concludes that integration should only take place in an integrated evidence-based model, not in a multicultural pluralistic model. Pluralism refers to an organizational model in which different parts exist next to each other without being integrated. Kaptchuck et al. (2005), however, express a rather different view. They argue that pluralism is the most ethical and desirable option, as there are unbridgeable epistemological differences between the medicines. Koutouvides (2004) acknowledges these epistemological differences, but does not regard them as obstacles to collaboration or even convergence. He argues that collaboration is the way forward, instead of confrontation. Bell et al. (2002) state that integrative medicine provides a bridge between these theoretical models / paradigms, because it accommodates both conventional treatments and CAM, emphasizing wellness and healing of the entire person (bio-psycho-socio-spiritual dimensions) in the context of a supportive and effective physician-patient relationship. Tataryn and Verhoef (2001) argue that integration can take place at different levels (patient, practitioner, department, hospital). In the Netherlands some authors feel integration is not at all an option. They strongly oppose the integration (and even the existence) of non-

conventional medicine (Renckens, 2004; Van den Berg & Hengeveld, 2010; see paragraph 'criticism').

We agree with Koutouvides (2004) and Bell et al. (2002); although there are epistemological differences in theoretical models (chapter 2), we think these differences can be bridged using a model based on the principles of evidence-based medicine and integrative medicine (chapter 3). Our model facilitates integration at the patient and practitioner level. It helps practitioners to provide safe and effective conventional, lifestyle and complementary medicine. Further, patients are informed and advised to be able to make responsible and healthy choices when using alternative medicine (Part II / chapter 3).

Part II: implementation

In the second part of this thesis we outlined our position on the integration of medicines and presented a working model / guideline for the judicious use of complementary and alternative medicine in conventional psychiatry (chapter 3). There were four reasons for formulating and implementing a working model of integrative psychiatry. First, the practice of integrative medicine / psychiatry is highly varied and idiosyncratic. There is a clear need for more consensus and clinical guidelines to optimize effectiveness, efficiency and scientific evaluation. Second, the concept of integrative medicine was formulated in the United States of America, but in the Netherlands different laws concerning alternative medicine apply. So there is a need to adjust the concept of integrative medicine to Dutch law. Third, the World Health Organization (2003) and the European Parliament (1997) have asked their member states to do research on complementary and alternative medicine, to integrate those therapies that have been proven effective and safe, to provide the public with reliable information, and to formulate policy. Fourth, in the Netherlands we witness heated debates on complementary / alternative medicine in which opponents and proponents frequently express prejudices. These prejudices hinder the development of a balanced policy.

We assessed the main prejudices for and against complementary and alternative medicine, and refuted them with founded arguments. We then formulated a clinical guideline on the judicious use of complementary and alternative medicine in conventional psychiatry. Until now 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. This is a first attempt to guide patients and professionals in what they can or should do concerning unconventional medicines in the Netherlands. To our opinion, it guards patients against malpractice and harm, while simultaneously maximizing treatment options based on the needs and preferences of patients.

This paper has been criticized for being called a 'protocol' although 'it is not based on best practice determined by psychiatrists as protocols should' (Van den Berg & Hengeveld, 2010). But there does not seem to be any consensus on definitions of protocols, guidelines and decision trees. These terms are used interchangeably. Our intention was to make clear that one should act judiciously, based on law and scientific evidence. To emphasize that, we used 'protocol' to emphasize that the steps as described in the decision tree are not merely suggestions but have to be followed.

Part III: effectiveness

In the third part we presented four studies to answer some of the questions on the effectiveness of integrative psychiatry. We did a comprehensive review on the efficacy and safety of complementary medicines for bipolar disorder (chapter 4). We found high-quality evidence for the effectiveness of select nutrients. We concluded that current evidence supports the integrative treatment of bipolar disorder using combinations of mood stabilizers and select nutrients. As this review was not performed in a systematic way, it could be subject to bias. Still, it offers a meta-view on the evidence base of complementary medicine for bipolar disorder. We also did a systematic review of natural medicines for schizophrenia (chapter 5). We found 105 high-quality RCTs (with a Jadad score of 3 or higher) that show emerging evidence for improved outcome by adding herbs or nutrients to antipsychotics. However, most study samples are small, duration is generally short, they only cover a modest part of the globe's geography, and most results need replication. Even systematic reviews can be subject to bias (Tricco et al., 2008). For that reason protocols to perform systematic reviews have been developed (www.cochrane.org), but these were not applied here. Although we did use Jadad scores to assess the quality of RCTs, some unintended bias cannot be ruled out.

The above-mentioned reviews have focused on RCTs because these are regarded the 'gold standard' in medical research. This is because the RCT has strong features that control for bias and confounding (e.g. randomization), which results in high internal validity. As a corollary, however, external or ecological validity is often compromised (Howard et al., 1996; Natan et al., 2000). 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) to answer 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?) or questions of mechanism (why does this treatment work?). 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 or experience sampling can be useful to answer these questions (Molenaar & Cambell, 2009; Hilliard, 1993; VandenBroucke et al., 2006; Nikles et al., 2004; Aan het Rot et al., 2012). Therefore, we did a single-subject study using time-series analysis to unravel the dynamic interplay between symptom and treatment variables in a multi-component treatment of anxiety disorder (chapter 6). We found that relaxation practice increased this patient's energy levels, and - via these - reduced his anxiety levels. Physical activity appeared to have the opposite effect, worsening the symptoms. Further, a feedback effect from energy to relaxation was found; increases in energy increased the patient's tendency to do his relaxation practices, indicating a positive spiral. Although the effects found in this paper were significant, they only applied to one patient, so the generalizability to the population was low. More studies are needed to confirm or refute our findings. The study did show the potential of high-intensity time-series designs to disentangle complex interactions in systems of multiple interconnected variables.

The overall outcome of integrative (mental) health care systems has hardly been investigated thus far (Verhoef, 2004). Since 2004 only a few routine outcome studies that addressed the effectiveness of treatments at a center for integrative

mental health have been published (Greeson et al., 2008; Mykleburst et al., 2008). So, we decided to evaluate the outcome of treatment at the Center for Integrative Psychiatry, using routine outcome measurement (ROM) (chapter 7). We discussed pitfalls associated with the assessment, analysis, and interpretation of ROM data, using data of 376 patients. 206 patients (55%) completed one or more follow-up measurements. Mixed-model analysis showed significant improvement in symptomatology, quality of life, and autonomy, and differential improvement for different subgroups. Effect sizes were small to large, depending on the outcome measure and subgroup. Subtle variations in analytic strategies influenced effect sizes substantially. Because of many problems inherent to the design and analysis of ROM data we could not draw conclusions about (comparative) treatment effectiveness. Still, this paper yielded some insights into the characteristics of patients visiting centers for integrative mental health, their diagnoses and their satisfaction with integrative psychiatry.

Criticism

During these years of research and practice of integrative psychiatry we sometimes encountered strong opposition and criticism (Kuipers & Gijsman, 2006; Van den Berg & Hengeveld, 2010; Renckens, 2013). Some criticism has been described and answered at the end of previous paragraphs. Others are discussed here.

Most of the critics state that we should not get involved in non-conventional medicines in any way, as they are ‘unscientific’. Medicine that is based on ‘ridiculous principles’ should not be investigated, so they say (e.g. Renckens, 2004). They think it is a waste of money and time. However, we feel that science should not be limited to conventional medicine, but can be applied to any medicine, as the scientific method is a way of relating to phenomena following certain rules and principles. In other words, it is not the subject that determines if it is scientific or not, it is the way in which the investigation and analysis are done. If we would decide by ourselves which phenomena should and should not be investigated in medicine, based on our subjective ideas, that would not be beneficial for the progress of medicine. Also, what seems ridiculous to one person may be convincing to another. Many patients use these medicines and pay for it; they seem to find them convincing. Who are we to decide that this is nonsense? Moreover, many findings in medicine seemed ridiculous and were rejected when they were first proposed (e.g. arteriosclerosis causes heart disease, vitamins prevent disease, microbes cause disease; Olshansky & Dossey, 2003). Therefore, we argue for an open and critical attitude.

Kuipers and Gijsman (2006) argued that ‘it has taken psychiatry many years to become a medical specialty. We have been working hard to get rid of vagueness, irrationality and unsubstantiated claims. We are now a scientific discipline. We need to armor ourselves against modern trends, magic and exotic religion’. We do agree that science should be differentiated from magic or religion. However, we think that showing an interest and respect for the opinion and preferences of patients, and trying to investigate therapies by means of proper scientific methods is not the same as being vague, irrational or magical. There is a need to be open to different perspectives on health and disease. Moreover it is an illusion to think that conventional psychiatry is scientific in all respects (Dobbs, 2013). Recently, the very basis of psychiatric diagnosis and classification, the Diagnostic and Statistical Manual of mental disorders (DSM), has been criticized by the National Institute of Mental

Health for being based on consensus rather than scientific evidence (Insel, 2013). The institute has already started to redirect its research focus away from DSM categories to research across categories or research on subdivisions of categories. When we are open to other perspectives, new opportunities might emerge. For instance, Van der Greef (2011) reported in Nature how systems biology applied to traditional Chinese medicine (TCM) yields promising results and opens possible new ways in conventional medicine. Reviews have shown positive outcome of Chinese herbal medicine (Rathbone et al., 2007), Ayurvedic medicine (Agarwal, 2010) and other complementary medicine (Hoenders et al., in preparation; chapter 5) when combined with antipsychotic drugs.

Renckens (2013) expressed strong criticism on our paper on wind direction and mental health (Bos et al., 2012; not part of this thesis). In this paper we used time-series analysis to study the relationship between weather parameters and symptomatology in a patient suffering from recurrent anxiety. Wind direction was related to the patient's energy levels; these were significantly lower when the wind blew from the southeast. The effects could not be explained by other weather parameters. Renckens (2013) asked whether we had lost our mind, doing research on the influence of weather on mental states. He invited readers to comment on our level of insanity in categories ('fool, damn fool, bloody fool, fucking fool'). While we acknowledge that the influence of wind on mental health is an unusual one, there is reason to assume it might exist, based on local reports (e.g. on 'ill winds' like Foehn, Mistral and Sirocco), other research (e.g. ecopsychology) and our data. Moreover, we used sound scientific methods to investigate this relationship. But that is not the point. What is most intriguing is the question: why do critics feel the need to devaluate, even offend us, for engaging in research on complementary / alternative medicine? Milders (2006) suggested it is out of fear. Whether or not it was out of fear, it seems reasonable to assume that the controversy between mechanism / reductionism and holism / vitalism, as described in chapter 2, is involved in these heated debates, because a challenge of strongly held convictions can provoke a strong emotional response.

Some psychiatrists argue that when patients ask doctors for advice on complementary or alternative medicine, they should refuse to give it or even discourage them to try it. But if we do not advice patients on (lack of) evidence for effectiveness and safety of these medicines, they will be more vulnerable to unsubstantiated claims made on the Internet. Also there is a risk for interactions between drugs and herbs (Ernst, 2003a). Only 3% of the user population is aware of this potential risk (Walter & Gray, 1999). So, even from a medical perspective it is important to know what patients buy and try. But beyond that, patients do want their medical doctors to advice them on complementary medicines (Gray et al., 1998; Hoenders et al., 2006). The World Health Organization (WHO, 2003) and European Parliament (EP, 1997) have also advised their member states to do so. Respecting patients' opinions and informing them can also improve the therapeutic relationship (Stevingson, 2001) and therewith 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 thereapeutic alliance (Wampold, 2001; Driessen et al., 2010; Baldwin et al., 2007; De Jong, 2011).

There is also criticism on applying lifestyle medicine. Some psychiatrists say: 'I am not trained to prescribe herbs, nutrients or lifestyle changes, that should not be work for doctors'. But we feel that any therapy that has been proven effective and safe in clinical trials for mental health problems should be known to and possibly prescribed by psychiatrists. The committee in charge of crediting conferences with

continuous medical education points did not agree to give points for a three day training in compassion (a training that builds on mindfulness with a focus on mildness and empathy), stating: 'systematic training of compassion is for now not relevant for doctors'. However, we feel that compassion and empathy are essential for doctors and all those involved in healthcare. It is critical for establishing and maintaining a good therapeutic relationship, which is one of the most powerful predictors of success in (psycho-)therapy (Wampold, 2001; Driessen et al., 2010; Baldwin et al., 2007; De Jong & Colijn 2010). Moreover, there is emerging scientific evidence for the positive effects of compassion training for psychiatric disorders (Gilbert & Proctor, 2006; Mayhew & Gilbert, 2008; Laithwaite et al., 2009).

Integrative research focus

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.

In this thesis we used different research methods in an effort to answer some of the research questions related to integrative medicine / psychiatry. Based on literature searches, we wrote essays on the conceptual foundation. Taking into account the Dutch law, scientific research, jurisprudence and rules of professional bodies, we wrote a treatment protocol for the judicious application of complementary medicine in conventional mental health care. We assessed the quality and results of RCTs on complementary medicine in two reviews. Then we used a single-subject study to unravel the interrelatedness of symptoms and treatment variables using time-series analysis. Finally, we provided some insights into the characteristics of patients visiting centers for integrative mental health, their diagnoses and their satisfaction with integrative psychiatry, using routine outcome monitoring data.

Future research

Research into integrative (mental) health is still in its infancy. Far less than 1% of the research budget in the United Kingdom and the United States of America is spent on complementary / alternative medicine (Ernst, 2003b). The rest is spent on conventional medicine. In the Netherlands the situation is probably not much different, although exact figures are lacking. This thesis is a small step towards a more evidence-based integrative psychiatry.

Future research in integrative psychiatry should be integrative in methodology and include: 1) pragmatic trials comparing integrative treatment approaches to conventional treatments to examine (cost-)effectiveness and safety aspects; 2) clinical trials that study patient-tailored multiple-component interventions with both quantitative outcome measures (e.g. laboratory tests and validated psychometric scales) and qualitative experiences (e.g. subjective perceptions of improved functioning, placebo and nocebo effects), in RCTs as well as single-subject time-series designs; 3) use of pharmacogenomic, epigenetic, and neuroimaging technologies to elucidate mechanisms of action; 4) exploration of the impact of lifestyle modification (e.g. diet, exercise, stress management) on mental health as

both preventatives and treatments; 5) studies of the interactions between specific pharmaceuticals and complementary or alternative therapies and medicines (potentially beneficial synergistic and potentially dangerous adverse or toxic effects) (Sarris et al., 2013); and last but not least 6) qualitative studies with epistemological consideration of the paradigms of widely used Eastern medicine such as TCM, Tibetan medicine and Ayurveda. These paradigms contain insights which fit well with an immunological view of health that is often at the basis of lifestyle interventions. This is an area where more of a systems approach is warranted than an approach that looks simply at the individual therapies of whole systems (e.g. acupuncture, herbal medicines, massage, etc) rather than at their underlying diagnostic and explanatory models. The latter, in the long run, holds the potential to yield important new insights for expanding the biomedical paradigm – with major implications for medical care and human health (Bodeker, 2012).

Finally

In this thesis we differentiated integrative medicine, as a new concept of health care, from conventional medicine / psychiatry, arguing that it may provide some solutions to current challenges in health care. Looking closer one might argue that most aspects of integrative psychiatry should just be part of conventional psychiatry. Most conventional doctors agree that the therapeutic relationship is central, that we should not only look at diseases but at the whole patient, and that focusing on health is as important as trying to eradicate symptoms. Only the third principle, the use of non-conventional medicines, remains controversial. So, is integrative psychiatry really different from conventional psychiatry? Is it really necessary to distinguish them? The answer is yes and no.

Yes, because even though these three principles *should* be part of conventional medicine, they usually are not. Concepts like the biopsychosocial model are acknowledged in theory, but rarely practiced fully. Moreover, the third principle often provokes strong emotional responses and prejudice, which are not evidence-based and hinder progress. That is why we discussed those responses extensively.

No, because most clinicians agree that these principles should be part of medicine. So, after differentiating at the start of this thesis we now arrive at integration once again, hoping that soon most aspects of integrative medicine are accepted and integrative psychiatry will just be ‘psychiatry’.

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Summary

Integrative medicine (IM) is a new concept of health care that was launched by a consortium of eight academic health centers in the USA in the late nineties of the past century. It has been defined as (1) the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, (2) focuses on the whole person, is (3) 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). Since its start there has been great interest from the medical and scientific community and a steady growth. Today fifty-five academic health centers in North America are active members of this consortium. Also in Europe (United Kingdom and Germany) Asia and Australia, IM initiatives regarding clincs and research have been undertaken.

Many research groups, health centers, educational, advocacy and policy activities related to IM exist, but the part of psychiatry / mental health care seems undervalued, especially as regards research. Because of that, we collaborated with researchers and clinicians from Australia and the United States of America to assess the need for IM in mental health care and to propose solutions to current challenges (Saris et al., 2013).

Mental illness now accounts for about one-third of adult disability globally, reflecting marked societal and personal suffering, and enormous social and economic costs. However, the most common treatments in psychiatry (medication and psychotherapy) have turned out to be not as effective as previously thought (Kirsch et al., 2008; Turner et al., 2008; Cuijpers et al., 2010; Cuijpers et al., 2011). So, it seems there is a need for change in the paradigm and practices of mental healthcare (Bracken et al., 2012). Integrative medicine in mental health care (Integrative Mental Health; IMH) may offer some answers to these challenges. It adopts the biopsychosociospiritual model, utilizing evidence-based treatments from different medical traditions. Besides mainstream interventions (e.g. psychopharmacology, psychosocial therapies) IMH incorporates the judicious use of evidence-based complementary and alternative (CAM) medicines and therapies in addition to health-promoting lifestyle changes (Sarris et al., 2013).

Part I: Conceptual foundation

As the use of complementary and alternative medicine (CAM) in conventional health care (implicit in part 3 of the definition) is the most controversial part of IM and because this subject led to heated debates in the Netherlands, we decided to focus our research on this part of IM. The heated debates seem to indicate that CAM provokes strong emotions. This can be explained by strong adherence to (opposing) paradigms: those in favor of CAM (the vitalism / holism paradigm) and those against (the mechanism / reductionism paradigm; Hoenders et al., 2008).

IM provides a bridge between these paradigms, because it accommodates both conventional treatments and CAM, emphasizing wellness and healing of the entire person (biopsychosociospiritual dimensions) in the context of a supportive and effective physician-patient relationship (Bell et al., 2002). Its success seems related to the fact that integration is not only a current tendency in medicine, but also a trend fitting the contemporary spirit of the age in which integration seems to be the most

common focus. It can be observed in religion, philosophy, spirituality and psychotherapy as well. It follows a period in which differentiation took central stage but did not lead to absolute, unquestionable truths (Hoenders et al., 2012).

Part II: Implementation

We did an inquiry into the use of CAM by psychiatric outpatients and found that 42% of nearly 600 participants had used CAM in the previous year, most of them with perceived good results, but mostly without telling their conventional doctor about this use. This may explain why we found, when asking their doctors, that they underestimated this use (Hoenders et al., 2006). Others have reported similar findings: 43% of patients with anxiety disorder (Bystritsky et al., 2012), and 53% of patients with depression (Wu et al., 2007) use complementary or alternative medicine (CAM). These patients perceived such treatments as improving their physical, emotional, cognitive, social, and spiritual functioning, reducing symptom severity and promoting recovery and wellness (Russinova et al., 2009).

Most patients in our study also reported that they want their conventional doctors to inform them about CAM and assist them in making health care choices (Hoenders et al., 2006). This is also what the European Parliament (1997) and World Health Organization (2003) have advised their membership states to do. Because of that, we felt there was a need to formulate a protocol to assist patients and doctors in using CAM in a judicious way. We felt it should answer patients' needs and wishes; respect their freedom of choice; offer western medicine and CAM that are safe and effective; protect against quackery and abuse; be based on Dutch law, the jurisprudence of the Medical Disciplinary Tribunal and the rules of the Dutch Association of Medical Practitioners (KNMG); and be based on scientific evidence. This resulted in the CAM protocol (Hoenders et al., 2011).

Part III: Effectiveness

The CAM protocol emphasizes the need for an evidence-based approach. To assess the evidence base for CAM we did reviews on complementary medicines for severe mental illness.

In a comprehensive review on bipolar disorder we found several positive controlled studies of nutrients (such as folic acid) and Chinese herbs in combination with conventional mood stabilizers and antipsychotic medications in bipolar depression, while branched-chain amino acids and magnesium seem effective (in small studies) in attenuating mania. In the treatment of bipolar depression evidence was mixed regarding to omega-3 fatty acids, while isolated studies provide provisional support for a multi-nutrient formula, n-acetylcysteine (NAC), and for L-tryptophan. We concluded that current evidence supports the integrative treatment of BD using combinations of mood stabilizers and select nutrients or herbs (Sarris et al., 2011).

In a systematic review on schizophrenia we found that high-quality research on natural medicines for schizophrenia and other psychotic disorders is scarce. However, there is emerging evidence for glycine, sarcosine, NAC, some Chinese and Ayurvedic herbs, ginkgo biloba and vitamin B6 in improving symptoms of schizophrenia when added to antipsychotics (glycine not when added to clozapine).

There is inconclusive or absent evidence for omega-3, D-serine, D-alanine, D-cycloserine, B vitamins, vitamin C, dehydroepiandrosteron (DHEA), pregnenolone (PREG), estradiol, inositol, gamma-hydroxybutyrate (GHB) and des-tyr-gamma-endorphin when added to antipsychotics. Omega-3 without antipsychotics might be beneficial in the prevention of schizophrenia. Ayurvedic herbs seem effective without antipsychotics in one large study. Other agents without antipsychotics (vitamin B3, vitamin C, sarcosine, glycine, protilerin) do not seem effective or have only been tested in single or small trials. Ginkgo biloba and vitamin B6 seem effective for diminishing side effects of antipsychotics (tardive dyskinesia and akathisia). The evidence for diminishing side effects of antipsychotics by omega-3, melatonin and DHEA is inconclusive. All identified agents produce only mild or no side effects. Most study samples are small, study and treatment duration is generally short, studies only cover a modest part of the globe's geography, and most results need replication (Hoenders et al., in preparation).

The next step was to assess the effectiveness of the integrative psychiatry approach in daily practice. Psychiatric research in the past 50 years has focused primarily on neurobiological mechanisms and psychotherapeutic techniques. More recent research has explored lifestyle moderators of mental health, mind-body therapies, and natural products (Sarris, 2011). At present there is a scarcity of real-practice research on integrative approaches in medicine and psychiatry (i.e. approaches that combine multiple interventions in a personalized manner), with most studies employing randomized control trial (RCT) designs to examine single interventions at a group level, thereby ignoring individual differences (Slade & Priebe, 2011; Molenaar & Campbell, 2009). Advances in research and clinical practice of psychiatry will take place when research methodologies permit the rigorous evaluation of complex interventions involving multiple therapeutic modalities (mirroring true clinical practice) to treat real-world clinical populations. So a truly integrative research focus is needed. While methodologically challenging, this approach may have the potential to elucidate the relative contributions of social, psychological, biological and spiritual factors in each unique patient's response to combined treatment modalities (Sarris et al., 2013).

Along these lines we did a single-subject study using time-series analysis to unravel the dynamic interplay between symptom and treatment variables in a multi-component treatment of anxiety disorder. We found that relaxation practice increased this patient's energy levels, and - via these - reduced his anxiety levels. Physical activity appeared to have the opposite effect, worsening the symptoms. Further, a feedback effect from energy to relaxation was found; increases in energy increased the patient's tendency to do his relaxation practices, indicating a positive spiral. Although the effects found in this paper were significant, they only applied to one patient, so the generalizability to the population was low. More studies are needed to confirm or refute our findings. The study did show the potential of high-intensity time-series designs to disentangle complex interactions in systems of multiple interconnected variables (Hoenders et al., 2012).

Also routinely assessed outcomes can be used to assess real-life effectiveness of treatments. We evaluated the outcome of treatment at the Center for Integrative Psychiatry, using routine outcome measurement (ROM). We discussed pitfalls associated with the assessment, analysis, and interpretation of ROM data, using data of 376 patients. The sample consisted of 115 men and 261 women. Mean age was 41.3 years (SD = 12.8). Fifty percent had a high educational level. Median illness duration was 11 years (IQR = 15). Median treatment duration was 288 days

(IQR = 356). The sample was highly heterogeneous as regards diagnosis. Mood (36%) and anxiety disorders (15%) (axis I of DSM IV) and borderline (8%) and type C personality disorders (18%; axis II) were most prevalent. Patients' satisfaction with the treatment center was good (median = 8; range 1 to 10). 206 patients (55%) completed one or more follow-up measurements. Mixed-model analysis showed significant improvement in symptomatology, quality of life, and autonomy, and differential improvement for different subgroups. Effect sizes were small to large, depending on the outcome measure and subgroup. Subtle variations in analytic strategies influenced effect sizes substantially. Because of many problems inherent to the design and analysis of ROM data we could not draw conclusions about (comparative) treatment effectiveness. Still, this paper yielded some insights into the characteristics of patients visiting centers for integrative mental health, their diagnoses and their satisfaction with integrative psychiatry (Hoenders et al., 2013).

Integrative research focus

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.

In this thesis we used different research methods in an effort to answer some of the research questions related to integrative medicine / psychiatry. Based on literature searches, we wrote essays on the conceptual foundation. Taking into account the Dutch law, scientific research, jurisprudence and rules of professional bodies, we wrote a treatment protocol for the judicious application of complementary medicine in conventional mental health care. We assessed the quality and results of RCTs on complementary medicine in two reviews. Then we used a single-subject study to unravel the interrelatedness of symptoms and treatment variables using time-series analysis. Finally, we provided some insights into the characteristics of patients visiting centers for integrative mental health, their diagnoses and their satisfaction with integrative psychiatry, using routine outcome monitoring.

Future research

Research into integrative (mental) health is still in its infancy. Far less than 1% of the research budget in the United Kingdom and the United States of America is spent on complementary / alternative medicine (Ernst, 2003). The rest is spent on conventional medicine. This thesis is a small step towards a more evidence-based integrative psychiatry.

Future research in integrative psychiatry should be integrative in methodology and include: 1) pragmatic trials comparing integrative treatment approaches to conventional treatments to examine (cost-)effectiveness and safety aspects; 2) clinical trials that study patient-tailored multiple-component interventions with both quantitative outcome measures (e.g. laboratory tests and validated psychometric scales) and qualitative experiences (e.g. subjective perceptions of improved functioning, placebo and nocebo effects), in RCTs as well as single-subject time-series designs; 3) use of pharmaco-genomic, epigenetic, and neuroimaging

technologies to elucidate mechanisms of action; 4) exploration of the impact of lifestyle modification (e.g. diet, exercise, stress management) on mental health as both preventatives and treatments; 5) studies of the interactions between specific pharmaceuticals and complementary or alternative therapies and medicines (potentially beneficial synergistic and potentially dangerous adverse or toxic effects; Sarris et al., 2013); and last but not least 6) qualitative studies with epistemological consideration of the paradigms of widely used Eastern medicine such as TCM, Tibetan medicine and Ayurveda. This is an area where more of a systems approach is warranted than an approach that looks simply at the individual therapies of whole systems (e.g. acupuncture, herbal medicines, massage, etc). This kind of research holds the potential to yield important new insights for expanding the biomedical paradigm – with major implications for medical care and human health (Bodeker, 2012; Van der Greef, 2011).

Finally

In this thesis we differentiated integrative medicine, as a new concept of health care, from conventional medicine / psychiatry, arguing that it may provide some solutions to current challenges in health care. Looking closer one might argue that most aspects of integrative psychiatry should just be part of conventional psychiatry. Most conventional doctors agree that the therapeutic relationship is central, that we should not only look at diseases, but at the whole patient and that focusing on health is as important as trying to eradicate symptoms. Only the third principle, the use of non-conventional medicines, remains controversial. So, is integrative psychiatry really different from conventional psychiatry? Is it really necessary to distinguish them? The answer is yes and no.

Yes, because even though these three principles *should* be part of conventional medicine, they usually are not. Concepts like the biopsychosocial model are acknowledged in theory, but rarely practiced fully. Moreover the third principle often provokes strong emotional responses and prejudice, which are not evidence-based and hinder progress. That is why we discussed those responses extensively.

No, because most clinicians agree that these principles should be part of medicine. So, after differentiating at the start of this thesis we now arrive at integration once again, hoping that soon most aspects of integrative medicine are accepted and integrative psychiatry will just be ‘psychiatry’.

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Summary in Dutch [Nederlandse samenvatting]

Eind jaren negentig werd door een Amerikaans consortium van acht academische ziekenhuizen een nieuw concept gelanceerd: Integrale geneeskunde ('integrative medicine'; IM). Integrale geneeskunde (1) stelt de therapeutische relatie tussen patiënt en hulpverlener weer centraal, (2) kijkt naar de gehele mens, (3) maakt op basis van wetenschappelijk onderzoek gebruik van alle geschikte therapeutische benaderingen, zorgprofessionals en disciplines, om zo (4) tot optimale gezondheid en optimaal herstel te komen (The Consortium, 2004). Vanaf die tijd is er voor deze nieuwe stroming veel interesse getoond vanuit de medische en wetenschappelijke wereld. Dit heeft er toe geleid dat er vandaag de dag vijfenvijftig medisch academische gezondheidscentra in Noord-Amerika actief lid zijn van het consortium. Ook in Europa (vooral Duitsland en Verenigd Koninkrijk), Azië en Australië zijn IM-initiatieven op het gebied van patiëntenzorg en onderzoek ontstaan.

Ondanks een toenemende interesse en toepassing van integrale geneeskunde blijft deze ontwikkeling binnen de geestelijke gezondheidszorg achterlopen, vooral op het gebied van onderzoek. Integrale geneeskunde toegepast in de geestelijke gezondheidszorg / psychiatrie wordt 'integrale psychiatrie' genoemd. Een integrale benadering binnen de (geestelijke) gezondheidszorg lijkt van belang omdat het mogelijk oplossingen kan bieden voor de hedendaagse problemen binnen de (geestelijke) gezondheidszorg (Sarris et al., 2013). Wereldwijd beslaan psychische stoornissen een derde van alle ziektelast onder volwassenen, hetgeen niet alleen persoonlijk lijden met zich meebrengt maar ook maatschappelijke problemen en hoge kosten. Tevens is gebleken dat, wanneer rekening gehouden wordt met publicatiebias, de meest gangbare behandelingen binnen de psychiatrie (medicatie en psychotherapie) minder effectief zijn dan eerder werd aangenomen (Kirsch et al., 2008; Turner et al., 2008; Cuijpers et al., 2010; Cuijpers et al., 2011). Het lijkt erop dat een nieuw paradigma nodig is binnen de geestelijke gezondheidszorg (Bracken et al., 2012). Een integrale gezondheidszorg (d.w.z. integrale geneeskunde en psychiatrie) biedt zo'n nieuw paradigma. Het hanteert een bio-psycho-sociaal-spiritueel model dat gebruik voorstaat van evidence-based behandelingen vanuit verschillende geneeskundige tradities. Het spirituele aspect verwijst hierbij naar zin- en betekenisgeving en naar existentiele vragen die een rol spelen bij (herstel van) ziekte (Koenig, 2000). Naast reguliere interventies (bijvoorbeeld psychofarmaca en psychosociale therapieën) maakt de integrale gezondheidszorg op zorgvuldige wijze gebruik van evidence-based complementaire en alternatieve medicatie en behandelingen en bevordert het tevens een gezonde leefstijl (Sarris et al., 2013).

Deel I: Theoretische achtergrond

Daar het gebruik van complementaire en alternatieve geneeswijzen (CAG) binnen de reguliere gezondheidszorg (impliciet onderdeel van deel 3 van de definitie van IM; zie eerste alinea hierboven) het meest controversiële onderdeel van integrale geneeskunde is en omdat dit onderwerp in Nederland tot verhitte discussies heeft geleid, hebben we besloten om ons onderzoek op dit onderdeel toe te spitsen. De verhitte discussies laten zien dat het onderwerp CAG een emotioneel beladen

onderwerp is voor veel mensen. Dit komt wellicht omdat er sterk aan tegengestelde paradigma's wordt vastgehouden: de meeste voorstanders van CAG hangen het paradigma 'vitalisme / holisme' aan, terwijl tegenstanders van CAG meestal het paradigma 'mechanisme / reductionisme' als uitgangspunt hanteren. Deze paradigma's verschillen categorisch en zijn daardoor moeilijk te verenigen. Dit in tegenstelling tot de andere verschillen tussen regulier en CAG, die dimensioneel zijn (Hoenders et al., 2008).

Integrale geneeskunde slaat een brug tussen deze twee paradigma's, omvat zowel de reguliere geneeskunde als CAG en benadrukt gezondheid en het herstel van de gehele persoon (bio-psycho-sociaal-spiritueel model) binnen een optimale therapeutische relatie (Bell et al., 2002). Het succes van de integrale geneeskunde kan onder andere verklaard worden door het feit dat integrale geneeskunde aansluit bij breder waargenomen tendensen tot integratie binnen de hedendaagse tijdgeest. Zowel in religie, filosofie, spiritualiteit als psychotherapie is deze trend te herkennen. Het lijkt een reactie op een voorgaande periode waarin juist de nadruk lag op differentiatie, een periode waarin geen absolute, onbetwistbare zekerheden werden gevonden (Hoenders et al., 2012).

Deel II: Toepassing

We hebben onderzoek gedaan naar het gebruik van CAG bij poliklinische patiënten in de GGz en ontdekten dat 42% van de bijna 600 ondervraagden CAG had gebruikt in het voorafgaande jaar. De meeste van hen rapporteerden positieve effecten, maar gaven ook aan dat zij hun CAG gebruik niet hadden besproken met hun reguliere arts, vooral uit angst voor een negatieve reactie. Dit lijkt te kunnen verklaren waarom de artsen in kwestie het gebruik van CAG door hun patiënten flink bleken te onderschatten (Hoenders et al., 2006). Andere onderzoekers rapporteerden vergelijkbare resultaten: 43% van patiënten met een angststoornis (Bystritsky et al., 2012) en 53% van patiënten met een depressie (Wu et al., 2007) gebruikten complementaire en alternatieve geneeswijzen (CAG). Deze patiënten gaven aan dat de behandelingen hielpen bij het verbeteren van hun lichamelijk, emotioneel, cognitief, sociaal en spiritueel functioneren, dat het de ernst van hun klachten verminderde en dat het ondersteunend was voor herstel en gezondheid (Russinova et al., 2009).

In ons eigen onderzoek gaven de meeste patiënten aan dat ze graag door hun reguliere arts geadviseerd wilden worden over het gebruik van CAG en dat ze graag ondersteund zouden willen worden in het maken van keuzes op dit gebied (Hoenders et al., 2006). Dit is in overeenstemming met wat het Europese parlement (1997) en de Wereld Gezondheid Organisatie (2003) hun leden hebben geadviseerd. Met dit in gedachten hebben we een protocol opgesteld voor artsen en patiënten om hen te helpen verstandige keuzes te maken wanneer het gaat om het toepassen en gebruiken van CAG. We wilden recht doen aan de diverse kenmerken, wensen en behoeften van patiënten; hun keuzevrijheid respecteren; zowel reguliere behandelingen als CAG aanbieden die bewezen effectief en veilig zijn; beschermen tegen kwakzalverij en misbruik; en ons baseren op de Nederlands wet, de jurisprudentie van het Medisch Tuchtcollege, de regels van de Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst (KNMG) en op wetenschappelijk onderzoek. Dit resulteerde in het CAG protocol (Hoenders et al., 2011).

Deel III: Effectiviteit

Het CAG protocol benadrukt het belang van een evidence-based aanpak. Om de wetenschappelijke onderbouwing van CAG verder in kaart te brengen hebben we twee (systematische) reviews uitgevoerd naar complementaire medicatie bij ernstige psychiatrische aandoeningen.

In een review naar de effectiviteit van complementaire geneeswijzen bij bipolaire stoornissen vonden we meerdere studies van hoge kwaliteit die een positief effect aantoonden van de combinatie van voedingssupplementen met reguliere stemmingsstabilisatoren of antipsychotica bij bipolaire depressie. Daarnaast lijken sommige specifieke aminozuren (BCAA) en magnesium een positief effect te hebben bij manie (in kleine studies). Ten aanzien van het effect van omega-3 vetzuren bij bipolaire depressie worden wisselende resultaten gevonden. Een positief effect van multivitaminen, N-acetylcysteïne en L-tryptofaan wordt in enkele studies gevonden (Sarris et al., 2011).

In een systematisch review naar schizofrenie werd duidelijk dat weinig onderzoek van hoge kwaliteit gedaan is om het effect van natuurlijke medicijnen bij schizofrenie of andere psychoses in kaart te brengen. Desondanks vonden we 105 RCT's met een Jadad score van 3 of hoger. In deze studies wordt bewijs gevonden voor verbetering van symptomen wanneer glycine, sarcosine, N-acetylcysteine (NAC), bepaalde Chinese en Ayurvedische kruiden, ginkgo biloba of vitamine B6 als aanvulling op een antipsychoticum wordt gegeven (dit gold echter niet voor glycine als aanvulling op clozapine). Er is geen of onvoldoende bewijs voor een effect van omega-3 vetzuren, D-serine, D-alanine, D-cycloserine, vitamine B, vitamine C, dehydroepiandrosteron (DHEA), pregnenolone (PREG), estradiol, inositol, gamma-hydroxybutyrate (GHB) en des-tyr-gamma-endorfine als aanvulling op antipsychotica. Omega-3 vetzuren zonder antipsychoticum lijken wel een positief effect te hebben op het voorkomen van schizofrenie. In een dubbelblinde RCT met 200 patiënten werd een positief effect van Ayurvedische kruiden zonder gebruik van antipsychotica aangetoond. Andere middelen die zonder een antipsychoticum werden aangeboden (vitamine B3, vitamine C, sarcosine, glycine, protilerine) zijn niet effectief gebleken of zijn alleen onderzocht in een enkel of klein onderzoek. Ginkgo biloba en vitamine B6 lijken bijwerkingen van antipsychotica te verminderen (tardieve dyskinesie en akathisie). Het effect van omega-3, melatonine en DHEA op het verminderen van bijwerkingen is onvoldoende bewezen. Hoewel de kwaliteit van de geïncludeerde studies goed is (dubbelblinde RCT's met een Jadad-score van 3 of hoger), zijn de meeste onderzochte groepen klein, is het tijdspad van de studie of de behandeling vaak kort, hebben de studies slechts betrekking op een klein deel van de wereldbevolking en dienen de meeste studies te worden gerepliceerd (Hoenders et al., in voorbereiding).

De volgende stap was het onderzoeken van het effect van een integrale psychiatrische aanpak in de dagelijkse praktijk. Onderzoek binnen de psychiatrie heeft zich de afgelopen 50 jaar vooral gericht op neurobiologische mechanismen en psychotherapeutische technieken. Recent onderzoek richt zich ook op het effect van leefstijl, mind-body therapieën en het gebruik van natuurlijke medicatie op de psychische gezondheid (Sarris, 2011; Walsh, 2011). Tot op heden is er weinig praktijkgericht onderzoek verricht naar de werking van een integrale benadering binnen de geneeskunde en psychiatrie. Het meeste onderzoek is gedaan naar op

zichzelf staande interventies, gemeten op groepsniveau middels RCT's, waarbij er niet gekeken werd naar individuele verschillen (Slade & Priebe, 2011; Molenaar & Campbell, 2009). Vooruitgang in onderzoek en praktijk kan worden geboekt wanneer de onderzoeksmethodologie het mogelijk maakt om complexe interventies, bestaande uit verschillende therapeutische behandelaspecten, gericht op de behandeling van klinische populaties in de praktijk te onderzoeken. Dit vraagt om een integrale onderzoeksfocus. Ondanks dat dit methodologisch gezien een uitdaging is, biedt deze aanpak wel de mogelijkheid om te onderzoeken welk aandeel sociale, psychologische, biologische en spirituele factoren hebben in het effect van bepaalde behandelcombinaties op unieke patiënten (Sarris et al., 2013).

Met dit in gedachten hebben wij een N=1 studie gedaan met tijdreeksanalyse om de complexe dynamiek van symptomen en behandelaspecten van een gecombineerde behandeling gericht op het verbeteren van een angststoornis te ontrafelen. We vonden voor de betreffende patiënt dat ontspanningsoefeningen het energieniveau verhoogden, en dat op deze manier de angstklachten afnamen. Beweging bleek echter juist een *negatief* effect op de angstklachten te hebben. Ook vonden we dat energie en ontspanning elkaar wederzijds positief beïnvloedden; een toename in energie vergrootte ook de neiging van de patiënt om zijn ontspanningsoefeningen te doen. Ondanks dat de gevonden effecten significant waren, beschrijft de studie slechts één persoon en dat maakt het moeilijk om de resultaten te generaliseren. Deze studie laat wel goed zien wat de mogelijkheden zijn van een individuele analyse van hoogfrequente tijdreeks-gegevens voor het onderzoeken van complexe interacties tussen meerdere elkaar onderling beïnvloedende factoren binnen een bepaald systeem (Hoenders et al., 2012).

Tenslotte onderzochten wij de effecten van behandeling in het Centrum Integrale Psychiatrie door gebruik te maken van Routine Outcome Monitoring (ROM). We beschrijven de valkuilen die zich voordoen bij het verzamelen, analyseren en interpreteren van gegevens bij dit type onderzoek aan de hand van de ROM-data van 376 patiënten die behandeld werden in ons centrum voor integrale psychiatrie. De steekproef bestond uit 115 mannen en 261 vrouwen met een gemiddelde leeftijd van 41,3 jaar (SD = 12,8). Vijftig procent was hoog opgeleid. Mediane ziekteduur was 11 jaar (IQR = 15). Mediane behandelduur van degenen die de behandeling hadden afgerond was 288 dagen (IQR = 356). De groep was zeer heterogeen wat betreft diagnose. Stemmingsstoornissen (36%) en angststoornissen (15%) (as 1 van de DSM-IV) en borderline (8%) en cluster-C persoonlijkheidsstoornissen (18%) (as 2) kwamen het meest voor. Van de patiënten met een voormeting hadden er 206 (55%) ook een of meerdere vervolgmetingen ingevuld. Een mixed-model-analyse liet zien dat klachten, kwaliteit van leven en autonomie significant verbeterden, en dat de mate van verbetering varieerde per subgroep. Effectgroottes varieerden van klein tot groot, afhankelijk van uitkomstmaat en subgroep. Kleine variaties in de analysestrategie hadden een aanzienlijk effect op de effectgroottes. We concludeerden dat de vele problemen die gepaard gaan met een ROM-design en de ROM-analyse het onmogelijk maken om valide conclusies te trekken over behandeleffecten en verschillen daarin tussen subgroepen. Desondanks laat dit artikel iets zien van de eigenschappen en diagnoses van patiënten die zich aanmelden bij een integrale zorginstelling en krijgen we zicht op hun tevredenheid met de geboden integrale psychiatrische zorg (Hoenders et al., 2013).

Een integrale onderzoeksfocus

Onderzoek binnen de geestelijke gezondheidszorg moet zich verbreden naar zowel de natuurwetenschappen als de sociale wetenschappen (Van Os, 2012; De Jong, 2013). Wetenschappelijke onderbouwing op basis van RCT's is belangrijk, maar door alleen deze informatiebron te gebruiken missen we belangrijke aanvullende inzichten vanuit andere goed onderbouwde onderzoeksmethoden (Slade & Priebe, 2001). Met andere woorden: naast een integrale behandelaanpak is ook een integrale onderzoeksaanpak nodig.

In dit proefschrift beschrijven we verschillende onderzoeksmethoden om verschillende onderzoeksvragen die leven binnen de integrale geneeskunde / psychiatrie te beantwoorden. Op basis van literatuuronderzoek schreven we essays over de theoretische achtergronden. Met de Nederlands wet, jurisprudentie, regels van beroepsorganisaties en wetenschappelijk onderzoek in het achterhoofd schreven we een behandelprotocol voor het zorgvuldig gebruik van complementaire geneeswijzen binnen de reguliere geestelijke gezondheidszorg. In twee reviews hebben we de kwaliteit en resultaten van RCT's naar het gebruik van complementaire medicatie in kaart gebracht. Daarnaast hebben we binnen een N=1 studie met behulp van tijdreeksanalyse de onderlinge verwevenheid van symptomen en behandelvariabelen blootgelegd. Tenslotte hebben we door het gebruik van Routine Outcome Monitoring een beeld gekregen van eigenschappen en diagnoses van patiënten die een integraal centrum voor psychiatrie bezoeken, en van hoe tevreden ze zijn met een integrale behandeling.

Toekomstig onderzoek

Onderzoek naar integrale (geestelijke) gezondheidszorg staat nog in de kinderschoenen. Minder dan 1% van het onderzoeksbudget van het Verenigd Koninkrijk en de Verenigde Staten wordt aan onderzoek naar complementaire en/of alternatieve geneeswijzen besteed (Ernst, 2003). Het overige budget gaat naar onderzoek gericht op reguliere geneeswijzen. Dit proefschrift is een kleine stap naar een evidence-based integrale psychiatrie.

Toekomstig onderzoek binnen de integrale psychiatrie zou gebruik moeten maken van een integrale methodologie en het zou de volgende elementen moeten bevatten: 1) pragmatische studies waarbij integrale behandelingen met reguliere behandelingen worden vergeleken om zo (kosten-)effectiviteit en veiligheidsaspecten te kunnen onderzoeken; 2) klinische studies met geïndividualiseerde multiple-component interventies met zowel kwantitatieve uitkomstmaten (laboratoriumtests en gevalideerde psychometrische schalen) als kwalitatieve uitkomstmaten (subjectieve ervaringen van verbeterd functioneren, placebo- en nocebo-effecten) waarbij naast RCT's ook single-subject time-series designs en experience sampling methoden worden gebruikt; 3) gebruik van farmacogenomische, epigenetische, en neuro-imaging technieken om werkingsmechanismen te verhelderen; 4) onderzoek naar het effect van leefstijlveranderingen op geestelijke gezondheid, zowel preventief als als onderdeel van behandeling; 5) studies die de interactie tussen bepaalde farmaceutica en complementaire of alternatieve behandelingen en medicatie onderzoeken (mogelijke gunstige synergetische en mogelijke negatieve of toxische effecten; Sarris et al., 2013); en last but not least 6) kwalitatieve studies naar de

werkingsmechanismen van veel gebruikte Oosterse geneeswijzen, zoals TCM (traditionele Chinese geneeswijzen), Tibetaanse geneeskunde en Ayurveda. Hierbij is meer een systeembenadering nodig dan een aanpak die alleen maar kijkt naar individuele onderdelen van hele geneeskundige systemen (zoals acupunctuur, kruiden, massage, etc). Dit soort onderzoek heeft de potentie om belangrijke nieuwe inzichten te genereren voor het verbreden van het biomedische paradigma – met belangrijke implicaties voor de geneeskundige zorg en de menselijke gezondheid (Bodeker, 2012; Van der Greef, 2011).

Tenslotte

In dit proefschrift presenteren we integrale geneeskunde/psychiatrie als een nieuw concept binnen de gezondheidszorg, onderscheiden we het van reguliere geneeskunde / psychiatrie en beargumenteren we dat het mogelijk een oplossing biedt voor hedendaagse problemen binnen de gezondheidszorg. Wanneer je er langer over nadenkt zou je kunnen stellen dat de meeste aspecten van integrale psychiatrie eigenlijk onderdeel (zouden moeten) zijn van reguliere psychiatrie. De meeste reguliere artsen delen immers de mening dat de therapeutische relatie centraal moet staan, dat we niet alleen moeten kijken naar symptomen maar naar de gehele patiënt, en dat de focus ook op gezondheid moet liggen in plaats van (alleen) op ziekteverschijnselen. Alleen het derde principe, het gebruik van complementaire / alternatieve geneeswijzen, blijft controversieel.

Dus, verschilt integrale psychiatrie nu echt van reguliere psychiatrie? Is het echt nodig om hier een onderscheid in aan te brengen? Het antwoord is ja en nee.

Ja, want ondanks dat deze principes standaard onderdeel *zouden moeten zijn* van reguliere geneeskunde, blijkt in de praktijk dat ze dit vaak niet zijn. Principes als het bio-psycho-sociaal model worden in theorie onderkend maar worden weinig in praktijk gebracht. Daarnaast blijken er betreffende het derde principe vaak heftige (emotionele) reacties los te komen en sterke vooroordelen te bestaan. De meerderheid van deze reacties en vooroordelen worden niet door wetenschappelijk onderzoek ondersteund en belemmeren derhalve de vooruitgang in de wetenschap en psychiatrie. Om die reden bespreken wij deze reacties en vooroordelen uitgebreid in de discussie van dit proefschrift.

Nee, omdat de meeste clinici het er over eens zijn dat deze principes onderdeel zouden moeten zijn van geneeskunde. Dus waar het aan het begin van dit proefschrift draaide om differentiatie, zijn we nu opnieuw aangekomen bij integratie: wij hopen dat de meeste aspecten van integrale geneeskunde geaccepteerd en geïntegreerd zullen worden en dat integrale psychiatrie gewoon ‘psychiatrie’ zal gaan heten.

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Martin Appelo, collega, vriend en co-promotor. Dank voor je steun, advies, humor en relativering (geen vlag op een modderschip). Elske Bos, collega-onderzoeker, vriendin en co-promotor. Dank voor je tomeloze inzet en zorgvuldigheid. Er ontgaat je niets. Dankzij jou is deze promotie op een hoger plan gekomen. Peter de Jonge, promotor, dank voor je bereidheid deel te nemen aan dit traject en voor je opbouwende kritiek. Joop de Jong, eerste promotor, dank voor je open-mindedness en je vertrouwen toen je dit avontuur negen jaar geleden met me aanging. Je was altijd beschikbaar voor steun en advies, maar liet mij ook veel ruimte om mijn eigen weg te gaan. Ik heb dat erg gewaardeerd.

Thanks to Adi Haramati, Gerry Bodeker and Joris Slaets, members of the PhD commission (leescommissie), who have generously dedicated their precious time to read and review the manuscript and to come from far away (United States of America and Malaysia) to participate in the pre-ceremony conference and the ceremony itself.

Dank aan Rikus Knegtering, Marjolein Boshuisen, Gineke Woltjes, alle AIOS en alle andere collega's van de A-opleiding van Lentis. Het werken als supervisor, mentor, docent en deelopleider volwassenenpsychiatrie met jullie allen is een dagelijkse bron van plezier en inspiratie.

Dank aan leden van het organiserend comité van het 2-jaarlijkse congres integrale psychiatrie (Martin Appelo, Elkana Waarsenburg, Bregje Hartogs, Karen van der Ploeg en Erik van den Brink) en aan alle ondersteuners (Alice Til, Anja Ellens, Gerke Terpstra, Rien Wijnen en het Grafisch Centrum, Petra Vellinga, Simon Broekema, Jenne Berghuis, Frans Weggers, Simona Perdon, Anne Helmus en 'huisband' TCQ). Het congres is elke keer weer een enorme klus, maar ook een groot plezier en bron van inspiratie. Op naar het zesde congres op 6 maart 2015!

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Thanks to Ron Glick, Jerome Sarris, James Lake and all other members of the International Network for Integrative Mental Health (INIMH). Thanks to all international friends and collegues in integrative medicine: Scott Shannon, Steve Goldfinger, Bernard Gesch, Andrew Weil, Rupert Sheldrake, Margaret Chesney, Barbara Frederickson, Paul Gilbert, Sunita Vohra, James Gordon, Dona Leova, Dean Ornish, Thierry Janssen, John Kabbat Zinn, Roberto Carris, Althea Gray, Kathi Kemper, Stephan Brunnhuber, Ruedi Schneider, Amchi Lobsang Tsultrim and Amchi Tseten.

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A special thank you to the late Prof dr David Servan-Schreiber; you were, and still are, a great source of inspiration, I cherish our friendship until this day.

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PhD portfolio

Peer reviewed publications in English:

Hoenders, H. J. R., Bartels-Velthuis, A. A., Vollbehr, N. K., Bruggeman, R., Knegtering, H., & De Jong, J. T. V. M. (In preparation). *Natural medicines in schizophrenia: a systematic review* Unpublished manuscript.

Hoenders, H. J. R., Bos, E. H., Bartels-Velthuis, A. A., Vollbehr, N. K., Van Der Ploeg, K., De Jonge, P., & De Jong, J. T. V. M. (2013). Pitfalls in the assessment, analysis, and interpretation of routine outcome monitoring (ROM) data; results from an outpatient clinic for integrative mental health. *Administration and Policy in Mental Health and Mental Health Services Research,* doi:10.1007/s10488-013-0511-7

Sarris, J., Glick, R., Hoenders, R., Duffy, J., & Lake, J. (2013). Integrative mental healthcare White Paper: Establishing a new paradigm through research, education, and clinical guidelines. *Advances in Integrative Medicine,* doi:dx.doi.org/10.1016/j.aimed.2012.12

Bos, E. H., Hoenders, R., & de Jonge, P. (2012). Wind direction and mental health: a time-series analysis of weather influences in a patient with anxiety disorder. *BMJ Case Reports, 2012* doi:10.1136/bcr-2012-006300

Hoenders, H. J. R., Appelo, M. T., & De Jong, J. T. V. M. (2012). Integrative medicine: a bridge between biomedicine and alternative medicine fitting the spirit of the age. *Sociology Mind,* (2), 441-446. doi:10.4236/sm.2012.24057

Hoenders, H. J. R., Bos, E. H., de Jong, J. T. V. M., & de Jonge, P. (2012). Temporal dynamics of symptom and treatment variables in a lifestyle-oriented approach to anxiety disorder: A single-subject time-series analysis. *Psychotherapy and Psychosomatics, 81*(4), 253-255. doi:10.1159/000335928

Hoenders, H. J. R., Appelo, M. T., van den Brink, E. H., Hartogs, B. M. A., & de Jong, J. T. V. M. (2011). The Dutch Complementary and Alternative Medicine (CAM) Protocol: To ensure the safe and effective use of complementary and alternative medicine within Dutch mental health care. *Journal of Alternative and Complementary Medicine, 17*(12), 1197-1201. doi:10.1089/acm.2010.0762

Sarris, J., Lake, J., & Hoenders, R. (2011). Bipolar disorder and complementary nedicine: Current evidence, safety issues, and clinical considerations. *Journal of Alternative and Complementary Medicine, 17*(10), 881-890. doi:10.1089/acm.2010.0481

Hoenders, H. J. R., Willgeroth, F. C., & Appelo, M. T. (2008). Western and alternative medicine: A comparison of paradigms and methods. *Journal of Alternative and Complementary Medicine, 14*(8), 894-896. doi:10.1089/acm.2007.0645

Peer reviewed publications in Dutch [Nederlandstalige publicaties] :

Hoffer, C., & Hoenders, H. J. R. (2010). Complementary, alternative and religious medicine. In J. T. V. M. De Jong, & S. Colijn (Eds.), *Cultural Psychiatry and Psychotherapy* [Complementaire, alternatieve en religieuze geneeswijzen] (pp. 451-468). Amsterdam, The Netherlands: De Tijdstroom.

Hoenders, H. J. R., Appelo, M. T., Van Den Brink, H., Hartogs, B. M. A., Berger, C. J. J., & Tamsma, H. H. (2010). Protocol for Alternative Medicine; towards a responsible application in mental health care. [Protocol voor alternatieve geneeswijzen; naar een verantwoorde toepassing in de GGz] *Tijdschrift voor Psychiatrie, 52*(5), 343-348.

Hoenders, H. J. R., Appelo, M. T., & Van Den Brink, H. (2008). Integrative Psychiatry in practice; research everything and keep the good. [Integrale Psychiatrie in de praktijk; onderzoek alles en behoud het goede] *Maandblad Geestelijke Volksgezondheid, 8*(9), 718-728.

Hoenders, H. J. R., Appelo, M. T., & Milders, C. F. A. (2006). Complementary and alternative medicine and psychiatry: Opinions and psychiatrists and patients [Complementaire en alternatieve geneeswijzen en psychiatrie: meningen van patiënten en psychiaters] *Tijdschrift voor Psychiatrie,* (9), 733-737.

Hoenders, H. J. R., & Wilterdink, J. (2004). Delirium bij een 73-jarige man na jarenlang ongewijzigd gebruik van betahistine. *Nederlands Tijdschrift Voor Geneeskunde, 148*(47), 2338-2341.

Other publications [overige publicaties]:

Hoenders, H. J. R., Appelo, M. T., & De Jong, J. T. V. M. (2012). Integrale geneeskunde: een brug tussen reguliere en alternatieve geneeswijzen passend bij de tijdgeest. *Tijdschrift Integrale Geneeskunde,* (1), 5-13.

Hoenders, H. J. R., Bos, E. H., De Jong, J. T. V. M., & De Jonge, P. (2011). Unraveling the temporal dynamics between symptom and treatment variables in a lifestyle-oriented approach to anxiety disorder. A time-series analysis. *GGz Wetenschappelijk, 15*(2), 11-30.

Milders, C. F. A., Hoenders, H. J. R., Van Den Brink, H., & Klijntunte, I. D. W. (2009). Geen diversiteit, zonder narriviteit. *Tijdschrift voor Psychiatrie,* (suppl 1), s205.

Hoenders, H. J. R., & Klijntunte, I. D. W. (2009). Integrale Psychiatrie in de praktijk; Evidence-based alternative medicine, en meer…. *Tijdschrift voor Psychiatrie,* (Suppl 1), s147.

Borgemeester, S., Appelo, M. T., & Hoenders, H. J. R. (2008). Complementary and alternative medicine in family practice: Opinions of family doctors and patients. [Complementaire en alternatieve geneeswijzen in de huisartsenpraktijk: de mening van huisartsen en patiënten] *GGz Wetenschappelijk, 12*(2), 26-32.

Hoenders, H. J. R. (2008). Naar een Integrale Psychiatrie. *Maandblad Geestelijke Volksgezondheid, 8*(9), 760.

Hoenders, H. J. R., Hartogs, B. M. A., & Van Den Brink, H. (2008). Gezondheidsbevorderende interventies in de GGz. *Tijdschrift voor Psychiatrie,* (Suppl 1), C83.

Hoenders, H. J. R., & Appelo, M. T. (2007). Reguliere en alternatieve geneeswijzen: pleidooi voor een integrale benadering. *Silhouet,* (2), 25-26.

Hoenders, H. J. R., & Appelo, M. T. (2007). Integrale Psychiatrie binnen Lentis. *Van Nature,* (4), 44-45.

Hoenders, H. J. R. (2005). Health for all with Integrated Medicine. *GGz Wetenschappelijk, 9*(2), 1-8.

Hoenders, H. J. R., Appelo, M. T., & Milders, C. F. A. (2004). Complementaire en alternatieve geneeswijzen en psychiatrie: feiten en meningen. *GGz Wetenschappelijk, 8*(2), 4-26.

Hoenders, H. J. R. (2003). Atomoxetine effectief voor ADHD bij volwassenen. *Tijdschrift voor Psychiatrie,* (45), 715-716.

International abstracts / presentations

Hoenders, H.J.R., Bos, E.H., Bartels-Velthuis, A.A., de Jong, J.T.V.M., de Jonge, P. (2013). An empirical illustration of pitfalls in assessment, analysis, and interpretation of data from routine outcome assessment (ROM) in an outpatient clinic for integrative mental health. ISCMR conference London, UK.

Hoenders, H.J.R., Bos, E.H., de Jong, J.T.V.M., de Jonge, P. (2012). Unraveling the temporal dynamics between symptom and treatment variables in a lifestyle-oriented approach to anxiety disorder: a time-series analysis. International research conference CAHCIM Minneapolis, USA.

Sarris, J., Lake, J. & Hoenders, H.J.R. (2012). Bipolar disorder and complementary medicine; current evidence, safety issues and clinical considerations. International research conference CAHCIM Minneapolis, USA.

Hoenders, H.J.R., Appelo, M.T., van den Brink, H., Hartogs, B.M.A., de Jong, J.T.V.M. (2009). The Dutch Complementary and alternative medicine (CAM) protocol. *European Journal of Integrative Medicine,* 1, 4, 254.

Hoenders, H.J.R., Willgeroth, F. & Appelo, M.T. (2009). Western and Alternative Medicine; a comparison of paradigms and methods. *European Journal of Integrative Medicine,* 1, 4, 189.

Hoenders, H.J.R., Appelo, M.T., Milders, C.F.A. (2009). The use of CAM bypsychiatric outpatients and the opinions on CAM and those of psychiatrists compared. *Alternative Therapies 15, (3), S147.*

Hoenders, H.J.R., Appelo, M.T., Willgeroth, F. (2009). Western and alternative medicine; a comparison of paradigms and methods. *Alternative Therapies, 15 (3), S176.*

Invited lectures and scientific presentations:

2013 **Natural medicine for schizophrenia?** *Speaker*
Phrenos psychosis congress. Zwolle; The Netherlands. (Natuurlijke geneeswijzen voor schizofrenie? Spreker. Phrenos psychosecongres, Zwolle; Nederland).

2013 **Lifestyle and self healing capacity: theory and practice**. *Chairman and speaker*.
Conference The doctor and nutrition. Haarlem; The Netherlands. (Leefstijl training en zelfhelend vermogen in de zorg: theorie en praktijk. Dagvoorzitter en spreker. Congres Arts en voeding, Haarlem; Nederland).

2013 **The conceptual foundation, implementation and effectiveness of integrative medicine in mental health care**. *Speaker.*
Farewell conference Joop de Jong, professor of Cultural and International Psychiatry, Free University, Amsterdam [De conceptuele basis, implementatie en effectiviteit van integrale geneeskunde in de geestelijke gezondheidszorg. Spreker. Afscheidscongres voor Joop de Jong, hoogleraar Culturele en Internationale Psychiatrie aan de Vrije Universiteit Amsterdam].

2012 **Routine outcome monitoring in an outpatient clinic for integrative mental health**. *Speaker.*
Lentis research conference. Zuidlaren; The Netherlands. (Routine outcome monitoring in een polikliniek voor integrale geestelijke gezondheid. Spreker. Lentis onderzoekscongres. Zuidlaren; Nederland).

2012 **Integrative medicine and psychiatry; theory and practice**. *Speaker.*
Conference The whole person. Utrecht; The Netherlands. (Integrative medicine en psychiatrie; theorie en praktijk. Spreker. Congres Heel de mens. Utrecht; Nederland).

2012 **Fifth conference on integrative psychiatry; interconnectedness.** *Chairman of the organizing committee and speaker.*
Groningen; The Netherlands. (Vijfde congres Integrale Psychiatrie; interconnectedness. Voorzitter organiserend comité en spreker. Groningen; Nederland).

2011 **The therapeutic relationship.** *Speaker.*
Farewell conference Dr. C.F.A. Milders, clinical instructor psychiatry, Lentis. Groningen; The Netherlands. (De therapeutische relatie. Spreker. Afscheidsymposium Milders, A-opleider Lentis. Groningen; Nederland).

2011 **Lifestyle training and self healing capacity.** *Speaker.*
Conference Lifestyle for Healthy Aging. Leeuwarden; The Netherlands. (Leefstijltraining en zelfhelend vermogen. Spreker. Congres Lifestyle for Healthy Aging, Leeuwarden; Nederland).

2010 **Western and Traditional Medicine: a comparison of paradigms and working methods, and a plea for integration.** *Speaker.*
International Conference on the modernization of TCM. Chengdu; China. (Westerse en traditionele geneeskunde; een vergelijking van paradigma en werkmodellen, en een pleidooi voor integratie. Spreker. Internationaal congres over de modernisering van TCM. Chengdu; China).

2010 **Fourth conference on integrative psychiatry; self-healing capacity.** C*hairman of the organizing committee and speaker.*
Groningen; The Netherlands. (Vierde congres Integrale Psychiatrie; zelfhelend vermogen. Voorzitter organiserend comité en spreker. Groningen; Nederland).

2010 **Integrative psychiatry & addiction.** *Speaker.*
Conference on Addiction. Solutions Healthcare. The Netherlands. (Integrale Psychiatrie & verslavingszorg. Spreker. Congres over verslaving, Solutions Healthcare, Nederland).

2010 **Lifestyle training & self healing capacity, focus on the rhythm of the breath.** *Speaker.*
Conference MCO Folia Orthica. The Netherlands. (Leefstijltraining & zelfhelend vermogen, focus op het ritme van de ademhaling. Spreker. Congres MCO Folia Orthica, Nederland).

2010 **Integrative Psychiatry: pros and cons**. *Speaker*
Discussion group. Spring conference of the Dutch union for Psychiatry (Integrale psychiatrie: voor- en nadelen, discussie groep Voorjaarscongres NVvP)

2009 **Western and alternative medicine, a comparison of paradigms and working methods.** *Speaker.*
Second European Conference on Integrative medicine. Berlin; Germany. (Westerse en alternatieve geneeskunde; een vergelijking van paradigma en werkmodellen. Spreker. Tweede Europese congres over integrale geneeskunde, Berlijn; Duitsland).

2009 **Integrative Psychiatry.** *Speaker.*
Conference on psychiatry & spirituality. InGeest mental health care. Amsterdam; The Netherlands. (Psychiatrie en zingeving. GGz InGeest. Amsterdam; Nederland).

2009 **Integrative psychiatry.** *Speaker.*
Conference Masterminds. Groningen; The Netherlands. (Integrale Psychiatrie. Spreker. Congres Masterminds. Groningen; Nederland).

2009 **Integrative psychiatry.** *Speaker.*
Conference on non-conventional medicine; complementary or alternative? Medilex. Utrecht. The Netherlands. (Integrale Psychiatrie. Spreker. Niet-reguliere behandelingen; aanvulling of alternatief? Medilex. Utrecht; Nederland).

2009 **Integrale Psychiatrie, Evidence-Based Alternative Medicine, and more….** *Speaker*
Spring conference of the Dutch union for Psychiatry. (Integrale psychiatrie: evidence-based alternatieve geneeswijzen en meer…Voorjaarscongres NVvP).

2009 **Without narrative, no diversity.** *Speaker*
Spring conference of the Dutch union for Psychiatry. (Zonder narrativiteit geen diversiteit. Spreker. Voorjaarscongres NVvP).

2008 **Third conference on integrative psychiatry: new perspectives on body and mind.** C*hairman of the organizing committee and speaker.*
Groningen; The Netherlands. (Derde congres Integrale Psychiatrie: nieuwe perspectieven op lichaam en geest. Voorzitter organisered comité en spreker. Groningen; Nederland).

2008 **Evidence-based alternative medicine.** *Speaker.*
Summerschool for residents psychiatry. The Hague; The Netherlands. (Evidence-based alternatieve geneeskunde. Spreker. Summerschool voor AIOS. Den Haag; Nederland).

2008 **Health improving interventions in mental health care.** *Workshop leader and speaker.*
Spring conference of the Dutch society for psychiatry. The Netherlands. (Gezondheidsbevorderende interventies in de GGz. Workshopleider en spreker. Voorjaarscongres NVvP. Nederland).

2008 **Integrative psychiatry.** *Speaker.*
Continuous Medical Education at Drenthe community mental health care. Assen; The Netherlands. (Integrale psychiatrie. Spreker. Refereeravond GGz Drenthe. Assen; Nederland).

2008 **Evidence-based alternative medicine; a contradictio in terminis?** *Speaker and co-organizer.*
Clinical scientific evenings; continuous medical education for family medicine. University of Groningen; The Netherlands. (Evidence-based alternatieve geneeskunde; een contradictio in terminis? Spreker en medeorganisator. Bijscholing Klinisch Wetenschappelijke Avonden Huisartsengeneeskunde Rijksuniversiteit Groningen).

2007 **Integrative research.** *Speaker and co-organizer.*
Conference on N=1 research, CAM network. Baarn; The Netherlands. (Integraal onderzoek. Spreker en mede organisator. Studiedag N=1 onderzoek, CAM netwerk. Baarn; Nederland).

2007 **Transcultural aspects of integrative psychiatry.** *Speaker.*
Conference Man, don't get annoyed, Lentis, Zuidlaren; The Netherlands. (Transculturele aspecten van Integrale psychiatrie. Spreker. Congres "Mens erger je niet", Lentis, Zuidlaren; The Netherlands).

2007 **Integrative psychiatry.** *Speaker.*
Conference Orthica: working on age. Amersfoort; The Netherlands. (Integrale psychiatrie. Spreker. Congres Orthica; Werken aan Leeftijd, Amersfoort).

2007 **Second conference on integrative psychiatry: In search of new solutions.** *Chairman of the organizing committee and speaker.*
Groningen; The Netherlands. (Tweede congres Integrale Psychiatrie: op zoek naar nieuwe oplossingen. Voorzitter organisered comité en spreker. Groningen; Nederland).

2007 **Integrative psychiatry.** *Speaker.*
Conference Fusion 2. The Dutch Association of Medical Practitioners. Rotterdam; The Netherlands. (Integrale Psychiatrie. Spreker. Congres Fusion 2. KNMG district Rotterdam; Nederland).

2006 **Integrative psychiatry.** *Speaker.*
Conference on transpersonal psychiatry. Roterdam; The Netherlands. (Integrale psychiatrie. Spreker. Congres Transpersoonlijke Psychiatrie, Rotterdam; Nederland).

2006 **Integrative psychiatry.** *Speaker.*
Conference on nutrition and behavior. University of Utrecht; The Netherlands (Integrale psychiatrie. Spreker. Congres Voeding en Gedrag. UMC Utrecht; Nederland).

2006 **Integrative psychiatry.** *Speaker.*
Workshop for team psychoses, Parnassia. The Hague; The Netherlands. (Integrale Psychiatrie. Spreker. Bijscholing Team psychosen, Parnassia, Den Haag; Nederland).

2006 **Integrative Psychiatry.** *Speaker.*
Congress Open University of Complementary Medicines. New York; USA. (Integrale psychiatrie. Spreker. Congres open universiteit voor complementaire geneeskunde. New York; USA).

2006 **Integrative Psychiatry.** *Speaker.*
International Congress on Tibetan Medicine. Madrid; Spain. (Integrale psychiatrie. Spreker. Internationaal congres over Tibetaanse geneeskunde. Madrid; Spanje).

2006 **Conference on integrative psychiatry: best of both worlds.** *Chairman of the organizing committee and speaker.*
Groningen; The Netherlands. (Congres Integrale Psychiatrie: het beste van twee werelden. Voorzitter organisered comité en spreker. Groningen; Nederland).

2006 **Integrative psychiatry.** *Speaker.*
Winterconference Astra Zeneca. Groningen; The Netherlands. (Integrale psychiatrie. Spreker. Wintersymposium Astra Zeneca. Groningen; Nederland).

2006 **Collaboration between conventional and alternative medicine.** *Speaker.*
Conference Fusion. The Dutch Association of Medical Practitioners. Hilversum; The Netherlands. (Samenwerking tussen reguliere en alternatieve geneeswijzen. Spreker. Congres Fusion. KNMG district Rotterdam; Hilversum; Nederland).

2005 **Complementary and alternative medicine; problems and sollutions in clinical practice.** *Speaker.*
Springconference of the Dutch society for psychiatry; The Netherlands. (Complementaire en alternatieve geneeswijzen; problemen en oplossingen in de praktijk. Spreker. Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie: Nederland).

2004 **Integrating Western Medicine and Traditional Medicine; why and how?** *Speaker.*
Conference Integrated Medicine. Colombo; Sri Lanka. (Integreren van Westerse geneeskunde en traditionele geneeskunde; waarom en hoe? Spreker. Congres integrale geneeskunde. Colombo; Sri Lanka).

2004 **Complementary and alternative medicine and psychiatry.** *Speaker.*
Conference of the Dutch society for psychiatry. Utrecht; The Netherlands. (Complementaire en alternatieve geneeswijzen en psychiatrie. Spreker. WetenSAPdag van de NvvP. Utrecht; Nederland).

2004 **Complementary and alternative medicine and psychiatry.** *Speaker.*
Second Dutch national CAM conference. Amsterdam; The Netherlands**.** (Complementaire en alternatieve geneeswijzen en psychiatrie. Spreker. 2e Nederlandse nationale CAM congres, Amsterdam; Nederland).

2004 **Integrating Western Medicine and Traditional Medicine; why and how?** *Speaker.*
Congress Integrated Medicine. Mexico city, Mexico. (Integreren van Westerse geneeskunde en traditionele geneeskunde; waarom en hoe? Spreker. Congres integrale geneeskunde. Mexico city, Mexico).

2004 **Western Medicine, Complementary and Alternative Medicine and Psychiatry.** *Speaker.*
World Peace Congress Integrated Medicine. Verbania; Italië. (Westerse geneeskunde, complementaire en alternatieve geneeskunde en psychiatrie. Spreker. Wereldvrede congres over integrale geneeskunde. Verbania; Italie).

2004 **The use of alternative medicine by native Dutch.** *Speaker.*
Springconference of the Dutch society for psychiatry. The Netherlands. (First prize for best oral presentation 2004). (Gebruik van alternatieve geneeswijzen door autochtone Nederlanders. Spreker. Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie. Nederland. *(prijs voor beste Orale Presentatie 2004)).*

2004 **Evidence-Based Alternative Medicine.** *Speaker.*
Spring conference of the Dutch society for psychiatry; The Netherlands.
(Evidence-based alternatieve geneeskunde. Spreker. Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie; Nederland).

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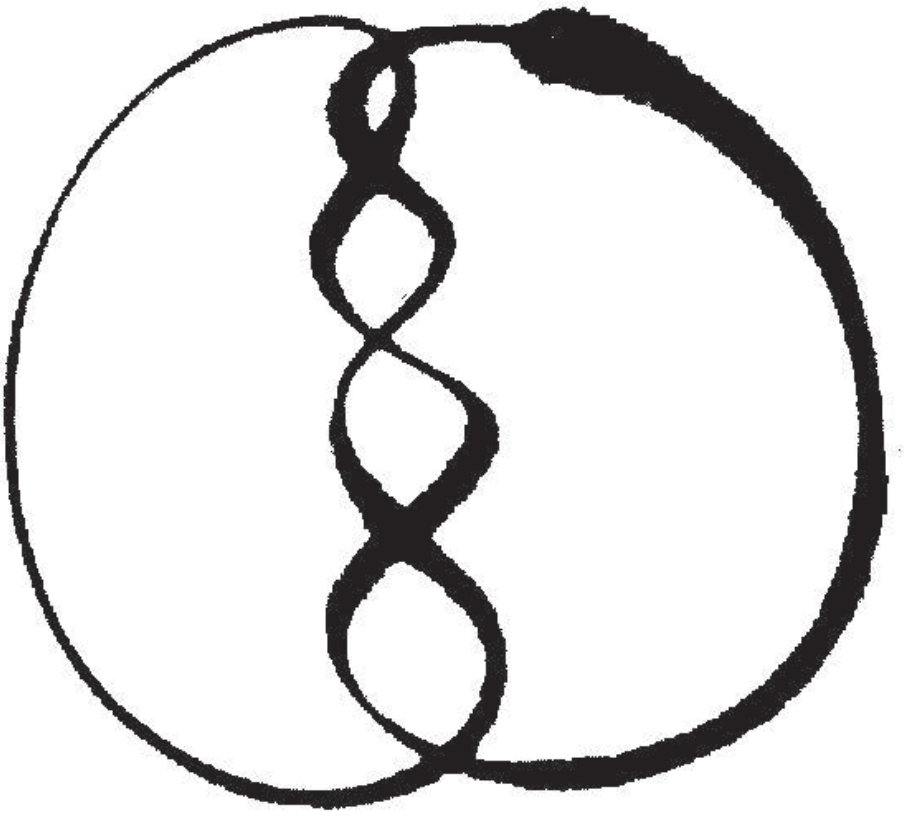
Curriculum Vitea

Rogier Hoenders was born on the 23rd of July 1972 in Groningen, the Netherlands. After finishing high school, he obtained his MD from the University of Groningen in 1998. Between 1998 and 2004 he did his residency psychiatry at Lentis mental health care, Groningen. His clinical instructor, Frits Milders, accepted his proposal for a final scientific presentation on the use of, and evidence for, complementary and alternative medicine (CAM). Frits also supported Rogier to do a written inquiry into the use of CAM by psychiatric outpatients. The results were published in the Dutch Journal for Psychiatry (Hoenders et al., 2006). Rogier got appointed as a psychiatrist in Winschoten in 2005. Inspired by two international conferences on integrative medicine (in Verbania, Italy and Colombo, Sri Lanka), the foundation of the Consortium of Academic Health Centers for Integrative Medicine (CAHCIM) in the USA, the publication of David Servan-Schreiber's book "Without Freud or Prozac", and also because of his own interest in different healing traditions, Rogier initiated the first Dutch congress on integrative psychiatry ('The Best of Both Worlds') in 2006, together with six colleagues. More than 1200 people participated in this first conference (including almost 10% of all Dutch psychiatrists). Since then, he has chaired the organizing committee of five consecutive congresses on integrative psychiatry. The committee now prepares for the sixth (www.congressintegratedpsychiatry.com). Rogier started an outpatient center for integrative psychiatry with two employees in the fall of 2006. This center has now expanded to 25 employees and 500 outpatients. In 2010 Rogier co-founded the International Network for Integrative Mental Health (INIMH; www.inimh.org). Today, Rogier works as a psychiatrist, clinical instructor psychiatry, researcher and head of the Center for Integrative Psychiatry and the Berkenhof of Lentis. He is a board member of INIMH. He is on the advisory board of the Lama Gangchen International Global Peace Foundation (LGIGPF), the Netherlands. He is married and lives in Zuidlaren, the Netherlands. When he is not working, he spents his time traveling, meditating, reading, running and singing. Every year, together with his wife and friends, he goes to the Borobudur for a meditation retreat.



The contents of this thesis

Despite important progress in psychiatry not all patients respond well to available treatments. There are also concerns about increasing costs and the quality of the therapeutic relationship, which seems threatened by managed care, focus on protocols, and a tendency to reductionism, narrowing the view to diseases or symptoms and losing sight of the whole person in his or her context. 'Integrative medicine' is a new concept in health care defined as: 'the practice of medicine that reaffirms the importance of the relationship between practitioner and patient, focuses on the whole person, is informed by evidence, and makes use of all appropriate therapeutic approaches, healthcare professionals and disciplines to achieve optimal health and healing'. Integrative medicine may provide some solutions to the problems raised. However, there is a paucity of research on the application of integrative medicine in mental health care ('integrative psychiatry'). We explored the conceptual foundation of integrative psychiatry in the first part of this thesis. The second part is about its implementation in Dutch mental health care. Taking into account the Dutch law, jurisprudence, rules of professional bodies, and scientific research, we wrote a treatment protocol for the judicious application of complementary medicine in conventional mental health care. In the third part we assessed evidence for the effectiveness of integrative psychiatry and some selected complementary medicines and lifestyle changes. In the discussion we respond to criticism and offer suggestions for future research.

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