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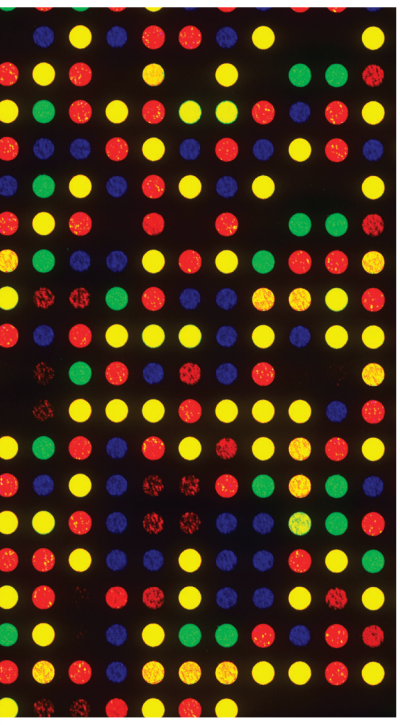
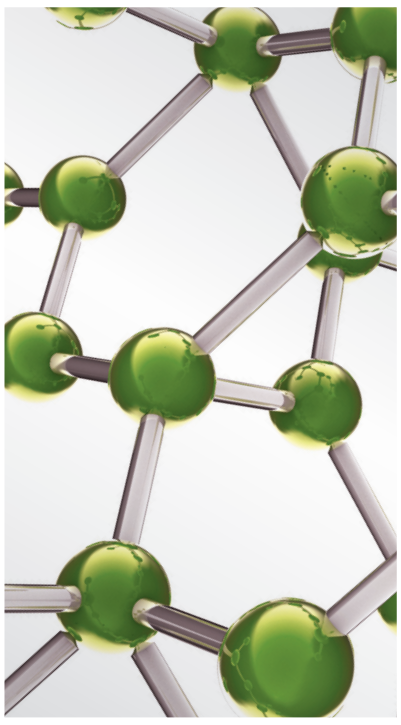
Evidence-Based Complementary and Alternative Medicine

CAM in Psychiatry

Guest Editors: Jörg Melzer, Hans-Christian Deter, and Bernhard Uehleke



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Hindawi Publishing Corporation
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http://dx.doi.org/10.1155/2013/293248

Editorial

CAM in Psychiatry

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Received 26 June 2013; Accepted 26 June 2013

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1. Aspects of Psychiatry

In western countries, the 19th century marks a turning point for the beginning of psychiatry as an academic discipline. Since this happened and psychiatry had left the asylums at the boundaries not only of cities but medicine itself, we can find quite a row of examples concerning integration [1]. Psychiatry has integrated many treatments into the therapeutic spectrum, for example, tricyclic antidepressants, SSRI, relaxation techniques like progressive muscle-relaxation or hypnosis, cognitive-behavioural, psychoanalytic, or systemic psychotherapy, even acupuncture according to the protocol of the National Acupuncture Detoxification Association (NADA) [2, 3] or lately mindfulness-based cognitive therapy [4]. However, three aspects seem suitable to understand the openness of psychiatry for new methods: (a) the fact that since decades, professional multidisciplinarity in psychiatry is a crucial basis for the in- and outpatient treatment (e.g., psycho-, ergo-, music-, physiotherapists, nutritionists, and social workers), (b) psychiatrists today need to have a double qualification in psychiatry and psychotherapy to be able to work according to (c), Engel's biopsychosocial model, which had been adopted as a solid basis for the previously mentioned.

2. Aspects of CAM

Traditional medicine has been present for centuries in different cultures around the globe (e.g., Ayurveda, Homeopathy, Kampo Medicine, Traditional European Medicine, Tibetan Medicine, and Traditional Chinese Medicine). However, with the development of modern medicine, traditional medicine was regarded as an old fashioned way of practice and theory, and consequently, traditional medicine mostly was not taught at medical schools and universities. Only few chairs or colleges for naturopathy or homeopathy in the US and some single chairs in Europe for hydrotherapy or naturopathy can be regarded as an exception to the rule in the 19th and 20th century. Nevertheless, traditional medicine remained in the cultures as a kind of folk medicine often provided by lay physicians and sometimes also by physicians with their institutions and inventions (e.g., Friedrich Bilz at Bilz'sche Naturheilanstalt, Germany, and his concept of combined naturopathy; Maximillian Bircher-Benner at Sanatorium Lebendige Kraft, Switzerland, and his Bircher-Muesli; Harvey Kellog at Battle Creek, USA, and his corn-flakes) [5, 6].

3. Research

Interestingly, the concept of Evidence-based Medicine (EbM) [7] brought a chance for CAM and traditional medicinal systems. Maybe this derived from the fact that EbM was new for the whole medical system and activated a new orientation in research. A young generation of academic protagonists in CAM adopted the promising paradigm of EbM and hundreds of systematic reviews; meta-analysis and new randomized controlled trials (RCT) brought clinical evidence for certain CAM methods (even when the mode of action remained unclear). So, a broader scientific acceptance for certain CAM interventions was achieved. Yet, next to evidence from RCTs with high internal validity, the argument

that interventions from CAM (the same accounts for psychotherapy) work by "placebo response" (or better: unspecific treatment effects) rather than specific therapeutic effects had been discussed as well [8]. The different CAM interventions, the effects of the physician/patient relationship, and other contextual factors seem to influence outcome as can be seen from various methodological settings (e.g., acupuncture versus sham acupuncture, individualized versus standardized homeopathy). It remains a challenge for research to use methods to evaluate these patient specific factors. From this point of view, collaboration and exchange between CAM with psychiatry and psychosomatic medicine seems promising.

4. CAM and Psychiatry

Funny enough and often overseen, there was a time for a kind of approach between CAM and psychiatry in the beginning of the 20th century. The German physician Georg Groddeck combined naturopathy with psychotherapy: he had a little naturopathic clinic in Baden-Baden and was a promising psychoanalyst in tense contact with S. Freud until they became kind of rivals over the concept of the Id [9, 10]. Another protagonist was the Swiss naturopathic physician M. Bircher-Benner who set up the system of Ordnungstherapy, which meant the combination of naturopathic somatotherapies with psychotherapy [4]. In aspects, this also had similarities with psychiatric Milieu therapy. This is no wonder, as for a time Bircher-Benner was a pupil of the Swiss psychiatrist August Forel and even adopted hypnosis from him.

From the concept of naturopathic Ordnungstherapy derived a short and punctual contact to the new direction in psychiatry, the psychosomatic medicine (PM) in German speaking countries, which somehow criticised the domination by the biological view [11]. But in the very beginning, CAM and PM failed to find a strong academic and practical connection with each other. Yet, today one might speculate about a renewed alliance under the term mind-body medicine, in which multidisciplinarity including various forms of psychotherapy and patient-centred healthcare [12] is combined with educational aspects for the patients.

5. CAM in Psychiatry

CAM in psychiatry seemed as a timely topic for a special issue of the eCAM journal, since the journal had focussed in its special issues on specific CAM methods (e.g., Tai-Chi, medical mushrooms), certain diseases (e.g., obesity, diabetes mellitus), or single research questions (e.g., neurobiology of acupuncture, network pharmacology). On the other hand, patients with psychiatric disorders use CAM (mostly add-on in 20 to 50% in depression and 20 to 40% in anxiety and much less in addiction disorders [13, 14]). Therefore, it is a crucial responsibility for physicians and researchers to evaluate efficacy and safety of CAM to secure patients' safety and interests.

Some psychiatric hospitals or departments have drawn attention for turning CAM into their daily practice. The reasons for this might be an increase in evidence for single CAM methods, the criticism of the evidence for conventional psychopharmacology [15], the strengthened awareness of its side effects [16, 17], or simply the marketing advantage in competition. However, by no mean do we expect to draw a representative picture in this issue of what is happening between psychiatry and CAM today. We present a somewhat random cross-sectional perspective among researchers in the field, deriving from the call for papers on the journals homepage and additionally contacting about 100 researchers or working groups we were aware of.

In its mixture of papers, this issue differs from earlier publications on CAM in psychiatry, like reviews on herbal medicine [18–20] or CAM [21], guidelines incorporating, for example, St. Johns' Worth for the treatment of mild to moderate single depressive episodes based on meta-analytic evidence [22–24], or the work of the International Network of Integrative Mental Health (INIMH), founded in 2010 and reviews of its protagonists on bipolar disorders or ADHS [25, 26]. So, we hope this special issue can contribute to further discussion on CAM in psychiatry—the subject may be named integrative mental health [27], mind-body medicine [28], or integrative psychiatry [29].

For herbal medicine, the most important spectrum of EbM methods could be covered with 3 studies: N. Brondino et al. systematically review preparations from *Ginkgo* for different psychiatric disorders. In their meta-analysis, they evaluate the Gingko-treatment not only for dementia but also as add-on in schizophrenia. The systematic review of Y. W. Wong et al. on different "traditional oriental herbal medicine" in ADHS gives an idea of the difficulty tracing a cultural/national origin of some herbal preparations in Asiatic countries and the need for profound EbM research. The RCT of R. Schellenberg et al. on a *Cimicifuga* preparation in menopause cannot answer the question whether the effects are vasomotoric or psychological but shows dose-dependent efficacy for both with a slightly modified questionnaire.

Concerning acupuncture/acupressure 3 studies were included: Y.-D. Kim et al. systematically review RCTs on post-traumatic stress disorder and give a meta-analytic evaluation of 2 RCTs on acupuncture plus moxibustion and necessary recommendations for future research. The small RCT of H. Y. Ching et al. examines efficacy of standardised auricular acupressure on body weight in chronically schizophrenic, hospitalised patients—a relevant question due to metabolic side effects of neuroleptic treatment. The pilot study of P. Bosch et al. is an example of integrating individualised acupuncture add-on to psychopharmacology for sleep improvement of schizophrenic and depressed patients in daily clinical practice giving hints on moderate clinical relevance and need for further research.

Referring to relaxation techniques, 3 studies give the following picture: the systematic review of F. Wang et al. on Qigong in different conditions leads to a meta-analysis in multimorbid patients, that is, diabetes and depression and a psychosomatic reflection. The survey of M. Nedeljkovic et al. examines a side of Taiji as a medical interventions, hardly examined so far: the effect of expectations of consumers and providers. Evidence from the pilot study of R. T. H. Ho et al. on efficacy of Tai-chi on movement/functioning in chronically schizophrenic patients seems encouraging for

conducting a future RCT in this clinical situation to try to improve patients' quality of life.

Light on aspects of healthcare shed 2 further studies: the observational study of E. Jeschke et al. examines care of a small network of anthroposophic physicians for depressed patients and raises questions concerning individualised versus guideline treatment. The research paper of F. W. Stahnisch et al. examines the impact of sociopolitical circumstances like the Flexner report in North America on hindering the so much needed research on CAM in the last century.

A lesson we have learned arose from a task not in focus of our integrative view: psychiatry has not yet integrated its different classification systems. We are aware of the International Classification of Diseases (ICD-10) of the World Health Organisation (WHO) or the Diagnostic Manual (DMS-IV) of the American Psychiatric Association (APA). Yet, we also had to face manuscripts based on the Chinese Classification of Mental Diseases (CCMD). Obviously, it was not only difficult but impossible for the authors to provide a solid sound comparison between CCMD and either ICD-10 or DSM-IV. Next to these classification systems common in one or the other region of the world, we would like to mention the difficulties with "traditional diagnostic systems" as well. For example, in traditional TCM, concepts of disease stand aside the previously mentioned modern classification systems. So, no publication on these two topics is presented here. We have to bear in mind that in a globalised world, much needs to be done to bridge the gap between different medical languages, classifications, and cultures in a somehow operational and confirmatory way yet, without cultural or scientific hegemony.

Acknowledgments

We thank the authors of this special issue for their contributions and cooperation in the peer-review process. We would like to express our sincere gratitude to all reviewers for their valuable comments in the peer review.

Jörg Melzer
Hans-Christian Deter
Bernhard Uehleke

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 915691, 11 pages
http://dx.doi.org/10.1155/2013/915691

Review Article

A Systematic Review and Meta-Analysis of *Ginkgo biloba* in Neuropsychiatric Disorders: From Ancient Tradition to Modern-Day Medicine

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Received 10 August 2012; Revised 25 February 2013; Accepted 24 March 2013

Academic Editor: Bernhard Uehleke

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Ginkgo biloba (Gb) has demonstrated antioxidant and vasoactive properties as well as clinical benefits in several conditions such as ischemia, epilepsy, and peripheral nerve damage. Additionally, Gb is supposed to act as potential cognitive enhancer in dementia. So far, several trials have been conducted to investigate the potential effectiveness of Gb in neuropsychiatric conditions. However, the results of these studies remain controversial. We conducted a systematic review and a meta-analysis of three randomised controlled trials in patients with schizophrenia and eight randomised controlled trials in patients with dementia. Gb treatment reduced positive symptoms in patients with schizophrenia and improved cognitive function and activities of daily living in patients with dementia. No effect of Gb on negative symptoms in schizophrenic patients was found. The general lack of evidence prevents drawing conclusions regarding Gb effectiveness in other neuropsychiatric conditions (i.e., autism, depression, anxiety, attention-deficit hyperactivity disorder, and addiction). Our data support the use of Gb in patients with dementia and as an adjunctive therapy in schizophrenic patients.

1. Introduction

Ginkgo biloba (Gb) is one of the most ancient seed plant, often referred to as a "living fossil." This large tree may live over 1000 years and reach 40 m of height. Originally native to China, Gb is now cultivated worldwide. Extract from Gb leaves has been used in traditional Chinese medicine for centuries to treat circulatory disorders, asthma, tinnitus, vertigo, and cognitive problems [1]. Today, Gb extracts are one of the most commonly taken phytomedicines globally [2] and are often prescribed in Europe as a nootropic agent in old age and dementia [3]. Of note, since 2000, Gb extract is included in ATC-classification as an anti-dementia drug together with cholinesterase inhibitors and memantine [4]. Gb extract contains mainly terpenoids, flavonol glycosides, and proanthocyanidins. The most prevalent of these three groups are the flavonol glycosides (quercetin, catechin). The terpenoids include ginkgolides and bilobalides, which represent unique components of Gb. Terpenoids, flavonoids and proanthocyanidins are thought to be responsible for the pharmacological properties of Gb [1]. On the basis of animal studies, several mechanisms have been proposed to explain the pharmacological properties of this plant: extract from Gb leaves inhibits platelet-activating factor [5] and enhances NO

production in vessels, with subsequent effect on peripheral and cerebral blood flow [6]. Gb extract is thought to module different neurotransmitter systems: it is a strong inhibitor of monoamine oxidase A and synaptosomal uptake of DA, 5-HT, and norepinephrine [7–9]. Additionally, Gb displays a free radical scavenger activity and has neuroprotective and antiapoptotic properties, such as inhibition of amyloid-β neurotoxicity and protection against hypoxic challenges and increased oxidative stress [10–12]. Several previous reviews have been mainly focused on the potential efficacy of Gb in dementia. However, inconsistent and controversial results have been reported [13–16]. On the other hand, to date no systematic review has been conducted on the effect of Gb on neuropsychiatric disorders other than dementia. Therefore, we aimed to perform a systematic review on the effects of Gb in different psychiatric conditions.

2. Methods

In April 2012, we searched the following databases: MEDLINE, EMBASE, PsycINFO, and the Cochrane Database of Systematic Reviews. The search terms were as follows: ginkgo biloba (gingko biloba; ginkgo; ginko; gingko; bilobalid*; egb 761) and dementia (dementia OR cognitive impairment OR Alzheimer), autism (autism OR autistic spectrum disorder), schizophrenia (schizophrenia OR psychosis OR psychotic disorder OR delusion), depression (depression OR major depression OR depressive symptom), anxiety (anxiety OR generalized anxiety disorder OR anxious), attention-deficit/hyperactivity (ADHD) (attention deficit disorder OR ADHD or attention deficit OR hyperactivity), and addiction. All search terms were searched individually in each database and combined together. The search strategy had no time restriction but was limited to articles in English, Italian, French, Spanish, and German. Additionally, all recovered papers were reviewed for further relevant references. Researchers in the field were reached to obtain additional or unpublished data, if available.

We selected controlled randomized clinical trials, yielding primary results on the effects of the administration of Gb extracts in neuropsychiatric patients. Every neuropsychiatric disorder was defined according to internationally valid diagnostic criteria such as the International Classification of Diseases (ICD) or the Diagnostic and Statistical Manual of Mental Disorders (DSM). Other inclusion criteria were a minimum number of participants of ten per group, a treatment period of at least 6 weeks, and the availability of a full-text publication. Of note, all the included studies in the meta-analysis were conducted using the standardized Gb extract Egb 761, which is the most commonly used form of Gb [17].

Two researchers (NB and SR) independently reviewed all information about the articles provided by the databases. Any discrepancies were solved by consensus. We assessed the quality of the study design, duration of the study, comparability of study groups, and clinical outcomes on different widely used rating scales.

The following rating scales were accepted for clinical outcomes: (1) dementia: cognition: Syndrom-Kurz test (SKT) [18], Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) [19]; activities of daily living (ADL): Alzheimer's Disease Activities-of-Daily-Living International Scale (ADL-IS) [20], Geriatric Evaluation by Relatives Rating Instrument (GERRI) [21], Gottries-Bråne-Steen-Activities of Daily Living (GBS-ADL) scale [22], Nürnberger Alters-Alltagsaktivitäten-Skala (NAA), and Nürnberger Alters-Beobachtungsskala (NAB) [23]; (2) schizophrenia: Scale for the Assessment of Positive (SAPS) [24] and Negative (SANS) Symptoms [25], Brief Psychiatric Rating Scale (BPRS) [26], (3) autism: Aberrant Behavior Checklist-Community (ABC-C) [27]; (4) Attention-Deficit/Hyperactivity Disorder (ADHD): Parent and Teacher ADHD Rating Scale-IV [28], Conners' Parent Rating Scale-Revised [29]; (5) anxiety: Hamilton Rating Scale for Anxiety (HAMA) [30], State-Trait Anxiety Inventory (STAI) [31]; and (6) tardive dyskinesia: Abnormal Involuntary Movement Scale (AIMS) [32].

When it was possible, data were pooled by means of meta-analysis. Effect measures on rating scales were expressed as standardized mean differences (SMDs) with the 95% CIs. A random-effects model (DerSimonian-Laird) was used to calculate a pooled effect estimate, because of heterogeneity. A P value <0.05 was regarded as statistically significant. Heterogeneity of effect sizes was evaluated by the I^2 statistic. An alpha error $P < 0.05$ and/or I^2 of at least 50% were taken as indicators of substantial heterogeneity of outcomes. If meta-analyses were not possible, the results of individual studies are presented. Meta-analyses were performed using Meta-Analyst and RevMan 5 for all calculations [33].

3. Results

Our literature search identified 1109 clinical publications. After the title/abstract screening, 113 publications were obtained for detailed evaluation (Figure 1). Summary of the final articles included is shown in Table 1. Overall, the methodology of the included studies was good (Figure 2).

3.1. Autism. A recent study involving 47 children with a DSM-IV-TR diagnosis of autism was identified [34]. Patients were randomly assigned to receive either Gb or placebo in adjunction to risperidone. The primary outcome was the ABC-C scale. There was no statistically significant difference between the two groups according to the aforementioned subscale. Thus, Gb seemed to be not an efficacious adjunctive therapy to risperidone. However, it appeared to be safe and well tolerated even in childhood.

3.2. ADHD. Salehi et al. [35] reported a double-blind trial of Gb versus methylphenidate in 50 ADHD patients. The investigators reported that Gb had no comparable efficacy in comparison with methylphenidate. Even if Gb determined significantly few side effects (especially insomnia and loss of appetite), methylphenidate determined a dramatic improvement in a range of symptoms.

3.3. Addiction. Only one double-blind randomized controlled study had been conducted so far involving 44 DSM-IV

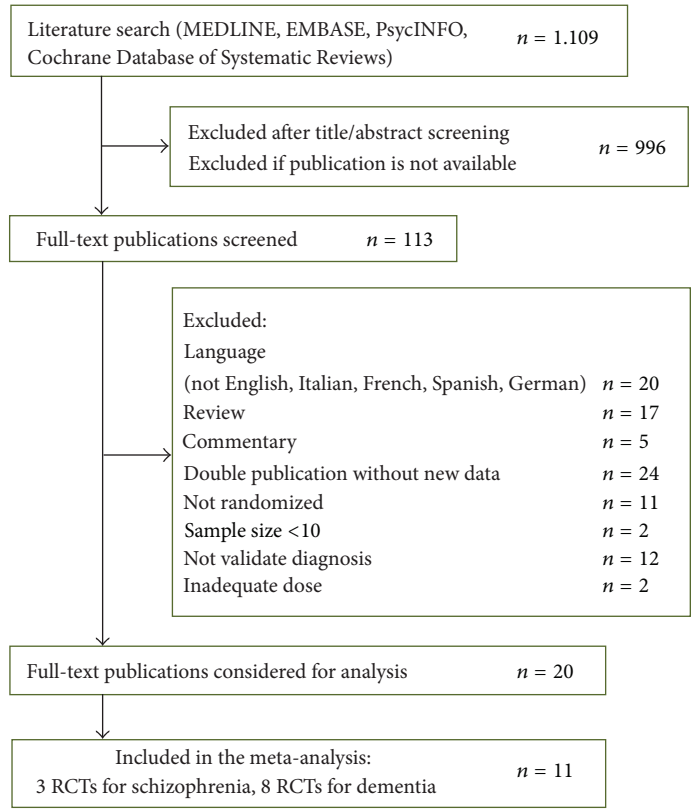

Figure 1: Flow chart of study selection.

cocaine-dependent men and women [36]. Each participant randomly received either piracetam, Gb, or placebo. The primary outcome was the relapse from abstinence (measured as self-reported relapse, treatment dropout, or positive urine toxicology screening). At the end of the study, no significant differences were observed between the three groups.

3.4. Generalized Anxiety Disorder (GAD). Only one study investigating the effects of Gb on GAD fulfilled the review criteria [37]. In 2007, 82 patients were randomly treated with Gb extract, at the dose of 480 mg/die ($n = 27$) or 240 mg/die ($n = 25$), or with placebo ($n = 30$). The primary outcome was represented by change on the HAMA scale (response defined as a reduction in HAMA total score of at least 50%). The authors reported a significant improvement in psychopathological symptoms. Response rates were 44% in the high-dose group, 31% in the low-dose group, and 22% with placebo. Additionally, the percentages of clinically significant responses were 81%, 67%, and 38% for the high-dose, the low-dose, and the placebo groups, respectively. Of note, there was a significant inverse dose-response relationship between the dose per Kg and the HAMA score. The safety of Gb extract appeared good.

3.5. Tardive Dyskinesia. Recently, Zhang et al. [38] evaluated Gb extract as a potential treatment for tardive dyskinesia in patients with chronic schizophrenia. One hundred and fifty-seven patients were randomized to Gb extract ($n = 78$, 240 mg/die) or placebo ($n = 79$) for 12 weeks. All participants were on antipsychotic medication (chlorpromazine equivalents were comparable between the two groups). Tardive dyskinesia severity, which represented the primary outcome of the study, was assessed by means of the Abnormal Involuntary Movement Scale (AIMS). A significant improvement was found in the Gb group in the AIMS score. It is interesting to note that, the percentage of responders (according to a decrease of at least 30% in the AIMS) was significantly higher in the treatment group (51.3% versus 5.1%). Despite the significant effect of Gb on movement symptoms, no significant effect of group was observed for psychopathological symptoms (representing a secondary outcome of the study), as both groups showed an improvement over time.

3.6. Schizophrenia. Three randomized clinical trials evaluating Gb extract in patients with schizophrenia were included in the analysis [39–41]. Two studies were double-blind and placebo controlled. Randomization procedure and methodology were considered adequate in all cases. Gb was used as an adjunctive therapy to different antipsychotics: clozapine (Doruk et al.) [39], haloperidol (Zhang et al.) [40], and olanzapine (Atmaca et al.) [41]. Mean chlorpromazine equivalent doses were comparable in the first two studies (8.3 and 8.4, resp.), while the third one used lower chlorpromazine equivalent doses (3.3). All studies included only patients with chronic schizophrenia. All three trials used SANS and SAPS

Table 1: General characteristics of the included studies.

Authors	Year	Gb dose	Type of study	Comparator	Concomitant medications	Outcome measure	Findings
Attention-deficit and hyperactivity disorder (ADHD)							
Salehi et al. [35]	2010	80 mg/day if weight <30 kg; otherwise 120 mg/day	Randomized, 6 week	Methylphenidate 20 mg/day if weight <30 kg; otherwise 30 mg/day	None	Parent and Teacher ADHD Rating Scale-IV	Significant improvement with methylphenidate
Autism							
Hasanzadeh et al. [34]	2012	80 mg/day if weight <30 kg; otherwise 120 mg/day	Randomized placebo controlled, 10 weeks	Placebo	Risperidone 2-3 mg/day according to weight	ABC-C	No difference
Cocaine addiction							
Kampman et al. [36]	2003	240 mg/day	Randomized placebo controlled, 10 weeks	Piracetam 4.8 g/day or placebo	None	Urine toxicology screen or self-report relapse	No significant difference of both piracetam or Gb to placebo
Dementia							
Herrschaft et al. [42]	2012	240 mg/day	Randomized placebo controlled, 24 weeks	Placebo	Antihypertensive, antithrombotic drug	SKT, NPI, AD CGI, ADL, QOL	Significant improvement with active treatment
Ihl et al. [43]	2011	240 mg/day	Randomized placebo controlled, 24 weeks	Placebo	Antihypertensive, antithrombotic drug	SKT, NPI, AD CGI, ADL, QOL	Significant improvement with active treatment
Napryeyenko and Borzenko [44]	2007	240 mg/day	Randomized placebo controlled, 22 weeks	Placebo	Antihypertensive, antithrombotic drug	SKT, NPI, ADL	Significant improvement
Schneider et al. [45]	2005	120 or 240 mg/day	Randomized placebo controlled, 26 weeks	Placebo		ADAS-cog	Improvement
van Dongen et al. [46]	2003	160 or 240 mg/day	Randomized placebo controlled, 24 weeks	Placebo		SKT, CGI, NAI-NAA	No differences between Gb and placebo
Le Bars et al. [47]	1997	120 mg/day	Randomized placebo controlled, 52 weeks	Placebo		ADAS-Cog, GERRI, CGIC	Significant improvement in ADAS-cog and GERRI
Maurer et al. [48]	1997	240 mg/day	Randomized placebo controlled, 12 weeks	Placebo		SKT, ADAS-cog, CGI	Significant improvement in SKT
Kanowski et al. [49]	1996	240 mg/day	Randomized placebo controlled, 24 weeks	Placebo		SKT, CGI, NBA	Significant improvement
Yancheva et al. [50]	2009	240 mg/day	Randomized versus donepezil or Gb and donepezil, 22 weeks	Donepezil 10 mg/day	Antihypertensive, antithrombotic drug	SKT, NPI, ADL	No significant differences between treatments
Mazza et al. [51]	2006	160 mg/day	Randomized placebo controlled, double blind, 24 weeks	Donepezil 10 mg/day	Benzodiazepines or antipsychotics at low dosage	MMSE, SKT, CGI	Significant improvement compared to placebo, no differences with donepezil

Table 1: Continued.

Authors	Year	Gb dose	Type of study	Comparator	Concomitant medications	Outcome measure	Findings
Generalized anxiety disorder (GAD)							
Woelk et al. [37]	2007	Two groups: low dose 240 mg/day; high dose 480 mg/day	Randomized placebo controlled, 4 weeks	Placebo	None	HAMA scale	Significant improvement compared to placebo, dose-response relationship
Schizophrenia							
Doruk et al. [39]	2008	120 mg/day	Randomized placebo controlled, 12 weeks	Placebo	Clozapine 350–500 mg/day	SANS, SAPS, BPRS	Significant improvement in negative symptoms with Gb
Zhang et al. [40]	2001	360 mg/day	Randomized placebo controlled, 12 weeks	Placebo	Haloperidol 0.25 mg/kg/day	SANS, SAPS, BPRS	Significant improvement in positive symptoms and negative symptoms with Gb
Atmaca et al. [41]	2005	300 mg/day	Randomized olanzapine and EGb versus olanzapine alone, 8 weeks	Placebo	Olanzapine 5–20 mg/day	SANS, SAPS	Significant improvement in positive symptoms with Gb
Tardive dyskinesia							
Zhang et al. [38]	2011	240 mg/day	Randomized placebo controlled, 12 weeks	Placebo	Antipsychotic or cholinergic agents	AIMS and SANS and SAPS	Significant change in AIMS score. No effect of Gb on psychopathological symptoms

ADHD: attention-deficit hyperactivity disorder; GAD: generalized anxiety disorder; ABC-C: Aberrant Behavior Checklist-Community; HAMA scale: Hamilton Rating Scale for Anxiety; AIMS: Abnormal Involuntary Movement Scale; SANS: Scale for the Assessment of Negative Symptoms; SAPS: Scale for the Assessment of Positive Symptoms; BPRS: Brief Psychiatric Rating Scale; SKT: Syndrom-Kurz test; NPI: Neuropsychiatric Inventory; AD CGI: Clinical Global Impressions Severity of AD; ADL: activities of daily living; QOL: quality of life; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; NAI-NAA: Nürnberger Alters Inventar-Nürnberger Alters-Alltagsaktivitäten-Skala; NAB: Nürnberger Alters-Beobachtungsskala; GERRI: Geriatric Evaluation by Relatives Rating Instrument; MMSE: Mini-Mental State Examination.

(ratings for this scale were however available only in two studies) as outcome measures for clinical improvement. Change scores for SANS ranged from −7.9 to −3.5 in the Gb groups and from −2.7 to 5.3 in the placebo groups, whereas change scores for SAPS ranged from −9.4 to −4.3 in the Gb groups and from −3.8 to −0.7 in the placebo groups. Standardized mean differences for SANS score were greater for Gb than for placebo, with SMD = −2.09 (95% CI −4.34; 0.148, $H = 5.52$) (Figure 3) but not significant. Heterogeneity was substantial ($I^2 = 97\%$). To perform sensitivity analysis, we decided to remove the study from Atmaca et al. which used lower chlorpromazine equivalent, in order to determine the impact of this trial on the results. Removing this trial did not significantly change our findings. After excluding this study, the SMD for negative symptomatology was −2.74 (95% CI −5.97; 0.48, $P = 0.10$). Heterogeneity remained substantial ($I^2 = 98\%$).

For SAPS, standardized change scores were significantly greater for Gb than for placebo, with SMD = −2.89 (95% CI −5.39; −0.38, $H = 3.46$, $P = 0.001$) (Figure 4). Heterogeneity was substantial ($I^2 = 92\%$).

3.7. Dementia. Ten studies fulfilled the inclusion criteria: meta-analysis was performed only on eight studies [42–49] which were comparable for clinical purposes. Eight studies were placebo controlled, while two studies were a head-to-head trial with donepezil as comparison group [50] or a triple-blind study with Gb, donepezil, and placebo [51]. The very different dosages of Gb and donepezil rendered meta-analytical examination unfeasible in the latter studies. All studies were randomized, double-blind trials. Overall, the methodological quality of the included studies was judged as adequate, with most studies using an intent-to-treat analysis. All studies considered the administration of a

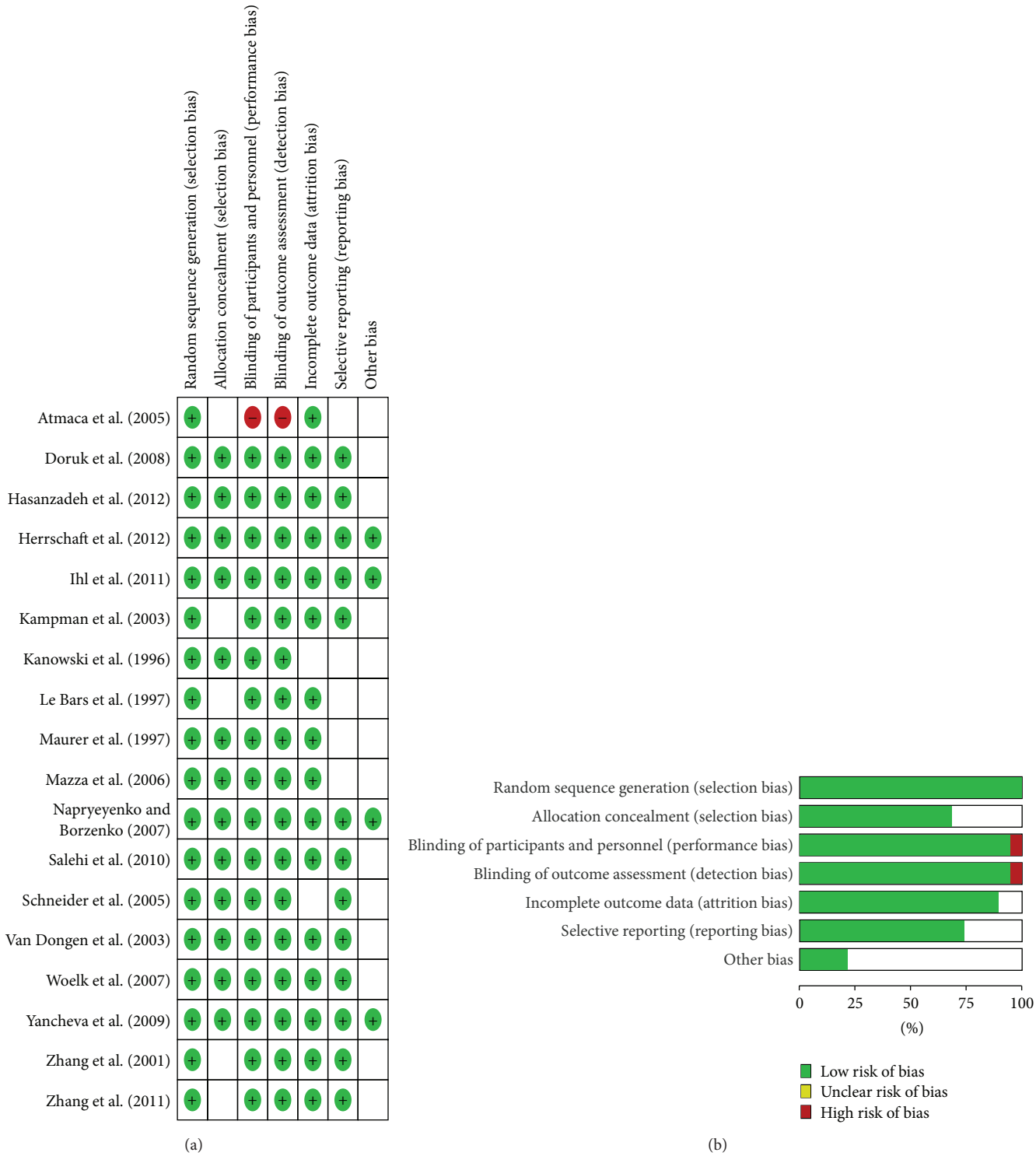

Figure 2: Assessment of the methodological quality of the included studies.

standardized extract (EGb761) in patients with Alzheimer's disease, but some sample groups also included patients with vascular dementia. In all included trials a standardized extract (EGb761) was used. For meta-analysis, we focused on the effect of Gb on cognition and ADL. Cognition was measured in two studies with the ADAS-cog [44, 47], whereas in the remaining six studies the SKT was applied. Mean differences for ADAS-cog varied between −0.3 and 1.3 in the Gb groups and from 0.9 to 1.0 in the placebo groups. Change scores in SKT ranged from −3.2 to −0.8 in Gb

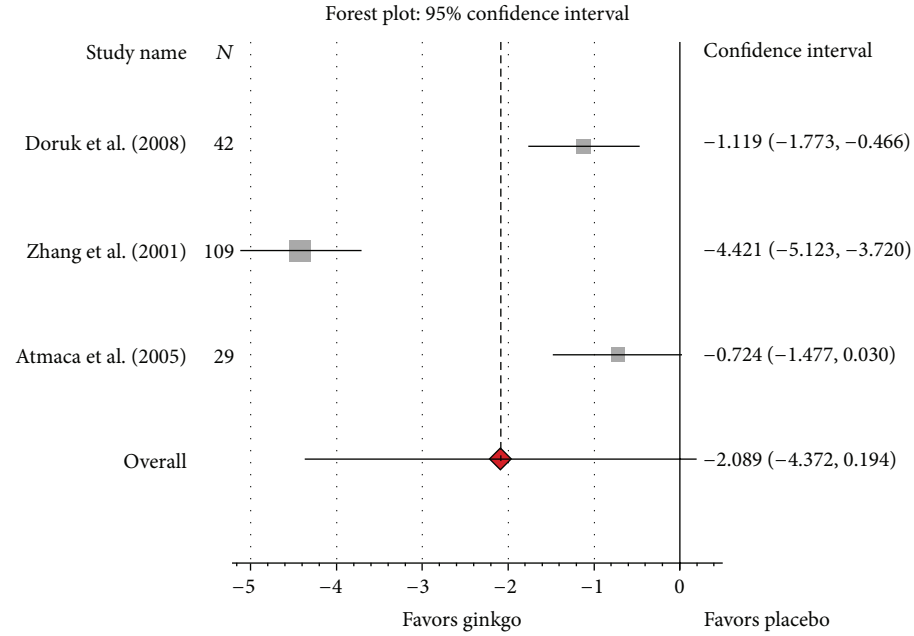

Figure 3: Pooled standardized mean difference compared with placebo for negative symptoms score (SANS).

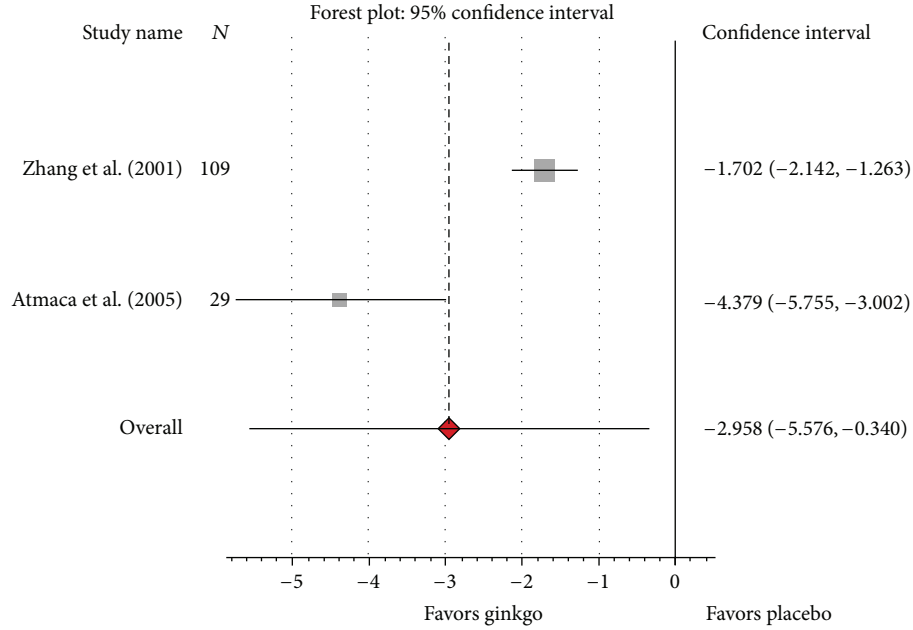

Figure 4: Pooled standardized mean difference compared with placebo for positive symptoms score (SAPS).

treated patients and from −1.2 to 1.3 in the placebo groups. Standardized mean differences were higher for Gb than for placebo, with SMD = −0.56 (95% CI −1.026; −0.095, $P = 0.001$) (Figure 5). Of note, heterogeneity was substantial ($I^2 = 96, 1\%$). If only studies using SKT were considered, we still observed an advantage for Gb compared to placebo, with SMD = −0.72 (95% CI −1.28; −0.017, $P = 0.001$): heterogeneity remained substantial ($I^2 = 96\%$). If we considered studies using ADAS-cog, Gb was not different from placebo, with SMD = −0.05 (95% CI −0.41; 0.30, P = ns). Heterogeneity remained substantial ($I^2 = 81\%$). To perform sensitivity analysis, we tried to remove the older trials in which the quality of methodological design was not as high as in most recent studies. After excluding these trials [47–49], our results did not significantly change (SMD = −0.49 (95% CI −0.59; −0.40), $P = 0.001$); of note, heterogeneity became higher ($I^2 = 98\%$).

ADLs were measured with different scales. Two studies used the ADL-IS [42, 43], two studies used the GERRI [47, 49], one study used the GBS-ADL subscale [44], one study

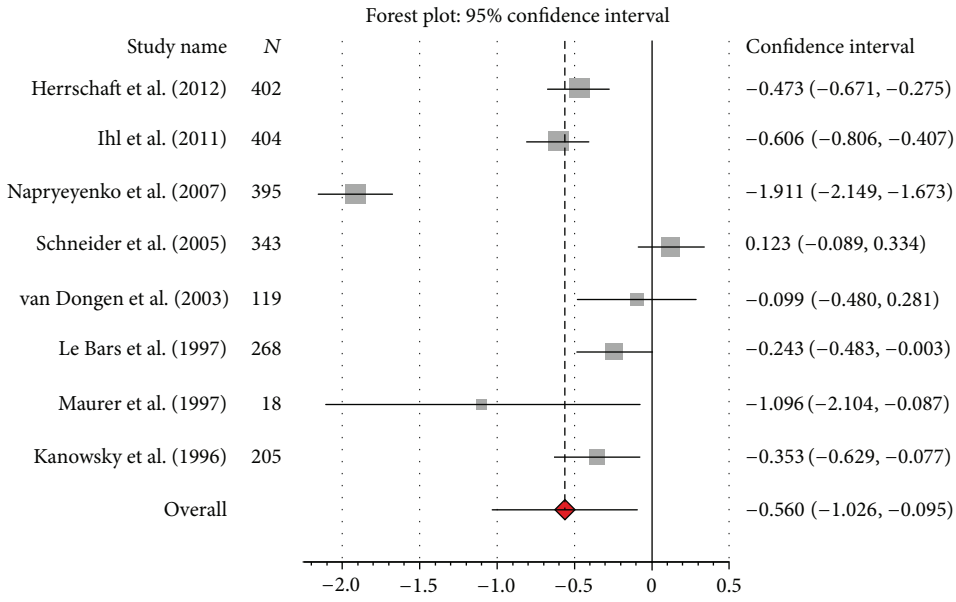

Figure 5: Pooled standardized mean difference compared with placebo for cognitive outcomes (ADAS-cog, SKT).

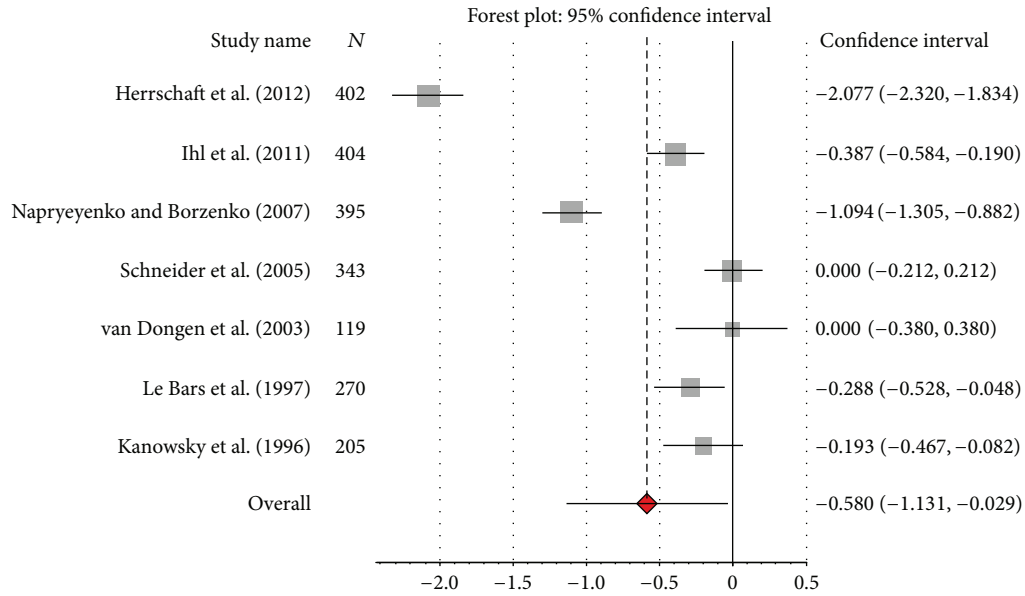

Figure 6: Pooled standardized mean difference compared with placebo for activities of daily living outcomes (ADL-IS, GERRI, GBS-ADL, NAA, and NAB).

used the Nürnberger Alters-Alltagsaktivitäten-skala (NAA, self-assessed) [46], and one trial used the Nürnberger Alters-Beobachtungsskala (NAB, caregiver rated) [49]. Mean differences varied in the Gb and the placebo groups between −1.9 and −0.05 and between −0.4 and 0.9, respectively. There was a significant difference in ADL standardized change scores between Gb and placebo, with SMD = −0.598 (95% CI −0.954; −0.251, $P = 0.001$) (Figure 6). Of note, we found substantial heterogeneity ($I^2 = 98\%$). If only studies using the same scale were pooled together, we still observed a difference between Gb and placebo, favouring Gb, for the ADL-IS (SMD = −1.06 (95% CI −1.21; −0.90), $P = 0.001$) ($I^2 = 99\%$). No difference between the two groups was observed for the GERRI (SMD = −0.04 (95% CI −0.10; 0.02), $P = 0.15$) ($I^2 = 72\%$). The two trials performing a comparison between Gb and donepezil reported no statistically significant differences between the

cholinesterase inhibitor and Gb in treating mild to moderate dementia. Both studies showed comparable treatment time, but the study of Ihl et al. [52] used significantly lower dose of both donepezil (5 mg instead of 10 mg/die) and Gb (160 mg versus 240 mg/die).

4. Discussion

The effect of *Ginkgo biloba* has been studied in a variety of neuropsychiatric conditions. However, the general lack of evidence prevents drawing conclusions regarding Gb effectiveness in many neuropsychiatric conditions, such as autism, ADHD, addiction, GAD, and tardive dyskinesia. Of all the psychiatric disorders reviewed, dementia has been the most extensively studied. Our meta-analysis of eight studies in dementia showed that Gb differed significantly from placebo, providing beneficial effects both in cognition and activities of daily living. Our results are consistent with a recent meta-analysis [13] on the effect of Gb on cognition. On the other hand, we found a significant difference between Gb and placebo for activities of daily living in patients with dementia which were not significant in the aforementioned report [13]. This difference may be at least in part due to the inclusion of a very recent study, yielding significant positive results in this area of functioning. We decided to pool together studies using different scales evaluating the same domain (i.e., SKT and ADAS-cog for cognition). Considering cognition, it has been reported that both ADAS-cog and SKT could be statistically compared [52]. Additionally, even if we separated the two scales, the beneficial effect of Gb remained evident at least for the SKT. Of note, we did not observe a significant improvement in heterogeneity. Considering the activities of daily living domain, there is a lack of studies using the same outcome scale; thus, we pooled together different questionnaires (measuring the same area) in order to improve power. However, if we considered only trials using the same outcome scale, we still observed a beneficial effect of Gb in the ADL-IS. Although there is clear heterogeneity, we were unable to explain it. Sensitivity analysis excluding trial with poorer methodological quality did not explain the heterogeneity. Under these circumstances, we dealt with the existence of heterogeneity using a random-effect model.

Notwithstanding the shortage of specific studies, available evidence also supports the use of Gb in chronic schizophrenia. In particular, Gb seems to exert a beneficial effect on positive psychotic symptoms. No significant effect on negative symptoms has been observed. Even if the three included studies were similar in design (inclusion/exclusion criteria, time, and Gb dosage), all patients were on antipsychotic medication. In particular, we performed sensitivity analysis excluding one study with different chlorpromazine equivalents. In fact, the study from Atmaca et al. used a lower dosage of chlorpromazine equivalent, even if the mean dose (16.8 mg/day) of the administered drug (olanzapine) was clinically appropriate. However, heterogeneity was not modified.

The beneficial effect of Gb in both dementia and chronic schizophrenia is however modest. Particularly, the mean effect observed in cognition is sometimes lower than what is considered clinically meaningful [52]. However, Gb was equal to donepezil in two recent clinical trials, thus potentially providing an evidence for its use in dementia, which to date could be treated with few pharmacological agents. Of note, Gb is generally used as an adjunctive therapy in schizophrenia, not as a first-line intervention, and, thus, even a small additional improvement could be valuable. Notably, all trials demonstrated an excellent safety profile for Gb.

Limitations should caution against overinterpretation of the findings. The included studies showed high heterogeneity, which could possibly have biased our results. Additionally, whether longer trials would yield more significant results in dementia and schizophrenia remains to be seen. Another potential limitation is that even though our search was systematic and rigorous, we could have missed eligible studies inadvertently.

5. Conclusion

Despite the heterogeneity of the clinical trials, available evidence is sufficient to support the use of Gb in patients with dementia and as an adjunctive therapy in schizophrenic patients. Despite the promising results, broad recommendations for the use of Gb in other neuropsychiatric conditions, such as ADHD, autism, and AD are still premature. A better understanding of the mechanisms of Gb effect in these conditions may be useful as well as linking Gb beneficial effects with other types of data such as fMRI or SPECT imaging. It should be considered to run major multicenter studies in order to shed more light on the effectiveness of Gb in dementia subgroups and schizophrenia. Hopefully, the design of the study should use currently available level of treatment and care, in order to provide a broader generalizability of the results.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or noprofit sectors. Anna Verna is an employee of nVH Italia Srl. All the other authors have no conflicts of interests.

Acknowledgments

The authors would like to acknowledge Dr. Robert Hoerr for the precious advice on the analysis of data. They would like to thank Dr. Shien Guo, Dr. Andy Suter, and Professor Ralf Ihl for their help in collecting manuscripts.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 969032, 10 pages
http://dx.doi.org/10.1155/2013/969032

Research Article

Sleep Ameliorating Effects of Acupuncture in a Psychiatric Population

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Received 19 March 2013; Revised 10 May 2013; Accepted 11 May 2013

Academic Editor: Melzer Jörg

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The interest of psychiatric patients for complementary medicine, such as acupuncture, is stable, but effect studies in psychiatry remain scarce. In this pilot study, the effects of 3 months of acupuncture treatment on sleep were evaluated and compared between a group of patients with schizophrenia ($n = 16$) and a group with depression ($n = 16$). Healthy controls were included in order to establish reference values ($n = 8$). Patients with schizophrenia and depression were randomly assigned to either a waiting list or a treatment condition. The Pittsburgh Sleep Quality Inventory was completed before and after the acupuncture treatment (individualized and according to traditional Chinese medicine principles) or the waiting list condition. Both acupuncture groups showed significant lower scores on the sleep inventory, which was not the case for the waiting list condition. Moreover, it was found that the effectiveness of the acupuncture treatment was higher in the patients with schizophrenia than in the patients with depression. Acupuncture seems able to improve sleep in this convenient sample of patients with long-lasting psychiatric problems and may be a suitable and cost-effective add-on treatment for this group, particularly if conducted group-wise.

1. Introduction

Interest in complementary and alternative medicine (CAM), such as acupuncture, has increased in popularity in Western societies in the last part of the twentieth century and there has been a continued interest ever since [1]. The use of CAM includes its application in psychiatric patients [2]. Two large groups that need long-term treatment are patients with depression and patients with schizophrenia. Besides the typical depressive or positive and negative symptoms, their disorders are characterized by marked disturbances of sleep [3–8]. Patients with schizophrenia show increased sleep latency, decreased total sleep time, and decreased sleep efficiency [3–5]. A bidirectional relationship between insomnia and depressive symptoms in patients with depression is described [6–8]. Sleep problems such as increased sleep latency, awakenings in the night or early in the morning with an incapability to go back to sleep, and decreased sleep efficiency are typical symptoms of depression, whereas hypersomnia and dream disturbances are also often reported. The sleep disorders appear to maintain or even deteriorate the mood disorder [9].

In Western psychiatry, a growing consumption of antipsychotic [10] and antidepressant drugs [11] can be seen. Antipsychotic application is seen as the cornerstone in therapy for patients with schizophrenia [12], whereas due to their positive

effects, antidepressants have found their place in the clinical guidelines for the treatment of, for instance, patients with depression [13]. Despite these clinical successes, a problem with pharmaceutical therapies [14], like any other therapy, is that they are subject to patient nonadherence and declining patient compliance [15, 16].

Previous research has shown that adherence to treatment correlates negatively with sleep disturbance and depression [17]. It seems that a lack of contact with this patient group makes it difficult to engage in a therapeutic relationship or to prescribe and monitor medication effectively. The medicines used to treat these conditions often cause drowsiness [18]. Patients are therefore often advised to take them at night which causes problems with sleep (e.g., excessive dreaming and increase in total sleep time in patients with schizophrenia [4]), even though taking them at night minimizes daytime drowsiness. Moreover, tiredness, drowsiness, and poor sleep interfere with the patient's ability to engage with therapeutic services because they are too tired, unmotivated and they do not see the point or do not want to take medicines that cause such adverse effects. Presumably, these are not the only factors that are of importance, but they seem highly relevant in patient groups that suffer from depression, as well as those that suffer from schizophrenia, since both diseases are prone to sleep disorders.

Acupuncture is part of Traditional Chinese Medicine (TCM), which in itself is a form of CAM that is based on thousands of years of practice [21]. One of the features of the TCM approach is the individualization of treatment, which relies on a symptom-based diagnostic process [22]. TCM diagnoses are based on clinical symptoms and signs that are completely discerned by the oriental medical practitioner [22].

Recent years have seen an increase in trials on particularly depression and acupuncture [23–25]. Various reviews, however, have concluded that evidence for the effects of acupuncture on depression still remains preliminary [26–28]. In particular methodological problems, such as different techniques (electro-, manual, or laser acupuncture), various control groups and study designs limit the generalization of the results [23, 29]. Although efforts have been made to standardize and optimize research and the way it is reported, further research is warranted [26, 30].

Even less research with acupuncture has been conducted on schizophrenia. Some literature research [31, 32] indicates that more research is necessary to draw firm conclusions on acupuncture's effectiveness in the treatment of schizophrenia. Moreover, even though some research was reported [33, 34], hinting in the direction of effectiveness and thereby providing the basis for future research, the existing research remains preliminary.

Acupuncture may be beneficial in the treatment of sleep disorders [35]. It can be used alone or combined with other interventions, since no interactions were found to date and adverse events related to treatment seem sufficiently controllable by providing thorough training [36]. Although some research has been conducted on acupuncture and sleep disorders [37–40], results are still tentative, particularly in patients with psychiatric disorders. Results call for research in a group, in which symptoms are prominent, since acupuncture's effectiveness is thought to rely on its homeostatic actions, striving to return the body to its normal physiological state. Therefore, it is thought that acupuncture has more effects on patients that experience serious problems than on healthy participants or patients with only mild symptoms [41].

This pilot study evaluates and compares the effects of acupuncture on the subjective quality of sleep in long-term patients with schizophrenia and patients with depression. It is a pragmatic trial and a first start to conduct research in an integrative treatment setting in which psychiatric treatment and TCM are combined.

2. Materials and Methods

2.1. Participants. In total the convenient sample consisted of 40 participants (13 men, 27 women). Sixteen of them (10 women, 6 men, mean age was 44.25 years, SD = 2.44) were diagnosed with schizophrenia, 16 of them (12 women, 4 men, mean age was 50.94 years, SD = 1.33) were diagnosed with depression. The healthy control group consisted of 5 women and 3 men (mean age was 36.75 years, SD = 12.43). Mean length of illness was 13.56 years (SD = 1.59) for the group with schizophrenia and 5.94 years (SD = 1.05) for the group with depression. The randomization function in Excel was used to randomly divide the patients into a treatment and a waiting list condition. For an overview of the descriptive statistics see Table 1 and for an overview of the medication used see Table 2.

Recruiting limitations resulted in a higher mean age in the depression waiting list condition than in the healthy control group ($P < 0.05$). There was a poster in the entrance section and in the waiting room that gave information on the study. Moreover, potential participants (diagnosed with schizophrenia F20.0 (paranoid schizophrenia), F20.5 (schizophrenic residuum), or depression F33.2 according to the ICD-10) [42] were identified and approached by their therapist at the LVR-Klinik Bedburg-Hau. Patients that agreed to participate did so voluntarily and signed an informed consent form; moreover, their therapist signed for their mental ability to understand the form. The Becks Depression Inventory-II [43] and Positive And Negative Symptom Scale (PANSS) [44] were used as inclusion criteria. The study was carried out in accordance with the Declaration of Helsinki [45] and was approved by the ethical committee of the Ärztekammer Nordrhein. Participants continued with their normal psychiatric treatment, including medication, alongside acupuncture. After the project, the medical files were checked for possible changes in medication during the time of the project. Moreover, possible use of sleep medication was mentioned by the patients on the Pittsburgh Sleep Quality Inventory (PSQI). Five of the patients with schizophrenia (all in the acupuncture condition) used sleep medication beforehand. Six of the patients with depression (2 in the acupuncture and 4 in the waiting list condition) and none of the healthy control group used sleep medication. Of the five patients in the schizophrenia and acupuncture

Table 1: Overview of the descriptive statistics of the convenient sample.

	Schizophrenia (SD)			Depression (SD)			Healthy control (SD)
	Total	Waiting list	Acupuncture	Total	Waiting list	Acupuncture	Total
Men	6	3	3	4	2	2	3
Women	10	5	5	12	6	6	5
Length of illness	13.56 (1.59)	12.63 (5.90)[a]	14.50 (7.07)[a]	5.94 (1.05)	4.38 (3.54)	7.50 (4.41)	0
Age	44.25 (2.44)	42.25 (10.99)	46.25 (8.57)	50.94 (1.33)	52.88 (5.59)[b]	49.00 (4.54)	36.75 (12.43)

According to the one-way ANOVA (groups as between subjects factor) at baseline: [a]Mean is significantly different ($P < 0.05$) from the depression waiting list group. [b]Mean is significantly different ($P < 0.05$) from the healthy control group.

Table 2: Overview of the medication used by the different groups at the start of the study.

Group	CPZ	Atypical	Typical	SSRI	Tricyclic antidepressives	SNRI and SSNRI	Others
Depression and acupuncture group	Chlorprothixene in 1 patient Promethazine in 1 patient Pipamperone in 1 patient 0.33 in 1 patient	In 2 patients	In 2 patients	In 4 patients	In 3 patients	In 3 patients	In 2 patients
Depression and waitlist group	Pipamperone in 1 patient 0.33 in 1 patient	In 1 patient	In 1 patient	In 4 patients	In 2 patients	In 3 patients	In 2 patients
Schizophrenia and acupuncture group	Amisulpride + 1 in 1 patient Zotepine + 1 in 1 patient Prothipendyl + 2 in 1 patient Fluphenazine + 3 in 1 patient 6 in 1 patient 4 in 1 patient 3.5 in 1 patient 1.83 in 1 patient	In 8 patients	In 3 patients	In 0 patients	In 1 patient	In 1 patients	In 4 patients
Schizophrenia and waitlist group	Fluphenazine + 3 in 1 patient 6 in 1 patient Pipamperone + 3.17 in 1 patient 1.83 in 1 patient 1 in 1 patient Zotepine and Chlorprothixene and Melperone + 4 in 1 patient 10 in 1 patient 3.5 in 1 patient	In 8 patients	In 3 patients	In 0 patients	In 2 patients	In 0 patients	In 4 patients

CPZ (Chlorpromazine Equivalents) were calculated using published equivalencies for oral conventional [19] and atypical [20] antipsychotics.
SSRI: selective serotonin reuptake Inhibitor, SNRI: serotonin norepinephrine reuptake inhibitor, SSNRI: selective serotonin norepinephrine reuptake inhibitor.

group, one of them used Prothipendyl (80 mg daily), one used Prothipendyl (40 mg daily), one used Sifrol (0.36 mg daily) one used Amitriptyline (50 mg daily), and one used Melperone (75 mg daily). In the depression and acupuncture group one patient used Chlorprothixene (30 mg daily) and one patient Pipamperone (40 mg daily). Finally in the depression and waiting list condition group one patient used Pipamperone (40 mg daily) and three patients Zopiclone (7.5 mg daily/when needed). Probably due to the natural course of the diseases and recruitment limitations, the group of participants diagnosed with schizophrenia had been in treatment significantly longer than those with depression. There were no gender differences within and between the groups. Exclusion criteria for the patients were substance abuse and/or epilepsy and other neurological conditions. For the control group, the exclusion criteria were the presence of neurological or psychiatric disorders.

2.2. Instruments

2.2.1. Pittsburgh Sleep Quality Inventory. The German version of the PSQI [46] was used in order to gain information on the subjective quality and quantity of sleep in the participants. This retrospective list contains questions about sleep during the last four weeks, information on the number of sleep disturbances, estimation on sleep quality, sleep duration, sleep latency and sleep times, use of medication, and sleepiness during the day. The questionnaire consists of 18 items, divided into 7 components that can be scored from 0 to 3. The PSQI Total Score results in the sum of the component scores and can be any score from zero to 21. A high score means sleep quality is bad. Five was originally seen as the cutoff score. Participants that score below 5 have a good sleep quality. However, there is a tendency to use 6 as a cutoff score [47] to be more selective. The internal consistency for the American

and Japanese versions was found to be good. Cronbach's alpha for the total score was .77 [48]. The validity of the PSQI in patients with primary insomnia was good, since a high correlation between PSQI scores and a sleep diary was obtained by Backhaus and colleagues [49]. Moreover, they found a significant correlation between the PSQI and polysomnographic measurements. These results were confirmed in research on the Chinese version of the PSQI [50]. In all, the PSQI has a high sensitivity and specificity for patients with insomnia [49] and also for patients with depression and schizophrenia [48].

2.3. Experiment

2.3.1. Needles. The needles (AcuPro C, Wujiang City Cloud & Dragon Medical Device Co., Ltd., China) that were used were 0.25×25 mm or 0.20×15 mm stainless steel (depending on the place of needling) single-use needles. The needles were placed according to TCM principles.

2.3.2. Intervention. The participants in the acupuncture groups were given acupuncture treatment once a week, twelve weeks in a row. Individualized acupuncture according to TCM principles was applied after careful individual diagnosis by a licensed oriental medical practitioner with more than 5 years of clinical experience [30]. Acupuncture treatment took place in a light room with (very) soft background music (Enya) playing. According to the demand of the ethics committee to decrease anxiety [51] as much as possible in patients with schizophrenia and to make them feel comfortable, music along with acupuncture was used. The music was kept constant over all participants and all sessions. There were 12 "relax" chairs in which it was possible to adjust the back and put the feet up, resulting in a near-lying position. It was, however, also possible to remain upright; this was left to the patients to decide for themselves. Due to the fact that acupuncture was applied with patients in a sitting or near-lying position, access to acupuncture points on the back was limited. Patients came into the room in intervals, in order to reduce waiting time. Treatment (after needles were inserted) lasted for one hour. After this hour, needles were removed. This group treatment setting made sure practitioners were directly at hand in case anxiety would arise and it was one of the important points that were made in the dialogue with the ethics committee. In case individuals had personal questions or sensitive matters that needed to be discussed prior to treatment, there was an empty room next to the treatment room where confidentiality could be assured. As there were two acupuncturists present, the other patients would not be left alone in the mean time.

All participants continued with regular treatment including appointments with their psychiatrists; this was not influenced by the project since acupuncture was used as an add-on treatment.

2.3.3. Procedure. All participants were tested in an experimental testing room in the clinic, by apprentices who were blind to group or time of testing. The healthy control group was tested at T1 (pretest) only. The participants with schizophrenia and depression were tested at T1 and T2 (posttest). After the tests at T1, participants were randomly divided into a treatment and a waiting list condition. The duration of the whole experiment was 13 weeks, which included 12 weekly acupuncture sessions and pre- and post-testing. At the end of the experiment, all participants received a debriefing and were individually informed about their own test results. Patients on the waiting list were given the opportunity to attend acupuncture treatment after T2 if they wanted to. The current study stopped at T2, although acupuncture treatment was given after T2 in order to provide equal treatment opportunities. The patients, however, were not tested afterwards and therefore these data were not included in the study. Moreover, any acupuncture that was provided after the study was part of their normal treatment, not of any study.

2.4. Statistics. Differences between the five groups on the subtests of the PSQI before the start of the treatment were analyzed with a one-way analysis of variance (one-way ANOVA) with groups as between subjects factor, followed by posthoc (Bonferroni) tests. Repeated measures analyses of variance were used to analyze possible differences on the PSQI Total Score and on the subtests of the PSQI pre- and posttreatment (in the four experimental groups), followed by posthoc (Bonferroni) t-tests if appropriate, that is, $t(7)$ in our pilot-study. A value of $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Acupuncture Points That Were Used. For more details see Table 3.

3.2. Pretest Results. Descriptive characteristics of the five different groups are shown in Table 4, as well as the outcomes of the posthoc tests following the one-way ANOVA. On some of the subtests differences were found between the healthy control and the psychiatric groups.

3.3. Evaluation of Sleep Quality between the Groups. All patients randomized and treated over 12 weeks in the depression and schizophrenia groups were analyzed (each $n = 8$). As can be seen in Table 5, post hoc t-tests for each subtest and group separately resulted in the following significant differences: the depression acupuncture group showed a significant reduction for PSQI Total Score $t(7) = 4.333$, $P = 0.003$. For the depression waiting list condition, no significant differences were found between the pre- and posttest measurements. A significant reduction for the schizophrenia acupuncture group was found for PSQI Total Score $t(7) = 2.393$, $P = 0.048$, for PSQI Latency $t(7) = 2.553$, $P = 0.038$, for PSQI Disorders $t(7) = 2.646$, $P = 0.033$, and for PSQI Medicine $t(7) = 2.646$, $P = 0.033$. No differences were found for the schizophrenia waiting list condition.

Table 3: Acupuncture points that were used.

Points/patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
EX-HN-1	12	12	12	12	12	12	11	12	12	11	12	12	11	12	12	12
DU-24									2	5	5	2				8
DU-14										1						
DU-17									1							
DU-18									1							1
DU-19									1							
EX-HN-3	5		1			2										
EX-HN-5	5		1			2									1	
LI-20						1										
ST-8	10	3	3	9	8		7	2		7	5		10	1	2	1
ST-7									1							
ST-6					2											
TB-21							1						1			
KI-23						2										
KI-24					1	2			1							
KI-25					1				1							
KI-26									1							
GB-6	1															
GB-7									1							
GB-8									1	1						
GB-13									2	1	2		1			9
GB-20	2				1											
SI-3	5		11							2	2		1			
SI-4												1				
SI-5															2	
HT-2					1											
HT-3	1	4	3		3	1	4	2								
LI-4	12	12	12	12	12	12	12	12	7	3	5	9	10	8	12	4
PC-6	3	2		1	4	2			1	1		2	1	1	1	
PC-7		1			4			2	5	4	2	1	2		1	7
HT-7	12	12	11	12	12	12	12	12	9	1	7	3	3	8	3	
HT-8					1											
LU-5												1			1	
LU-6													8			
LU-7	1	11	8		5	3	3	12	8		1		3	5	1	
TB-5	5		10	3			2						2			
TB-6												1				
LI-7	1	2	1			2	10		2	1		1	1			
LI-11	6	6	3	12	10	1	12	6	5	10	8	8	8	11	12	11
CV-12																2
CV-14									1							
CV-15								1								
CV-16					1								1			
CV-17	7	2	3	7	10	1	7	9		12	3	6	9	9	8	11
CV-18					2									3	1	
ST-21										3						4
ST-25	4								2	1		3	5		1	3
CV-5											1					
CV-4	3	8	9		2			9								
KI-10			1	2												

Table 3: Continued.

Points/patients	D1	D2	D3	D4	D5	D6	D7	D8	S1	S2	S3	S4	S5	S6	S7	S8
SP-10	7	6	9			2	3	1				1				
BL-39													1			
BL-40													1	3		
SP-9	12	12	12	12	11	12	12	12	7	6	10	9	12	12	12	3
GB-34	8	7	5	7	8	6	5	6	1			1				4
ST-36	12	12	12	8	12	12	2	12	7	1	3	8	9	8	9	2
ST-40	1	1		12			11		1	10	9	3	2	4	2	9
SP-6	12	12	12	12	12	12	12	11	11	4	12	8	12	11	12	10
KI-3	11	12	12	12	12	12	12	12	1	2	4	7	11		12	
KI-5														2		
KI-6	9	8	9			5	8	12	2							2
LR-3	10	12	11	12	10	4	7	10	10	9	6	8	10	9	5	7
LR-1	2			2	4											
SP-4	4	4	1	11	4	7	9	7	1			2				
BL-60			2					2					1	3		
BL-62													2			
ST-44									2	7			1	3		7
ST-45				6			2				1			1		
GB-41												1				1
GB-44	3			9	6		2		1	5				4		2
GB-45														1		
BL-67	1	1			6	5		3	2		1	1	11	1		
Eye of the knee						8		3		5				6		
BAXIE						3										

D: patient with depression, S: patient with schizophrenia.

Table 4: Corrected means and SDs of the PSQI subtest scores at baseline (T1) for all groups.

PSQI subtest	Schizophrenia waiting list (SD)	Schizophrenia acupuncture (SD)	Depression waiting list (SD)	Depression acupuncture (SD)	Healthy (SD)
Total score	5.75 (1.91)	8.50[b] (4.21)	9.63[b] (4.57)	8.50[b] (3.02)	3.50 (2.07)
Subjective sleep quality	1.00 (0.76)	1.00 (0.76)	1.63 (0.52)	1.38 (0.52)	0.75 (0.46)
Latency	0.87 (1.36)	1.88 (1.13)	1.50 (1.07)	1.50 (0.93)	0.50 (0.54)
Duration	0.25 (0.46)	0.38 (1.06)	1.00 (1.41)	0.50 (0.93)	0.63 (0.74)
Efficiency	1.38 (1.51)	1.00 (1.07)	1.13 (1.55)	1.00 (1.31)	0.25 (0.71)
Disorders	0.88 (0.35)	1.38 (0.52)	1.63 (0.74)	1.50 (0.54)	0.88 (0.35)
Medication	0.00[a] (0.00)	1.88[b] (1.55)	1.25 (1.49)	0.75 (1.39)	0.00 (0.00)
Daytime sleepiness	1.38 (0.52)	1.00[b] (0.76)	1.50 (0.93)	1.88 (0.84)	0.50 (0.54)

According to the one-way ANOVA (groups as between subjects factor) and post hoc tests at baseline: [a]Mean is significantly different ($P < 0.05$) from the schizophrenia acupuncture group. [b]Mean is significantly different ($P < 0.05$) from the healthy control group.

3.4. Side Effects. Two patients reported bruising as a side effect after one of the acupuncture treatment sessions. Moreover, one patient reported having been extremely tired after the first session. Otherwise, no side effects were reported.

4. Discussion

In this pilot study, the effects of three months of acupuncture treatment on subjective sleep quality were investigated in a group of patients with schizophrenia and a group of patients with depression that were diagnosed by their therapists according to the ICD-10 [42]. All patients were chronically ill. Significant improvements were found on the PSQI Total Score for both treatment groups, indicating that patients slept better after 12 acupuncture treatments. The waiting list condition groups showed no significant improvements. As was suggested by Hametner and colleagues [47], a cutoff score of 6 can be used in order to clinically divide patients with sleep problems from patients with good sleep. The patient group with schizophrenia falls below this clinically relevant score after treatment. The patient group with depression has

Table 5: Corrected pretest (T1) means of the PSQI for all five groups and posttest (T2) means of the PSQI for the four groups with patients.

PSQI subtest	Schizophrenia waiting list			Schizophrenia acupuncture			Depression waiting list			Depression acupuncture			Healthy control
	T1	T2	*P*	T1	T2	*P*	T1	T2	*P*	T1	T2	*P*	T1
Total score	5.75	4.88	0.576	8.50	5.50	0.048*	9.63	9.00	0.493	8.50	6.88	0.003**	3.50
Subjective quality	1.00	0.75	0.170	1.00	0.50	0.170	1.63	1.50	0.685	1.38	1.00	0.080	0.75
Latency	0.87	0.75	0.732	1.88	0.75	0.038*	1.50	1.63	0.685	1.50	1.12	0.197	0.50
Duration	0.25	0.13	0.598	0.38	0.63	0.351	1.00	0.75	0.451	0.50	0.63	0.351	0.63
Efficiency	1.38	0.63	0.365	1.00	1.50	0.407	1.13	1.38	0.563	1.00	0.75	0.170	0.25
Disorders	0.88	0.88	1.00	1.38	0.88	0.033*	1.63	1.63	1.00	1.50	1.13	0.080	0.88
Medication	0.00	0.38	0.351	1.88	0.38	0.033*	1.25	0.13	0.094	0.75	0.75	1.00	0.00
Daytime sleepiness	1.38	1.38	1.00	1.00	0.88	0.685	1.50	2.00	0.104	1.88	1.50	0.080	0.50

Difference T1-T2 within the groups: $^{*}P < 0.05$, $^{**}P < 0.005$.

improved and although the differences might not seem large, they seem borderline clinically relevant.

Three subscales (PSQI Latency, PSQI Medication, and PSQI Disorders) showed significant improvements in the schizophrenia group, but not in the depression group. This indicates that the patients with schizophrenia took more benefit from acupuncture than the patients with depression. Of note, these patients fell asleep faster and even approached normal levels on the subtest (PSQI Latency), meaning that patients with schizophrenia lay awake less long before falling asleep after acupuncture treatment and that they reached levels that are commonly found in healthy controls. They also used less medication in order to sleep and reached normative levels also on the subtest for sleep disorders. Five of the patients with schizophrenia (from the acupuncture condition) used sleep medication of different kinds beforehand, whereas four of them answered that they had stopped using this medication during the time of the acupuncture treatment. Moreover, one of the patients in the waiting list condition of this group, who had not used sleep medication beforehand, started using sleep medication. On the other hand, six of the patients with depression (two in the acupuncture group and four in the waiting list condition) used sleep medication beforehand of which 4 (in the waiting list condition) stopped using this medication and one of the other patients in the waiting list group started to use sleep medication. There were no differences between or within the depression groups on medication use as reported by the patient.

The intervention phase lasted three months (12 treatments) only. Future studies might consider whether the novelty factor of this intervention or the short-term availability implies that patients are more likely to attend. It is not known whether patients would be so keen to attend acupuncture were it available as part of their normal treatment package. There were no withdrawals from the acupuncture or waiting list groups in this study. In this clinic, as part of the normal treatment package, patients can choose to visit treatment groups like, for instance; a psychosis education group, sleep training, depression group, social competency training group or a memory training. All of these groups last 10 to 12 times and have a dropout rate between 30 to 40%. These differences between the regular groups and this study might be caused by the small amount of appointments in the waiting list condition as well as a positive experience in the acupuncture groups. This impression is supported by the absent dropout and the comments made by participants (that reported, for instance: feeling less tired, more relaxed, and better able to sleep), that they were satisfied with the treatment and keen to have it. On the other hand, it is important to note that the participants were largely self-selecting (as they are in every group they attend in this clinic) and therefore more likely to come to the treatments anyway. However, in order to draw more firm conclusions, it would have been better to implement a measure of treatment satisfaction in the study.

Some participants reduced their medication, in consultation with their psychiatrist, as a result of the acupuncture treatment. These participants saw this as a benefit of the acupuncture. Medication reduction is usually seen as positive by patients. It is felt to be a sense of improvement or achievement. It may be that the promise of a reduction in medication through acupuncture may be a motivational factor for attendance at acupuncture treatments. On the other hand, it is important to note that there are possible pitfalls in reducing medication as well. It has been described that patients with schizophrenia who improve through the use of acupuncture and as a result reduce or even stop taking medication may become more vulnerable to breakdown [52]. Further research is needed to confirm these subjective comments that were reported by the patients in this study and to investigate the possibility that acupuncture may be misused as an excuse for nonadherence with conventional medication.

Limitations. Since the study involves acupuncture, it is obvious that the problem of the absence of a suitable control group or placebo needs to be mentioned [30]. In this study, it was chosen to investigate the "normal" or "real-world" manual individualized acupuncture treatment that any patient would

receive if they should go to an oriental medical practitioner. The use of a standardized protocol for acupuncture is, besides the National Acupuncture Detoxification Association (NADA) protocol that is used for addiction and trauma [53], unheard of in clinical TCM practice. The use of such a standardization would therefore not shed any light on the possible effect that an acupuncture add-on treatment (that patients seek outside our psychiatric clinics) would have on patients and would not be generalisable to routine clinical practice [54]. In this study, a pragmatic randomized controlled trial (RCT) was used; this approach attempts to answer a "real-world" question whether acupuncture as add-on treatment improves sleep more than without this treatment. Our overall goal was to deliver better treatment to patients and this implies that we have to evaluate what can be done in daily practice. MacPherson [55] paraphrased this issue by stating that "the question in acupuncture research should be rather whether acupuncture is of better value than what is currently on offer instead of asking whether acupuncture is better than placebo?"

Due to the ethical problems related to discontinuing treatment with antipsychotic and antidepressant drugs, patients continued their medication during the study. We have listed the doses in Chlorpromazine equivalents and information on medication that was used in Table 2. Due to the fact that psychiatric patients use a wide variety of medication, it was not possible, within the convenient sample in our monocenter pilot study, to include only those that use the same medication and medication doses.

One more limitation of the study is the fact that a second baseline might have been used; it is recommended for future research.

Since the ethics committee required group treatments due to the fact that a practitioner needed to be present at all times, a limitation was that some participants talked to each other before, during, or after treatment sessions. It was not possible to control for the content of these conversations.

Finally, the number of patients in the present study is relatively small. Therefore, in further research it is necessary to increase the sample size, though, despite the small numbers, significant improvements in sleep quality were found.

There is anxiety about giving acupuncture to people with schizophrenia in Europe, since it is not normally practiced and people in psychiatric hospitals are not normally left alone with needles or other dangerous objects. Moreover, anxiety exists about the needles becoming part of hallucinations or psychotic thoughts. For instance, patients might think that they are being radiographic controlled through the needles. The present study further proves that people with schizophrenia can be safely treated with acupuncture and that the use of needles did not evoke negative emotional reactions.

It is important to realize that in this pilot study, positive results were obtained in a group of patients with schizophrenia that have been ill for more than 10 years. Length of illness was analyzed more specifically and it was found that, although there was a difference between the schizophrenia and depression experimental and waiting list groups when it comes to this factor, it did not account for the more significant results in the group with schizophrenia.

It is obvious that the positive outcomes of this pilot study warrant further and larger-scale research, but the tentative conclusion is that the present study shows that acupuncture seems to influence sleep in a positive way in sleep-disturbed patients and seems a suitable add-on treatment in psychiatry, even in patients with long-term depression or schizophrenia.

Disclosure

None of the authors had financial interests in this research.

Acknowledgments

The authors thank all attending participants for their willingness to participate in this study and the director of the LVR-Klinik Bedburg-Hau: Dr. Marie Brill. She made this research possible and she created possibilities to combine clinical and research work on a daily basis. Furthermore, they thank the following apprentices for their help in testing the patients: Isabell Gladen, Lara Werkstetter, Julia Lennertz, Ines Kirchberg, Lena Groetelaers, Mira Scholten, Astrid Schulz-Elze, Adam Cichon, and Mara Cofalla.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 615857, 12 pages
http://dx.doi.org/10.1155/2013/615857

Review Article

Acupuncture for Posttraumatic Stress Disorder: A Systematic Review of Randomized Controlled Trials and Prospective Clinical Trials

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Received 9 August 2012; Accepted 15 October 2012

Academic Editor: Hans-Christian Deter

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To evaluate the current evidence for effectiveness of acupuncture for posttraumatic stress disorder (PTSD) in the form of a systematic review, a systematic literature search was conducted in 23 electronic databases. Grey literature was also searched. The key search terms were "*acupuncture*" and "*PTSD.*" No language restrictions were imposed. We included all randomized or prospective clinical trials that evaluated acupuncture and its variants against a waitlist, sham acupuncture, conventional therapy control for PTSD, or without control. Four randomized controlled trials (RCTs) and 2 uncontrolled clinical trials (UCTs) out of 136 articles in total were systematically reviewed. One high-quality RCT reported that acupuncture was superior to waitlist control and therapeutic effects of acupuncture and cognitive-behavioral therapy (CBT) were similar based on the effect sizes. One RCT showed no statistical difference between acupuncture and selective serotonin reuptake inhibitors (SSRIs). One RCT reported a favorable effect of acupoint stimulation plus CBT against CBT alone. A meta-analysis of acupuncture plus moxibustion versus SSRI favored acupuncture plus moxibustion in three outcomes. This systematic review and meta-analysis suggest that the evidence of effectiveness of acupuncture for PTSD is encouraging but not cogent. Further qualified trials are needed to confirm whether acupuncture is effective for PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) develops following a stressful event or situation of an exceptionally threatening or catastrophic nature, which is likely to cause pervasive distress [1]. PTSD is classified as an anxiety disorder and is typically defined by the coexistence of 3 clusters of symptoms, namely, *reexperiencing*, *marked avoidance*, and *hyperarousal* [2]. The prevalence rates of PTSD have been reported as 6–25% [3], and approximately 25–30% of people experiencing a traumatic event may go on to develop PTSD [4].

Current first-line PTSD therapies include trauma-focused cognitive behavioral therapy (CBT), stress inoculation training, and pharmacotherapies [5]. Complementary and alternative medicine (CAM) interventions include a range of therapies that are not considered standard to the practice of medicine in the USA. CAM therapies are widely used by mental health consumers, including veterans, and numerous stakeholders have expressed strong interest in fostering the evidence base for these approaches in PTSD [6]. In addition, approximately 21% of CAM users met diagnostic criteria for at least one problematic mental disorder, according to one study [7].

Acupuncture is commonly recognized worldwide as a mainstream CAM therapy. Acupuncture is the practice of inserting a needle or needles into certain points in the

body, known as meridian acupuncture points, for therapeutic or preventive purposes [8]. Numerous studies have shown that acupuncture is well tolerated by patients, safe, and cost effective compared to routine care [9].

Additionally, acupuncture is widely used in mental disorders such as anxiety disorders [10], dementia [11], eating disorders [12], schizophrenia [13], sleep disorders [14], and substance-related disorders [15, 16]. Electroacupuncture is effective in rat models of stress and thus might be a useful adjunct therapy in stress-related anxiety disorders [17]. Acupuncture has positive effects in PTSD patients, although the evidence is still lacking as to its true efficacy for this condition [18].

There have been two reviews published on acupuncture or its variants for PTSD [19, 20]. David Feinstein reviewed 2 randomized controlled trials (RCTs) and 6 outcome studies which tested whether brief psychological exposure with acupoint tapping was effective for PTSD or not and its conclusion was not confirmative [19]. Also Michael Hollifield reviewed acupuncture for PTSD referring one published and one unpublished clinical trial and suggested further definitive research is needed because of lack of well-conducted RCTs [20]. However, there has been no systematic review published to date fully summarizing the current total evidence about the quality and effectiveness of acupuncture for PTSD. For this reason, we conducted a systematic review of RCTs and prospective clinical trials to assess critically whether acupuncture improves the symptoms of PTSD and to make recommendations for future research based on gap areas identified in this review.

2. Methods

2.1. Data Sources and Search Strategy. Following the COSI model [21], we searched the following electronic databases over time periods from their inception to July 2012: Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE through PubMed, EMBASE, Allied and Complementary Medicine Database (AMED), CINAHL, Pilots, Google, Korean databases (which include DBpia, Korea Institute of Science and Technology Information (KISTI), KoreaMed, Korean traditional knowledge portal, OASIS, RISS, the National Assembly Library, and The National Library of Korea), Chinese databases (which include China Academic Journal, http://www.cqvip.com and WANFANG DATA), and a Japanese database (Japan Science and Technology Information Aggregator Electronic). We also searched the grey literature; unpublished trials were searched via the Register of the Controlled Trials databases (http://www.controlled-trials.com and http://www.clinicaltrials.gov), and we communicated with identified experts in the field of acupuncture and PTSD, searched our departmental files, and pearled the references of all included articles for other relevant articles perhaps not picked up through other methods of searching.

The key search terms were "(acupuncture OR acup*) AND (stress disorders, post-Traumatic OR posttraumatic stress disorder OR posttraumatic stress disorder OR PTSD)." MeSH strategy was applied to ensure the most powerful search where applicable. Search strategies were adjusted for each of the databases. Personal contacts were made with the original authors of the searched studies to identify any potential missing data from the publications.

2.2. Study Selection. Two psychiatrists (J. H. Lim and H. W. Kang) actively participated in the study selection process based on clinical expertise, and two experienced researchers (B. C. Shin, C. Cindy) monitored the whole process of systematic review. All reviewers were fully trained in the systematic review process executed.

2.2.1. Types of Studies. The review was not restricted by study design, however, study should be prospective clinical trials. We included RCTs and nonrandomized controlled trials that compared acupuncture or its variants with a control or control groups. We also included uncontrolled clinical trials (UCTs) of acupuncture for PTSD to give our research question a more solid ground or to make recommendations for future research. However, we separately analyzed RCTs and others, and interpreted more weighted on RCTs because of research quality following the validity of evidence. No restrictions were imposed on studies with regard to blinding, languages, or year published.

2.2.2. Types of Participants. We selected all studies including patients with PTSD diagnosed by any set of criteria, DSM-IV or ICD-10, regardless of gender, age, nationality, or outpatient therapy or inpatient therapy.

2.2.3. Types of Interventions/Controls. Clinical trials investigating any type of needling acupuncture, specifically classical acupuncture, electroacupuncture, auricular acupuncture were included. We also included trials that included acupuncture as a more complex intervention, that is, acupuncture plus another intervention if the comparison group was that other intervention. We included trials using control groups with no treatment, sham/placebo acupuncture, and conventional treatments for PTSD patients. We excluded laser acupuncture and acupoint stimulation such as acupressure, moxibustion, tapping, and so forth because of the lack of needling. We excluded trials with controls that acted as "healthy participants."

2.2.4. Types of Outcome Measures. The most recent guideline for treatment of PTSD [5] includes the following major outcomes: 1st: "reduction in severity of PTSD symptoms"; 2nd: "prevention/reduction of trauma-related comorbid conditions"; 3rd: "patient adherence to treatment plan"; 4th:"response to treatment"; 5th: "social, occupational, adaptive, and interpersonal functioning"; 6th: "quality of life" and 7th: "rate of relapse." The main outcome measures were any relevant PTSD scales as clinician-administered PTSD scale (CAPS), depression scale, and anxiety scale. Other scales as related to impairment, proportion of patients recovered were extracted following predefined protocol.

2.3. Screening, Data Extraction, and Quality Assessment. After screening titles and abstracts retrieved through our search, we excluded all articles that did not match our inclusion/exclusion criteria according to the predefined eligibility criteria mentioned above. Then, expected inclusions were carefully read in full text, and final inclusion was decided by two independent reviewers (Y. D. Kim, I. Heo) by matching method. If studies were written in languages incomprehensible for the reviewers, all articles not written in native language were translated by colleagues. Then we first classified these by the eligibility criteria. If there was a need for full text review, we evaluated these after translation. Data were extracted independently based on predefined characteristics to describe each study (refer to Table 1) by the two reviewers. All disagreements were resolved by discussion and consensus, or by the first author. The Cochrane risk of bias for assessing the quality of included RCTs [22], the CONSORT 2010 checklist for reporting quality of RCTs [23] and the revised standards for reporting interventions in clinical trials of acupuncture (STRICTA) guideline for reporting quality of acupuncture trials [24] were used to evaluate the methodological quality of the included publications. All reviewers were fully trained in the quality assessment and data extraction methodology.

2.4. Data Synthesis and Statistics. Two authors (Y. D. Kim, B. C. Shin) calculated effect estimates (effect size: ES) to summarize the effects of acupuncture on each outcome by recalculation for mean and standard deviation (SD) because all original data were continuous ones. The standardized mean difference (SMD) and 95% confidence interval (CI) on each outcome measurement were calculated using Cochrane Collaboration software (Review Manager (RevMan) Version 5.1.7 for Windows. Copenhagen: The Nordic Cochrane Centre). For meta-analysis, we pooled data across studies using weighted mean difference (WMD) because same measurement was used. Random effect model was used because clinical heterogeneities were expected across the studies. To assess the heterogeneity among the trials, Chi-square test and the Higgins I^2 test were used.

3. Results

3.1. Study Description. The searches retrieved 136 potentially relevant articles. After screening the titles and abstracts, we excluded 120 studies (Figure 1). 16 articles were read in full and evaluated. Subsequently, 5 studies were excluded because 1 was a controlled trial but the control group members were healthy subjects [30], 1 was active status not recruiting [31], 1 was recruiting status [32], and 2 were completed but with the results not published [33, 34]. Finally 9 RCTs and 2 UCTs were identified. Of 9 RCTs published, Zhang et al. RCT [25] was split or duplicated published with same data [25, 35–39]. So we included only 1 RCT with full data [25] from the 6 RCTs [25, 35–39]. Consequently, 4 RCTs [18, 25–27] and 2 UCTs [28, 29] met our inclusion criteria. Figure 1 sums up the search results based on a four-phase flow diagram in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement format [40]. The key data are summarized in Table 1. One RCT originated from the USA [18], while all the others were from China [25–29]. All RCTs adopted a parallel-group design. Two of them were two-parallel-arm group designs [26, 27], one was a three-parallel-arm group design [18], and one was a four-parallel-arm group design [25]. Two RCTs [18, 25] were based on a sample size calculation, whereas the other two RCTs [26, 27] did not report this.

The four RCTs evaluated 543 PTSD patients (mean sample size per arm: 49). The duration of treatment was 1 to 12 weeks. A table showing baseline clinical characteristics for each group was reported in only one RCT [18].

3.2. Interventions. One RCT compared needle acupuncture to cognitive-behavioral therapy (CBT) and a waitlist control [18], and another used electroacupuncture only or with moxibustion or with auricular acupuncture versus oral selective serotonin reuptake inhibitors (SSRIs) [25]. One RCT tested electroacupuncture plus moxibustion versus oral SSRI [26], and one RCT compared acupoint stimulation plus CBT to CBT alone [27]. One UCT [29] used just acupuncture, the other UCT [28] used electroacupuncture plus auricular acupuncture and moxibustion. 1 RCT [18] and 1 UCT [29] used manual stimulation without electrical stimulation, and the other 3 RCTs [25–27] and 1 UCT [28] used electrical stimulation.

3.3. Outcomes

3.3.1. Acupuncture versus CBT/Acupuncture versus Waitlist Control/CBT versus Waitlist Control. One high-quality RCT evaluated the effect of acupuncture against CBT and a waitlist control [18]. No statistical difference was found between acupuncture and CBT. But, acupuncture treatment was statistically superior to waitlist control on four outcome measures; posttraumatic symptom scale-self report (PSS-SR) (ES, −0.98; $P = 0.001$), Depression: self-rated Hopkins symptom checklist-25 (HSCL-25) (ES, −0.68; $P = 0.02$), Anxiety: HSCL-25 (ES, −0.91; $P = 0.003$), and Impairment: Sheehan Disability Inventory (SDI) (ES, −0.64; $P = 0.03$, Table 1). The CBT was also statistically superior to waitlist control on four outcome measures; PSS-SR (ES, −0.85; $P = 0.004$), Depression: HSCL-25 (ES, −0.80; $P = 0.008$), Anxiety: HSCL-25 (ES, −0.79; $P = 0.008$), Impairment (ES, −0.64; $P = 0.03$). The therapeutic effects of acupuncture and CBT were similar on the ESs [41] (Table 1).

3.3.2. Acupuncture versus Oral SSRI. One RCT evaluated the effect of electroacupuncture versus oral SSRI [25]. No statistical difference was found between two groups.

3.3.3. Acupuncture Plus CBT versus CBT Alone. One RCT assessed the effect of acupoint stimulation plus CBT in comparison to CBT alone [27]. Recalculation of the mean difference (MD) revealed a favorable effect of acupoint stimulation plus CBT in terms of IES-R (ES, −1.56; $P < 0.00001$) and the self-compiled questionnaire (ES, −0.59; $P = 0.01$) (Table 1).

Table 1: Summary of randomized controlled trials and prospective clinical trials of acupuncture for posttraumatic stress disorder.

First author [ref] (year) country	Population	Study design	Sample size/N, analyzed	Intervention/control group (regime)	Treatment session	Main outcomes	Intergroup difference	Comments
RCT ($n = 4$)								
Hollifield [18] (2007) U.S.A.	28 out of 84 identified childhood abuse/ Others, unknown trauma	3 arm parallel, open	84/73	(A) AT + AAT ($n = 29$)/ (B) CBT ($n = 28$) (C) WLC ($n = 27$)	24 sessions	(1) PTSD scale (PSS-SR) (2) Depression (HSCL-25) (3) Anxiety (HSCL-25) (4) Impairment (SDI)	(1) A versus B: $P = 0.36$, MD, −0.26 [−0.83, 0.30] A versus C: $P = 0.001$, MD, −0.98 [−1.58, −0.38] B versus C: $P = 0.004$, MD, −0.85 [−1.44, −0.27] (2) A versus B: $P = 0.92$ MD, 0.03 [−0.53, 0.59] A versus C: $P = 0.02$, MD, −0.68 [−1.27, −0.10] B versus C: $P = 0.008$, MD, −0.80 [−1.38, −0.21] (3) A versus B: $P = 0.39$, MD, −0.25 [−0.81, 0.31] A versus C: $P = 0.003$, MD, −0.91 [−1.51, −0.32] B versus C: $P = 0.008$, MD, −0.79 [−1.37, −0.21] (4) A versus B: $P = 0.98$, MD, −0.01 [−0.57, 0.55] A versus C: $P = 0.03$, MD, −0.64 [−1.22, −0.06] B versus C: $P = 0.03$, MD, −0.64 [−1.22, −0.07]	The AT group had significantly better improvements in PTSD symptoms than the WLC group. But, there was no statistically significant difference between the AT group and the CBT group.
Zhang [25] (2010) China	Earthquake	4 arm parallel, open	276/256	(A) EA ($n = 69$) (B) EA + moxa ($n = 69$) (C) EA + AAT ($n = 69$)/ (D) Oral SSRI ($n = 69$)	36 sessions	(1) PTSD scale (CAPS) (2) Depression (HAMD) (3) Anxiety (HAMA)	(1) A versus D: $P = 0.43$, MD, −0.13 [−0.47, 0.20] B versus D: $P = 0.88$, MD, −0.03 [−0.36, 0.31] C versus D: $P = 0.55$, MD, −0.10 [−0.44, 0.23] (2) A versus D: $P = 0.14$, MD, −0.25 [−0.59, 0.08] B versus D: $P = 0.34$, MD, −0.16 [−0.50, 0.17] C versus D: $P = 0.23$, MD, −0.21 [−0.54, 0.13] (3) A versus D: $P = 0.34$, MD, −0.16 [−0.50, 0.17] B versus D: $P = 0.64$, MD, −0.08 [−0.41, 0.25] C versus D: $P = 0.54$, MD, 0.11 [−0.23, 0.44]	The therapeutic effect of EA was not better than that of oral SSRI.
Zhang [26] (2010) China	Earthquake	2 arm parallel open	92/81	(A) EA + moxa ($n = 46$)/ (B) Oral SSRI ($n = 46$)	36 sessions	(1) PTSD scale (CAPS) (2) Depression (HAMD) (3) Anxiety (HAMA)	(1) A versus B: $P < 0.00001$, MD, −1.77 [−2.26, −1.29] (2) A versus B: $P < 0.00001$, MD, −1.96 [−2.46, −1.46] (3) A versus B: $P < 0.00001$, MD, −1.53 [−2.00, −1.07]	EA plus moxa was more effective than oral SSRI therapy.
Zhang [27] (2011) China	Earthquake	2 arm parallel open	91/90	(A) Acupoint Stimulation + CBT ($n = 67$)/ (B) CBT ($n = 24$)	3~4 sessions*	(1) PTSD scale (IES-R) (2) PTSD scale (self compiled questionnaire)	(1) A versus B: $P < 0.00001$, MD, −1.56 [−2.08, −1.04] (2) A versus B: $P = 0.01$, MD, −0.59 [−1.07, −0.12]	The acupoint stimulation plus CBT showed better efficacy than CBT therapy alone.
UCT ($n = 2$)								
Wang [28] (2009) China	Earthquake	UCT	69	EA + AAT + moxa	36 sessions	(1) The number of cured/improved/non-improved	Not applicable	Treatment was effective in 65 out of 69 (94.2%).

Table 1: Continued.

First author [ref] (year) country	Population	Study design	Sample size/N, analyzed	Intervention/control group (regime)	Treatment session	Main outcomes	Intergroup difference	Comments
UCT ($n = 2$)								
Yuan [29] (2009) China	Earthquake	UCT	34	AT	20 sessions	(1) The number of cured/improved/non-improved	Not applicable	AT was effective in 31 out of 34 (91.2%).

Abbreviations: RCT: randomized controlled trial; UCT: uncontrolled clinical trial; AT: classical acupuncture; EA: electro-acupuncture; moxa, moxibustion; AAT: auricular acupuncture; CBT: cognitive behavioral therapy; WLC: waitlist control; SSRI: selective serotonin reuptake inhibitors; PSS-SR: posttraumatic symptom scale-self report; HSCL-25: self-rated Hopkins symptom checklist-25; SDI: Sheehan Disability Inventory; MD: mean difference; CAPS: clinician-administered PTSD scale; HAMD: Hamilton depression rating scale; HAMA: Hamilton anxiety rating scale; IES-R: Chinese version of the incident effect scale revised; * treated a time every other day for 1 week.

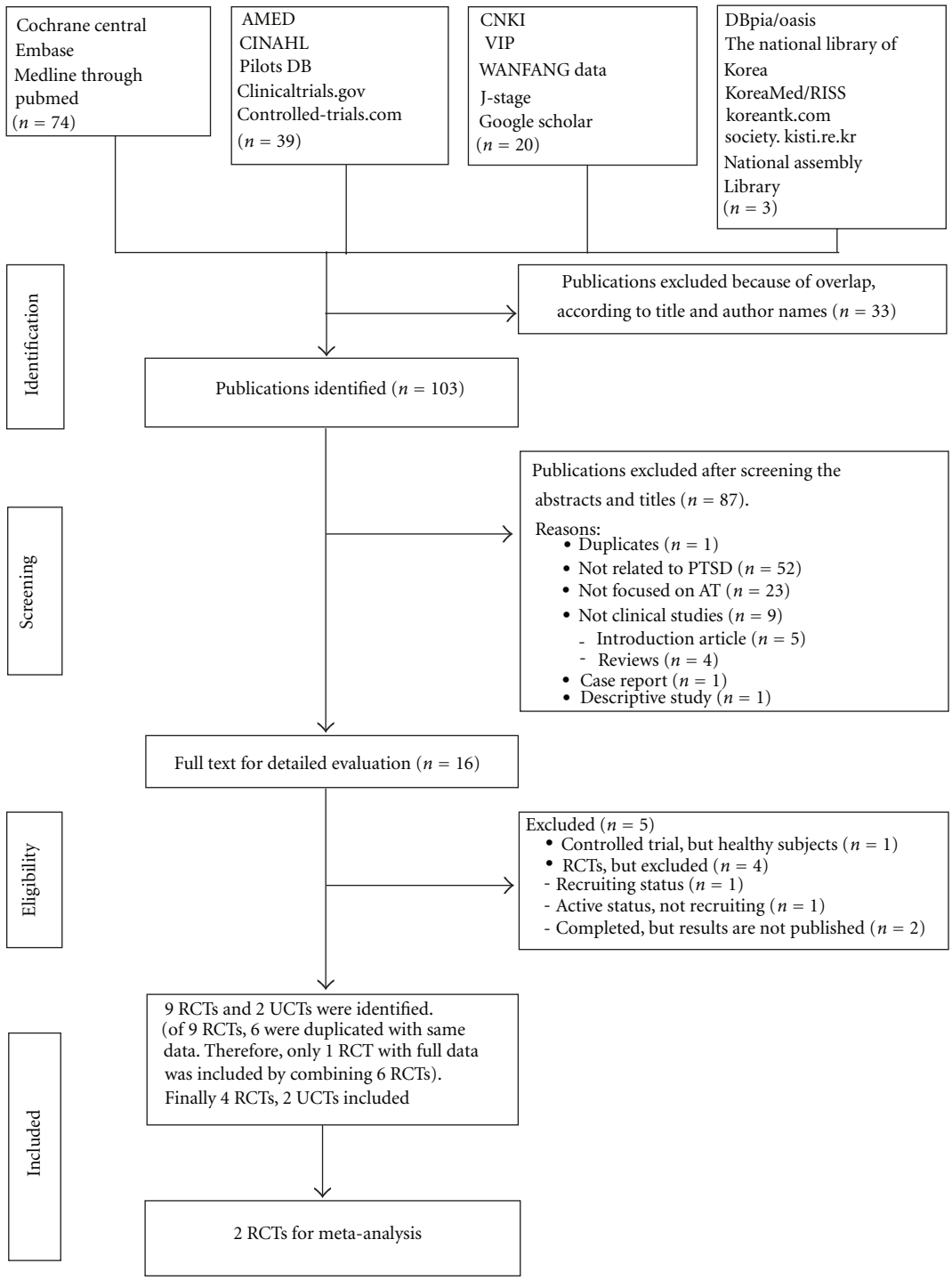


Figure 1: Flow chart of the trial selection process. PTSD: posttraumatic stress disorder; RCT: randomized controlled trial; UCT: uncontrolled clinical trial; AT: acupuncture.

3.3.4. Acupuncture Plus Moxibustion versus Oral SSRI. Two RCTs assessed the effects of electroacupuncture plus moxibustion against oral SSRI [25, 26]. One RCT reported no statistical difference between the two groups [25]. However, the other RCT showed that electroacupuncture plus moxibustion was statistically superior to oral SSRI on outcome clinician-administered PTSD scale (CAPS) (ES, −1.77; $P < 0.00001$), depression (ES, −1.96; $P < 0.00001$), and anxiety (ES, −1.53; $P < 0.00001$) [26] (Table 1).

The meta-analysis of electroacupuncture plus moxibustion versus oral SSRI showed a significant favorable effect of electroacupuncture plus moxibustion on outcome CAPS (2 studies, $n = 115$, ES, −3.19; 95% CI: −3.93 to −2.46, $P < 0.00001$, heterogeneity: $\chi^2 = 0.50$, $P = 0.48$, $I^2 = 0\%$),

Table 2: Cochrane risk of bias of included randomized controlled trials.

First author [ref] (Year)	Hollifield [18] (2007)	Zhang [25] (2010)	Zhang [26] (2010)	Zhang [27] (2011)
(1) Random sequence generation (selection bias)	L (computerized randomization)	L (computerized randomization)	U	U
(2) Allocation concealment (selection bias)	L (central allocation)	L (sequentially numbered, opaque sealed envelopes)	U	U
(3) Blinding of participants (performance bias)	H	H	H	H
(4) Blinding of outcome assessment (detection bias)	L (mentioned)	L (mentioned)	U	U
(5) Incomplete outcome data (attrition bias)	L (mentioned)	U	U	U
(6) Selective reporting (reporting bias)	U	U	U	U
(7) Other sources of bias (other bias)	U	U	U	U

L: low risk of bias; H: high risk of bias; U: unclear.

depression (2 studies, $n = 115$, ES, −1.76; 95% CI: −2.21 to −1.31, $P < 0.00001$, heterogeneity: $\chi^2 = 1.04$, $P = 0.31$, $I^2 = 4\%$), and anxiety (2 studies, $n = 115$, ES, −1.14; 95% CI: −1.44 to −0.84, $P < 0.00001$, heterogeneity: $\chi^2 = 0.62$, $P = 0.43$, $I^2 = 0\%$) (Table 4).

3.3.5. Acupuncture Treatment in 2 UCTs. Two UCTs evaluated acupuncture treatment for total 103 earthquake-caused PTSD patients and showed effectiveness of 94.2% [28] and 91.2% [29], respectively (Table 1).

3.3.6. Adverse Events. Of all 6 studies, 2 RCTs described adverse events related to needle acupuncture [18, 25]. One study noted that some patients (original paper did not report the exact number) mentioned roughness of operational practices, fear of needles, bleeding, hematoma, pain, and fainting [25]. Another study reported just one perceived adverse effect (kidney pain) as a reason for withdrawal from acupuncture treatment [18]. No serious adverse events were reported.

3.4. Risk of Bias and Reporting Quality

3.4.1. Risk of Bias in Included RCTs Based on Cochrane Criteria. The risk of bias was low in one RCT [18], whereas one trial [25] had a moderate risk of bias and two trials [26, 27] had a high risk of bias in most categories (Table 2). Two RCTs employed adequate sequence generation methods and allocation concealment [18, 25], whereas the other two [26, 27] failed to report those categories. Assessor blinding was reported in the former two RCTs [18, 25]. The risk of bias for incomplete outcome data was low in only one RCT [18]. In all, the four included RCTs had an unclear risk of bias in terms of selective reporting and other sources of bias.

3.4.2. Reporting Quality of 4 Included RCTs Based on CONSORT 2010 Checklist. Many leading medical journals and major international editorial groups have endorsed the CONSORT statement, and the statement facilitates critical appraisal and interpretation of RCTs [23]. For this reason, the current review assessed the reporting quality of included RCTs based on the CONSORT 2010 guideline. The 4 included RCTs described 22 items (59.5%) [18] among 37 items, 15 items (40.5%) [25], 9 items (24.3%) [26], and 8 items (21.6%) [27] according to the CONSORT 2010 checklist [23].

3.4.3. Reporting Quality of 4 Included RCTs Based on Revised STRICTA. The STRICTA reporting guideline is an extension of CONSORT was designed to improve the completeness and transparency of reporting of interventions in controlled trials of acupuncture [24], so that such trials may be more accurately interpreted and readily replicated [24]. The reporting quality of acupuncture was high for two of the included RCTs [18, 25], medium in one [26], and low in remaining RCT [27]. The 4 included RCTs reported 16 of 17 items (94.1%) [18], 15 items (88.2%) [25], 13 items (76.5%) [26], and 8 items (47.1%) [27] according to the revised STRICTA guideline. The two high-quality trials [18, 25] presented almost all items transparently except one or two items, whereas the low-quality trial [27] did not describe clearly even the reported 8 items (Table 3).

4. Discussion

This is the first systematic review and meta-analysis of prospective clinical trials on the effectiveness of acupuncture for treatment of PTSD. Only 4 RCTs and 2 UCTs met the inclusion criteria for this review. Our main finding of this review is that acupuncture is effective for PTSD based on one high-quality RCT [18] and a meta-analysis.

The high-quality RCT showed that acupuncture had statistically significant effects compared to a waitlist control, although no statistical difference was found between

Table 3: Reporting quality of 4 included RCTs based on revised STRICTA.

Checklist item	Hollifield et al. [18] (2007)	Zhang et al. [25] (2010)	Zhang et al. [26] (2010)	Zhang et al. [27] (2011)
(1) Acupuncture rationale				
(1a) Style of acupuncture	TCM	TCM	TCM	n.r.
(1b) Reasoning for treatment provided	A paper by Napadow et al., 2005 [42]	A paper by Hollifield et al., 2007 [18]	A paper by Hollifield et al., 2007 [18]	n.r.
(1c) Extent to which treatment was varied	2 types of AT (1) AT: 25 fixed needles plus up to 3 flexible needles within 15 points (2) AAT: ≥6 vaccaria seeds	Fixed interventions (A) EA only (B) EA + moxa (C) EA + AAT	Fixed interventions EA + moxa	Fixed intervention
(2) Details of needling				
(2a) Number of needle insertions per subject per session	(1) AT: 25 plus up to 3 needles (2) AAT: ≥6 vaccaria seeds	(1) EA: 8 needles (2) AAT: 6 vaccaria seeds	EA: 8 needles	unclear.
(2b) Names of points used	(1) AT: bilateral at LR3, PC6, HT7, ST36, SP6, GB20, BL14, 15, 18, 20, 21 and 23/unilateral at Yintang (2) AAT: unilateral at Shenmen, Sympathetic, Liver, Kidney, Lung points	(1) EA: bilateral at GB20/unilateral at GV24, EX-HN1, GV20 (2) AAT: unilateral at Subcortex, Shenmen, Sympathetic, Heart, Liver, Kidney (3) moxa: bilateral at BL23, BL52/unilateral at GV4	(1) EA: bilateral at GB20/unilateral at GV24, EX-HN1, GV20 (2) moxa: bilateral at BL23, BL52/unilateral at GV4	Unilateral at left PC8
(2c) Depth of insertion	(1) AT: 1/4 to 1/2 inch (2) AAT: not inserted	(1) EA: 0.5 to 1.2 cun (2) AAT: not inserted	EA: 0.5 to 1.2 cun	n.r.
(2d) Responses sought	(1) AT: n.r. (2) AAT: not applicable	(1) EA: de-qi (2) AAT: not applicable.	EA: de-qi	n.r.
(2e) Needle stimulation	(1) AT: manipulation (2) AAT: self-massage on the seeds for 15 min/d	(1) EA: electrical stimulation, 100 Hz (2) AAT: 1-2 min pressure	EA: electrical stimulation, 5~8.3 Hz	A Japanese stimulator with 50 Hz was used
(2f) Needle retention time	(1) AT: 25–40 min (2) AAT: unclear	(A) 30 min (B) 30 min (C) 30 min	30 min	Unclear, but the left PC8 was stimulated for 30 min
(2g) Needle type	(1) AT: Viva needles, 34 g (2) AAT: vaccaria seeds	(1) EA: 0.30 mm × 40 mm (2) AAT: vaccaria seeds	n.r.	n.r.
(3) Treatment regimen				
(3a) Number of treatment sessions	24 sessions	36 sessions	(1) EA: 18 sessions (2) moxa: 36 sessions	3~4 sessions*
(3b) Frequency and duration of treatment sessions	Twice a week, 1 hour per session, 12 weeks	Three times a week, 12 weeks	(1) EA: three times a week, 6 weeks (2) moxa: three times a week, 12 weeks	A time every other day for 1 week
(4) Other components of treatment				
(4a) Details of other interventions administered to the acupuncture group	Patients were taught how to use vaccaria seeds for symptom management	(3) moxa: 30 g and 20 min/session, wooden moxibustion box 20 mm × 15 mm × 12 mm	(2) moxa: 20 min/session	CBT
(4b) Setting and context of treatment	n.r.	n.r.	n.r.	n.r.

Table 3: Continued.

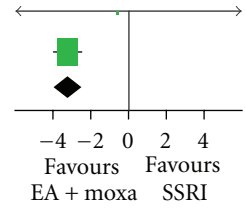
Checklist item	Hollifield et al. [18] (2007)	Zhang et al. [25] (2010)	Zhang et al. [26] (2010)	Zhang et al. [27] (2011)
(5) Practitioner background				
(5) Description of participating Acupuncturists	Doctor of Oriental Medicine in New Mexico with 4 years postgraduate TCM clinical experience	n.r.	n.r.	n.r.
(6) Control or comparator interventions				
(6a) Rationale for the control or comparator	(B) A review by Bisson and Andrew, 2005 [43] (C) not applicable	Approval of FDA	n.r.	n.r.
(6b) Precise description of the control or comparator	(B) CBT (C) WLC	(D) Oral SSRI (Paroxetine 20 mg, once/day, 12 weeks)	Oral SSRI (Paroxetine 20 mg, once/day, 12 weeks)	(B) CBT

Abbreviations: RCT: randomized controlled trial; TCM: traditional Chinese medicine; n.r: not reported; AT: classical acupuncture; EA: electro-acupuncture; moxa, moxibustion; AAT: auricular acupuncture; CBT: cognitive behavioral therapy; WLC: waitlist control; SSRI: selective serotonin reuptake inhibitors.
*treated a time every other day for 1 week.

Table 4: Meta-analysis of acupuncture for posttraumatic stress disorder. PTSD: posttraumatic stress disorder; CAPS, clinician-administered PTSD scale; HAMD, Hamilton depression rating scale; HAMA, Hamilton anxiety rating scale; EA, electro-acupuncture; moxa, moxibustion; SSRI, selective serotonin reuptake inhibitors;

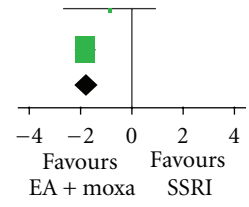
(a) PTSD scale (CAPS).

Study or subgroup	EA + Moxa			SSRI				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Zhang et al., 2010 [25]	−36.15	21.72	69	−35.58	22.12	69	1.0%	−0.57 [−7.88, 6.74]	
Zhang et al., 2010 [26]	−17.17	1.84	46	−13.95	1.76	46	99.0%	−3.22 [−3.96, −2.48]	
Total (95% CI)			**115**			**115**	**100.0%**	**−3.19 [−3.93, −2.46]**	
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.50$, df = 1 ($P = 0.48$); $I^2 = 0\%$									
Test for overall effect: $Z = 8.55$ ($P < 0.00001$)									



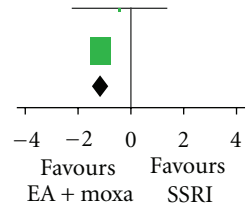
(b) Depression (HAMD).

Study or subgroup	EA + Moxa			SSRI				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Zhang et al., 2010 [25]	−7.42	5.58	69	−6.55	5.1	69	6.2%	−0.87 [−2.65, 0.91]	
Zhang et al., 2010 [26]	−7.27	0.93	46	−5.45	0.91	46	93.8%	−1.82 [−2.20, −1.44]	
Total (95% CI)			**115**			**115**	**100.0%**	**−1.76 [−2.21, −1.31]**	
Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 1.04$, df = 1 ($P = 0.31$); $I^2 = 4\%$									
Test for overall effect: $Z = 7.72$ ($P < 0.00001$)									



(c) Anxiety (HAMA).

Study or subgroup	EA + Moxa			SSRI				Mean difference	Mean difference
	Mean	SD	Total	Mean	SD	Total	Weight	IV, random, 95% CI	IV, random, 95% CI
Zhang et al., 2010 [25]	−6.51	5.26	69	−6.08	5.43	69	2.9%	−0.43 [−2.21, 1.35]	
Zhang et al., 2010 [26]	−5.48	0.75	46	−4.32	0.75	46	97.1%	−1.16 [−1.47, −0.85]	
Total (95% CI)			**115**			**115**	**100.0%**	**−1.14 [−1.44, −0.84]**	
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.62$, df = 1 ($P = 0.43$); $I^2 = 0\%$									
Test for overall effect: $Z = 7.39$ ($P < 0.00001$)									



acupuncture and CBT. Also the therapeutic effect of acupuncture was similar with CBT therapy based on the trial. Additionally, the clinical improvement related to acupuncture or CBT lasted for at least 3 months after the end of treatment in the high-quality RCT.

The meta-analysis showed that acupuncture plus moxibustion was superior to oral SSRI for PTSD. But, we should interpret these results with caution because the meta-analysis was based on one medium-quality RCT [25] and one low-quality RCT [26].

One RCT [27] showed that acupoint stimulation plus CBT was more effective than CBT alone in reducing PTSD symptoms. However, acupuncture treatment was not described transparently. Therefore, this result had doubtful reliability.

We found a similar pattern of reporting quality when comparing the Cochrane risk of bias [22] with the CONSORT 2010 checklist [23]. Two of the included studies [18, 25] had a high reporting quality in terms of acupuncture based on the revised STRICTA guideline [24]. All the studies failed to describe in detail adverse effects related to acupuncture.

We would like to emphasize the clinical importance of acupuncture for PTSD. Acupuncture might be useful in emergency medicine [44]. A recent case series study suggested possible effectiveness of acupuncture in emergency conditions involving PTSD and emotional trauma [45]. In addition, acupuncture is a conveniently portable medical device for taking emergency measures, and it is very cheap, safe, and easy to handle for trained practitioners.

According to a study [46], during long-term SSRI therapy, the most troubling adverse effects were sexual dysfunction, weight gain, and sleep disturbance. The incidence rate of sexual dysfunction was reported as 2% to 7% [47]. Mean weight gain of 10.8 kg (24 lbs) was found after 6 to 12 months of paroxetine therapy [48]. On the other hand, for acupuncture, "mild" adverse events of such as bleeding, bruising, pain on needling occurred in rate of 6.8% (2,178 out of 31,822 sessions) [49]. And no serious adverse events were reported in total 66,229 treatment sessions according to two studies [49, 50]. Therefore acupuncture may be a relatively safe alternative for PTSD in contrast to SSRI, if long-term therapy is needed for treatment.

This systematic review has several limitations. First, although we made strong efforts to retrieve all RCTs on the subject, the evidence reviewed is potentially incomplete because only one rigorous study was included. Second, because there was no RCT on PTSD with a sham acupuncture control, we could not evaluate the effects of acupuncture compared to an inert placebo control [51]. Third, study design was quite different across the four included RCTs. Two RCTs [18, 25] compared acupuncture with different controls (CBT and oral SSRI), and the other two RCTs [26, 27] employed acupuncture as a cointervention of moxibustion and CBT. These very different designs across studies prevented us from abstracting a firm conclusion. Furthermore, the paucity of included trials and the suboptimal methodological quality of the primary data overall, except for one high-quality trial, are also important vulnerabilities of this review.

In total, from these drawbacks we could suggest several important recommendations for future research in this area. One is a need for appropriate controls such as sham/placebo control or other relevant active controls for testing the efficacy or effectiveness of acupuncture for PTSD in the design of parallel RCT or comparative effectiveness research. The second is outcomes should be used by validated one as primary one is PTSD scale and the secondary one is depression or anxiety with safety reporting. The third is high methodological quality is strongly required, as adequate randomization with allocation concealment, blinding of participants and assessors, or sample size estimation for power of trial, with following guideline of CONSORT and STRICTA.

5. Conclusions

The results of this systematic review and meta-analysis suggest that evidence of the effectiveness of acupuncture for PTSD is encouraging but not cogent, because only two RCTs were included in meta-analysis, and it is too small to verify the efficacy of acupuncture. For the future researches, sham-controlled RCTs [52] or comparative effectiveness researches [53] are required to test efficacy and effectiveness of acupuncture for PTSD. To prevent performance bias and detection bias, blinding of participants and outcome assessment should be kept in future trials, too.

Disclosure

The authors report no financial relationship or other relevant to the subject of this paper.

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Evidence-Based Complementary and Alternative Medicine
Volume 2013, Article ID 152738, 16 pages
http://dx.doi.org/10.1155/2013/152738

Review Article

The Effects of Qigong on Anxiety, Depression, and Psychological Well-Being: A Systematic Review and Meta-Analysis

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Received 24 July 2012; Revised 3 October 2012; Accepted 14 October 2012

Academic Editor: Melzer Jörg

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Introduction. The effect of Qigong on psychological well-being is relatively unknown. This study systematically reviewed the effects of Qigong on anxiety, depression, and psychological well-being. *Methods*. Using fifteen studies published between 2001 and 2011, a systematic review was carried out and meta-analyses were performed on studies with appropriate homogeneity. The quality of the outcome measures was also assessed. *Results*. We categorized these studies into three groups based on the type of subjects involved as follows: (1) healthy subjects, (2) subjects with chronic illnesses, and (3) subjects with depression. Based on the heterogeneity assessment of available studies, meta-analyses were conducted in three studies of patients with type II diabetes in the second group, which suggested that Qigong was effective in reducing depression (ES = −0.29; 95% CI, −0.58–0.00) and anxiety (ES = −0.37; 95% CI, −0.66–0.08), as measured by Symptom Checklist 90, and in improving psychological well-being (ES = −0.58; 95% CI, −0.91–0.25) as measured by Diabetes Specific Quality of Life Scale. Overall, the quality of research methodology of existing studies was poor. *Conclusions*. Preliminary evidence suggests that Gigong may have positive effects on psychological well-being among patients with chronic illnesses. However the published studies generally had significant methodological limitations. More high-quality studies are needed.

1. Introduction

The word "Qigong" is a combination of two concepts: "Qi," the vital energy of the body, and "gong," the skill of working of the Qi. Together, Qigong (or Chi Kung) means cultivating energy [1]. Qigong is based on Taoist philosophy and traditional Chinese medicine theories to cultivate Qi. It has a history of several thousand years, and is a highly popular practice, particularly in China, for health maintenance, healing, and increasing vitality [2]. Qigong can be divided into various categories such as static Qigong, dynamic Qigong, internal Qigong (*neiqi*), and external Qigong (*waiqi*) [3].

Qigong exercises consist of a series of orchestrated practices including body posture, movement, breathing, and meditation, all of which have been designed to enhance Qi function—that is, to draw upon natural forces to optimize and balance energy within, through the attainment of deeply focused and relaxed states [4]. An overview of the research literature pertaining to internal Qigong yields more than a dozen forms that have been studied on their effects on health outcomes, including Guo-lin, Chun-Do-Sun-Bup, Vitality or Bu Zheng Qigong, Eight Brocade, and Medical Qigong [5, 6]. As a form of gentle exercise, Qigong is composed of repetitive movements that are used for strengthening and stretching the body, increasing circulation of various fluids (blood, synovial, and lymph), enhancing balance, and building awareness of how the body moves through space

[6]. From the perspective of Western philosophy and science, it could be hypothesized that Qigong, like other meditation techniques, elicits the Relaxation Response and alleviates the dysregulation of the hypothalamic-pituitary-adrenal axis [7]. The potential psychological benefits derived from the practice of Qigong may include relaxation, exposure, desensitization, deautomatization, catharsis, and counterconditioning [8].

As a form of complementary and alternative medicine, Qigong has been used to treat medical conditions such as high blood pressure [9, 10], bone loss [11], and weight-loss maintenance [12]. Short-term Qigong training appears to improve functions of the respiratory [13] and immune systems [14]. Various health claims about Qigong have been made for: hypertension [15–17], Parkinson's disease [18], Type II diabetes [19], cancer [7, 19], cardiac disease [20], pain reduction among post-surgery patients, and patients with injury, arthritis, and fibromyalgia [21, 22].

Several Qigong review articles have been published, which mainly focus on the effects of Qigong on specific medical conditions such as hypertension [17], cancer [19], and geriatric patients [23]. However, for health practitioners, it is still unclear whether Qigong can be recommended as an effective therapy for emotional problems and for improving psychological well-being. The purpose of this meta-analysis was to systematically review the effects of Qigong on psychological outcomes. Due to the limited number of studies in this area, we reviewed Qigong studies which reported on a relatively wide spectrum of outcomes including mood, anxiety, psychological well-being, self-efficacy, and quality of life.

2. Materials and Methods

2.1. Data Searches and Study Selection. Since many Qigong studies were conducted in China and published only in Chinese language journals, the authors included three researchers from China and five researchers from the U.S. Electronic relevant publications from both Chinese and English databases were reviewed. Two reviewers searched and screened the titles and abstracts of the studies identified by the search against the eligibility criteria for English databases independently. One reviewer searched and screened the studies in Chinese. For potentially eligible studies, the full text publications were obtained and criteria reapplied. Disagreement was resolved by discussion. A professional librarian was consulted in our search process.

Research articles published in English on the effects of Qigong on mood and depression were identified from the following databases: from the inception to 2011 on Medline, PubMed, PsycINFO, Cochrane Reviews, Ovid, EBSCOhost, and all of the journals in the Harvard Countway Library of Medicine. Research articles published in Chinese on the effects of Qigong on mood and depression were identified from the following Chinese databases: from the inception to 2011 on CNKI, Wan Fang Med Online, and VMIS. For English databases, the key words used included a combination of MeSH and free text terms: "Qigong/Qi Gong/Gong, Qi/Ch'i Kung/Kung, Ch'i", "mood," "depression," "anxiety," "emotional well-being," and "psychological well-being" as main subject headings, text words in titles, and abstracts. For Chinese databases, the key words used included equivalent Chinese terms as main subject headings, text words in titles, and abstracts.

According to the selection criteria, interventions were restricted to Qigong. Other psychological interventions such as yoga and meditation were excluded; mixed interventions (e.g., acupuncture and Qigong in combination) were excluded (as described in Figure 1). The primary outcomes evaluated were psychological, with particular emphasis on mood, anxiety, depression, self-efficacy, and quality of life.

To be included in the meta-analyses, studies needed to have either a randomized controlled trial (RCT) or quasi-experimental (Q-E) design. The process of study selection was described in Figure 1. A study was operationally defined as RCT in this paper if the allocation of participants to treatment and comparison groups was reported to be randomized. If allocation of participants was done through a systematic sequence (e.g., alternate days of the week) without randomization, the study was operationally defined as having a Q-E design in this paper. Studies that did not use any type of comparison group, or did not report any comparison results between groups, or used mixed interventions were excluded. Duplicate publications were also excluded. Titles and abstracts gathered from the databases were first reviewed for relevance to this paper. The full text of papers that met the inclusion criteria were then obtained, and findings were summarized.

2.2. Data Extraction and Quality Assessment. We assessed the characteristics of the original research and extracted data accordingly. Some basic information was collected based on date of publication, study sites, language of study, and clinical domains (see Table 1). The methodological quality of RCTs was evaluated based on six criteria: adequate sequence generation, allocation concealment, blinding which including the blindness adopted during the conduct and analysis of the studies, completeness of outcome data, selective reporting, and other potential biases, for which the compliance assessment, similarity of comparison groups at baseline and appropriateness of the statistical analyses should be assessed [24, 25] (Table 2).

Findings of 15 studies were tabulated regarding sample characteristics (i.e., total sample size, age, gender, number of participants in Qigong group), duration, intervention style, design of control measures being used, and main outcomes (Table 3). Two reviewers extracted data and assessed the quality of each study independently. Strength of interreviewer agreement was expressed using Cohen k coefficient [26]. Disagreement was initially resolved by discussion. When related data were not provided in articles, trial authors were contacted through e-mail or phone.

2.2.1. Assessment of Heterogeneity. If substantial clinical, methodological, or statistical heterogeneity existed, study

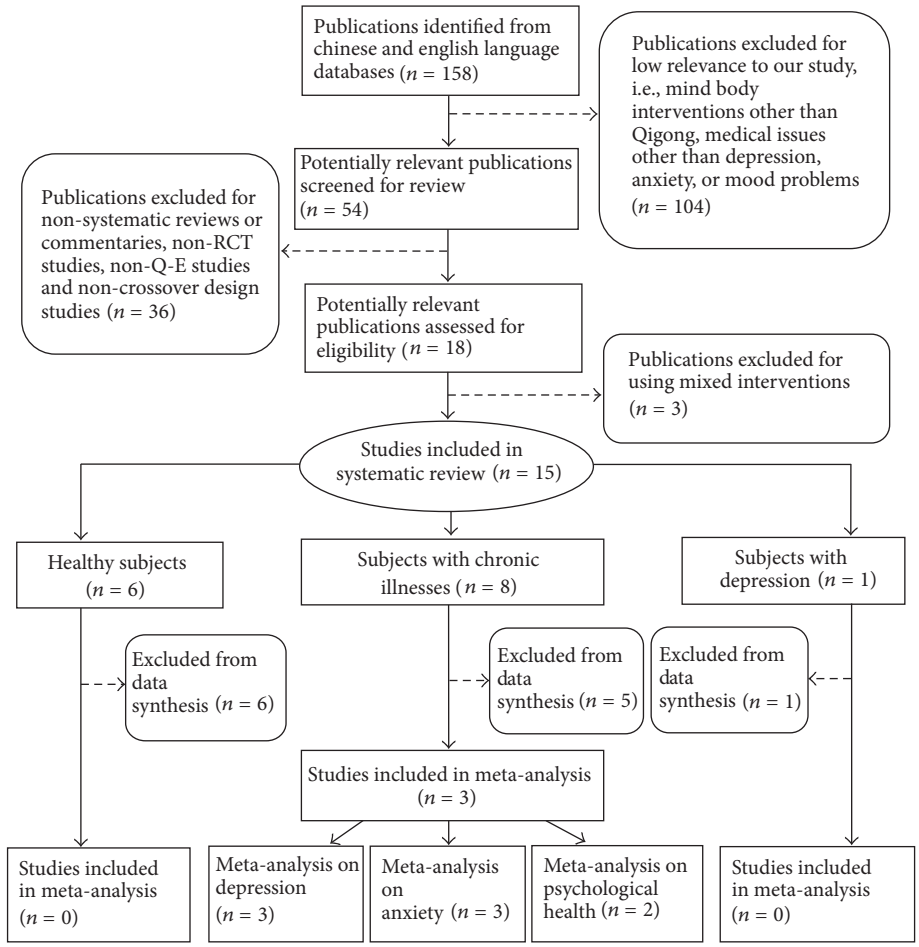


Figure 1: Flow chart of the study selection process.

Table 1: Summary of Qigong studies reviewed.

	No. of studies	Study ID no.
Date of publication		
2001–2005	4	16, 32, 35, 41
2006–2011	13	28, 29, 30, 31, 33, 34, 36, 37, 38, 39, 40
Study sites		
US	1	33
China and Hong Kong	11	28, 29, 30, 31, 32, 36, 37, 40, 41
Others (Sweden, Australia, Korea)	5	16, 34, 35, 38, 39
Language of study		
Chinese	6	28, 29, 30, 31, 36, 37
English	11	16, 32, 33, 34, 35, 38, 39, 40, 41
Clinical domains		
Chronic physical illnesses	1	41
Cancer	1	38
Depression	1	40
Type II diabetes	4	28, 30, 31, 36
Hypertension	2	16, 32
No medical condition	8	29, 33, 34, 35, 37, 39

Table 2: Methodological quality of Qigong studies reviewed.

Lead author	Adequate sequence generation	Allocation concealment	Blinding	Completeness of outcome data	Selective reporting	Other potential biases
Cheung [34]	Y	Unclear	Y	Y	Unclear	Y
Griffith [35]	Y	Unclear	Unclear	Y	Unclear	Unclear
Huo [28]	Y	Unclear	Unclear	Y	Unclear	Unclear
Jin [29]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Johansson [36]	Unclear	Unclear	Unclear	Y	Unclear	Unclear
Lee [16]	N	Unclear	Unclear	Y	Unclear	Unclear
Lee [37]	Y	Unclear	Y	Y	Unclear	Unclear
Lin [32]	Y	Y	Unclear	N	N	Unclear
Liu [33]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Oh [38]	Y	Unclear	Unclear	Y	Unclear	Unclear
Skoglund [39]	Unclear	Unclear	Unclear	N	Unclear	Unclear
Tsang [40]	Unclear	Unclear	Y	Y	Unclear	Y
Tsang [41]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Wang [30]	Unclear	Unclear	Unclear	Unclear	N	Unclear
Zhang [31]	Y	Y	Unclear	N	Y	Unclear

results were not combined by means of meta-analysis. Clinical heterogeneity usually came from patients' characteristics (age, gender, etc.). Methodological heterogeneity refers to differences between studies in terms of methodological factors, such as sequence generation and concealment of allocation [24]. If the studies did not have these heterogeneities, we performed a meta-analysis and determined whether they showed statistical heterogeneity by visually inspecting the forest plots and by using a standard χ^2-test with a significance level of $\alpha = 0.1$, given the low power of such tests. Statistical heterogeneity was specifically examined with I^2 [25], where I^2 values of 50% or more indicate a substantial level of heterogeneity [27]. When heterogeneity was found, we attempted to determine potential reasons for it by examining individual study characteristics.

2.2.2. Assessment of Reporting Biases. Because all 15 studies we reviewed had small samples, funnel plots were used in an exploratory analysis to assess the potential existence of small study bias if 9 or more studies were included in one meta-analysis. If less than 9 studies were included in the meta-analysis, we considered that a potential risk of selective reporting existed [24].

2.2.3. Data Statistical Analysis and Quality Assessments of Outcome Measures. Since all outcomes were continuous variables, if the same measurement was used across studies, effect size (ES) was determined by calculating the mean difference between groups. If the same underlying concept was measured but different outcome measurements were used, ES was determined by calculating the standardized mean difference between groups.

Because of the different trials implemented various styles of Qigong, if any trials with three or more treatment arms were identified, we made two assumptions for the analysis. Firstly, if the trial was comparing two or more styles of Qigong versus control, then the data for those Qigong arms were combined to give one comparison of Qigong intervention versus control for that trial.

Secondly, if the trial was comparing Qigong versus two or more controls, then the data for those control arms were kept separate, and the data for that trial were included in the appropriate control categories.

Overall outcome was assessed by pooling the ES of each study. In view of the heterogeneity, random-effects model was used for pooling. All analyses were conducted using Review Manager 5 (Version 5.0; The Chinese Cochrane Centre, The Cochrane Collaboration; Chengdu, China). We assessed the quality of the outcome of measures using GRADE profiler version 3.

3. Results

3.1. Study Description. Fifteen studies published between 2001 and 2011 were included in this systematic review. Of these, 6 were published in Chinese and identified from Chinese databases [28–33] and 9 were published in English and identified from English databases [15, 34–41]. Disagreement for articles included was on 5 of 20. They were excluded after discussion.

Only one of these studies was conducted in the United States; the majority ($n = 9$) of the remaining studies were conducted in China, including Hong Kong. In six studies, effects of Qigong interventions were examined in healthy adults without any specific medical conditions. The majority of the studies, however, targeted individuals with a variety of chronic conditions, including diabetes ($n = 4$), depression ($n = 1$), cancer ($n = 1$), and hypertension ($n = 2$) (Table 1).

Table 3: Summary of Qigong studies reviewed 2.

Group	Lead author	Sample size	Age (y)	Intervention (Qigong) and controls	Duration	Psychological well-being related measures	Psychological well-being related outcomes
Healthy subjects	Griffith [35]	$N1 = 50$ 11 males, 39 females $N2 = 25$	Mean age 51	G1 Qigong practice G2 Wait-list (control)	6 weeks	Perceived Stress Scale, SF-36	Qigong improved perceived stress and social interaction subscale of the SF-36 versus control.
	Jin [29]	$N1 = 105$ $N2 = 35$	60–69	G1 Health qigong G2 Tai Chi (control) G3 Fitness Yangko (control)	12 weeks	SDS, SAS, SRHMS	SAS reduced significantly in G1, G1, G3. SDS reduced significantly in G1, G3.
	Johansson [36]	$N1 = 59$ 8 males, 51 females $N2 = 28$	Mean age 50.8	G1 Qigong (Jichu Gong) G2 Lecture (control)	4 days intensive	POMS, STAI	POMS-depression, anger, fatigue, STAI-state anxiety scores reduced significantly in G1.
	Lee [37]	$N1 = 20$ Male only $N2 = 10$	Mean age 26	G1 Qigong (Korean Qi-therapy) G2 Placebo (control)	70 minutes	The Spielberger Anxiety Inventory-State, MT	Qigong improved anxiety versus control.
	Liu [33]	$N1 = 100$ $N2 = 50$	College students	G1 eight-section Brocade qigong G2 unclear (control)	12 weeks	SCL-90	Qigong improved SOM, O-C, I-S and PAR versus control. SOM, O-C, DEP, ANX, HOS, other symptoms and mean score reduced significantly in G1.
	Skoglund [39]	$N1 = 42$ 9 males, 33 females $N2 = 21$	42–54 Mean age 48	G1 Qigong (Shuxingpingxegong) G2 Wait-list (control)	6 weeks	Questionnaire about health state, health grading and grading of stress, a visual analogue scale (similar to a thermometer), SF12 (a short version of SF-36)	The health related quality of life was improved significantly after Qigong.
Subjects with chronic illnesses	Cheung [34]	$N1 = 91$ 37 males, 51 females (88 subjects completed) $N2 = 47$	Mean age 54 (88 subjects completed)	G1 Goulin qigong G2 Conventional exercise (control)	16 weeks	SF-36, BAI, BDI	No significant difference found between the two groups.
	Huo [28]	$N1 = 80$ 28 males, 41 females (69 subjects completed) $N2 = 40$	Mean age 64.2 (69 subjects completed)	G1 Eight-Section Brocade qigong G2 Health education (control)	12 weeks	SDS, DMQLS	Qigong improved SDS, total score, physiological dimension, satisfactory dimension of quality of life versus control. SDS, total score, physiological dimension, satisfactory dimension of QOL reduced significantly in G1. Satisfactory dimension of QOL reduced significantly in G2.
	Lee [16]	$N1 = 46$ $N2 = 22$	40–65 Mean age 53 (36 subjects completed)	G1 Qigong exercise G2 Wait-list (control)	8 weeks	The general self-efficacy scale, Exercise self-efficacy, the scale to measure the effect of emotion on exercise	Self-efficacy and other cognitive perceptual efficacy variables improved significantly in G1.

Table 3: Continued.

Group	Lead author	Sample size	Age (y)	Intervention (Qigong) and controls	Duration	Psychological well-being related measures	Psychological well-being related outcomes
Subjects with chronic illnesses	Lin [32]	$N1 = 108$ 28 males, 80 females $N2 = 81$	37–70 Mean age 58 (94 subjects completed)	G1 eight-section Brocade qigong G2 eight-section Brocade and static qigong G3 Static qigong G4 Treatment as usual (control)	4 months	MMPI, SCL-90, DSQL	MMPI: SI, difference of Pd in G3, difference of Pd, Pt and Sc in G2 were improved versus control. Pd, Pt and Sc reduced significantly in G2. Hy, Pd and Pa reduced significantly in G3; Pd, Sc increased significantly in G4. SCL-90: SOM in G1 were improved versus control. SOM, O-C, DEP and GSI reduced significantly in G1. O-C, HOS and GSI reduced significantly in G2. DSQL: total score, physical score, psychological score, social score and treatment score in G2, total score, social score and treatment score in G3, treatment score in G1 were improved versus control. Difference of total score, physical score and social score in G1, G2, G3, difference of psychological score and treatment score in G2 were improved versus control. Total score, physical score and psychological score reduced significantly in G2, G3. Social score and treatment score reduced significantly in G2. Total score, physical score and social score increased significantly in G4.
	Oh [38]	$N1 = 162$ 69 males, 93 females $N2 = 81$	31–86 Mean age 60	G1 modified qigong G2 group therapy (control)	10 weeks	Functional Assessment of Cancer Therapy—General (FACT-G), the Functional Assessment of Cancer Therapy—Fatigue (FACT-F), POM.	Qigong improved QOL, fatigue and mood disturbance versus control.
	Tsang [41]	$N1 = 50$ 26 males, 24 females $N2 = 25$	≥65 Mean age 75	G1 eight-section Brocades qigong G2 traditional remedial rehabilitation (control)	12 weeks	GDS, Perceived Benefit Questionnaire, WHOQOL-BREF[HK], ASSEI	Physical health, activity level, psychological health, social relationship, and health in general improved significantly in G1.
	Wang [30]	$N1 = 54$ 23 males, 31 females $N2 = 27$	41–70 Mean age 58.8	G1 eight-section Brocade qigong G2 treatment as usual (control)	4 months	SCL-90	Qigong improved O-C, DEP, ANX and HOS versus control 2 months later. HOS reduced significantly in G1 4 months later.
	Zhang [31]	$N1 = 90$ 29 males, 61 females $N2 = 60$	37–69 Mean age 57.8 (78 subjects completed)	G1 eight-section Brocade and relaxation qigong G2 Liuzijue and relaxation qigong G3 Treatment as usual (control)	4 months	SCL-90, DSQL	SCL-90: SOM and PSY in G2 were improved versus control. Difference of SOM and PSY in G1, G2 were improved versus control. GSI, mean score and SOM reduced significantly in G1, G2. PST and DEP reduced significantly in G1. I-S, HOS and PSY reduced significantly in G2. QOL: physical score in G1, G2 were improved versus control. Psychological and social score reduced significantly in G2. Social score reduced significantly in G3.

Table 3: Continued.

Group	Lead author	Sample size	Age (y)	Intervention (Qigong) and controls	Duration	Psychological well-being related measures	Psychological well-being related outcomes
Subjects with depression	Tsang [40]	$N1 = 97$ $N2 = 41$ 16 males, 66 females (82 subjects completed)	≥65 Mean age 82 (82 subjects completed)	G1 Qigong practice G2 Newspaper reading (control)	16 weeks	GDS, CGSS, PWI, GHQ-12, ASSEI, Perceived Benefit Questionnaire	Qigong improved mood, self-efficacy, personal well-being, physical and social domains of self-concept versus control 8 weeks later. 16 weeks later, the improvement generalized to the daily task domain of the self-concept.

Total Sample Size ($N1$); number of participants recruited in Qigong group ($N2$); Group 1 (G1); Group 2 (G2); Group 3 (G3); Group 4 (G4); Health Status Survey Short Form (SF-36); Self-rating depression scale (SDS); Self-rating anxiety scale (SAS); Self-rated Health Measurement Scale (SRHMS); Profile of Mood States (POMS); the State and Trait Anxiety Inventory (STAI); Tuchman's mood thermometer (MT); Symptom Checklist 90 (SCL-90); Somatization (SOM); Obsessive-compulsive (O-C); Interpersonal sensitivity (I-S); Paranoid Ideation (PAR); Depression (DEP); Anxiety (ANX); Hostility (HOS); Beck Anxiety Inventory (BAI); Beck Depression Inventory (BDI); Diabetes Specific Quality of Life Scale (DMQLS); Minnesota MultiPhasic Personality Inventory (MMPI); Diabetes Specific Quality of Life Scale (DSQL); Social introversion (SI); Psychopathic deviate (Pd); Psychasthenia (Pt); Schizophrenia (Sc); Hysteria (Hy); Paranoia (Pa); Global Severity Index (GSI); The Geriatric Depression Scale (GDS); the Hong Kong Chinese Version World Health Organization Quality of Life: Abbreviated Version (WHOQOL-BREF[HK]); Self-concept Scale (ASSEI); Psychoticism (PSY); Positive Symptom Total (PST); the Chinese General Self-efficacy Scale (CGSS); Personal Well-being Index (PWI); General Health Questionnaire-12 (GHQ-12).

Table 2 presents the methodological quality of the 15 studies reviewed. All studies, with the exception of one Q-E study [15], were RCTs. Ten studies used a two-arm design with one intervention and one control group, and the remaining four adopted a three-arm design which used either a different type of Qigong [33] or a psychoeducational group [28, 36, 41] as the second comparison group. The interrater agreement as measured by kappa (κ) was 0.901 ($P < 0.0005$).

Seven studies described the randomization process. One study reported that the randomization was performed by a statistician who had prepared a randomization list before the study started [34]. Four studies reported that the randomization was performed through the use of computer-generated numbers [31, 32, 35, 38]. Two studies used a random-number table [28, 37]. The other seven studies did not clearly report the process of randomization [29, 30, 33, 36, 39–41]. One study allocated the participants according to their place of residence [15], which cannot be considered a sufficient randomization. Two studies specified allocation concealment by using the allocation sequences sealed in opaque envelopes [31, 32].

Blinding was described in only three studies. One study adopted a single blind run-in period [34]. Another study reported that the treatment order was randomly determined and subjects did not know their treatment [37]. The other study adopted a double-blind method as to group assignment of treatment procedure [40]. Blinding the participants to the allocation was not adopted in one study while the other blindness such as study analysis was not described clearly [38]. The majority of studies addressed incomplete outcome data. Three studies used intention-to-treat analyses [31, 34, 38]. Eight studies reported the number of drop-outs and related reasons [15, 28, 34–38, 40]. Three studies reported the number of drop-outs, but did not explain the reasons for drop-outs [31, 32, 39]. Two studies described the periods of follow-up [15, 40]. Through careful reading of the study and contacting the study authors for additional information, we tried to examine whether there was selective reporting of outcomes. Two studies reported all outcome measurements [30, 32]. One study did not address all of the outcomes [31]. For the majority of the studies, the existence of selective reporting could not be determined due to inadequate information.

Five studies described the methods to evaluate the adherence of patients to intervention [30, 34, 35, 38, 39]. Comprehensive comparisons of demographic and baseline information were presented in eight studies [28, 31, 32, 34, 35, 38, 40, 41], two of which reported that some demographic characteristics were unbalanced among comparison groups at baseline [34, 40]. The statistical methods in all of the included studies were considered appropriate for the analyses performed.

Table 3 summarized the 15 studies with regard to effects of Qigong on psychological well-being outcomes. The study sample sizes ranged from 20 to 162, with a total of 1154 research participants. Among them, 593 subjects received Qigong intervention. All studies recruited participants aged 18 years and up with the majority in their middle adulthood. Two studies targeted participants aged 65 and older [40, 41], and one study recruited young adults in college settings [33]. Most studies include mixed gender groups, though one study included males only [37].

The durations of the interventions ranged from 70 minutes to 4 months. Interventions of 3-4 months' duration appeared to be the norm for demonstrating changes while maximizing study enrollment and adherence. Among the Qigong intervention studies, the most popular form was the "Eight Section Brocade Exercise." During and outside of group practice sessions, peer learning and discussions to facilitate social interaction and mutual support were encouraged since these may be important therapeutic ingredients. In most of the studies, control groups received treatment as usual and routine medical check-up. Three studies utilized a waitlist as the control group [15, 35, 39].

While all included studies reported on psychological outcomes, only the study by Tsang et al. targeted participants with a psychiatric disorder [40]. The remaining studied either healthy subjects or subjects with chronic medical conditions, and examined psychological factors as secondary goals of the study.

The most frequently reported psychological benefits were decreased depressive symptoms and improved mood, reported in seven studies [28–31, 36–38], as evidenced by scores on depression scales (e.g., Hamilton Depression Severity Index-17, Self-Rating Depression Scale, Center for Epidemiological Studies Depression Scale, etc.). Depression was shown to improve significantly in studies comparing Qigong to an inactive control, newspaper reading [40], usual care, psychosocial support, or stretching/education controls [30]. General measures of mood (e.g., Profile of Mood States) improved significantly for those practicing Qigong compared to a wait-list control group [15]. In two studies, depressive symptoms improved, but the change was not statistically significant, for both Qigong and for exercise comparison groups [34, 41].

Participants in the intervention groups also demonstrated reduced anxiety [29–31, 37, 41], as assessed by scales such as the Self-Rating Anxiety Scale. Anxiety decreased significantly for participants practicing Qigong compared to an active exercise group [15, 34].

Three studies reported statistically significant improvements in somatic symptoms among the intervention group as evidenced by scales such as the Symptom Checklist-90 and Somatization Scale [28]. In these studies, participants also reported lower perceived stress and intensity of pain compared with the control group.

Some studies employed measures of physical health and biomarkers, including blood pressure [15], cholesterol levels [30, 31], fasting blood sugar [29, 30, 32], and triglycerides [29, 30]. In one study examining biomarkers related to stress response, norepinephrine, epinephrine, and blood cortisol levels were significantly decreased in response to Qigong compared to a wait-list control group [15].

Improvement of overall quality of life (QOL) was the second most frequently mentioned benefit reported in six studies [28, 29, 31, 34, 40, 41]. In studies with heterogeneous participants (including healthy adults, patients with cancer,

post-stroke, arthritis, etc.), at least one of the components of QOL was reported to be significantly improved by Qigong compared to newspaper reading [40] or traditional remedial rehabilitation [41]. In one study, Qigong showed improvements in QOL compared to an exercise intervention, but the results did not reach statistical significance [34]. With a few exceptions, the majority of studies indicate that Qigong holds great potential for improving QOL in both healthy and chronically ill patients.

Self-efficacy was generally assessed in the RCTs as a secondary outcome related to the problem area under investigation (e.g., efficacy to manage a disease or pain symptom, or in the case of falls among the elderly, feeling more confident that one will not fall). The perceived ability to handle stress or novel experiences [15, 40] and exercise self-efficacy [15] were found to be enhanced in the Qigong intervention groups relative to control groups.

3.2. Meta Analyses for Three Subgroups. We categorized the studies into three groups based on the type of subjects for further analysis as follows: (1) healthy subjects, (2) subjects with chronic illnesses, and (3) subjects with depression. Only one RCT recruited subjects with depression [40] and therefore no meta-analysis was needed for this group. Six RCTs were included in the group of studies with healthy subjects [29, 33, 35–37, 39]. Meta-analysis was not performed in this group. One study recruited only male participants, which made it hard to compare to other studies [37]. Another study used a crossover design with each participant serving as his or her own control without a separate comparison group [39]. The remaining four studies used different groups as controls, including a lecture [36], Tai Chi and fitness Yangko [29], a waitlist [35], and an unclearly described control [33].

Eight RCTs were included in the group of studies of patients with chronic illnesses [5, 28, 30–32, 34, 38, 41]. Five studies were excluded from the meta-analysis. One study was quasi-experimental [15], and another study had a high dropout rate (32% in the intervention group and 35% in the control) [38]. The other three studies were excluded since they used a different control group than the three RCTs included in meta-analysis, which used treatment as usual and no Qigong intervention as control. Three of the excluded studies used the following control conditions—conventional exercise [34], traditional remedial rehabilitation under the supervision of qualified professionals [41], and health education [28].

After assessment of heterogeneity and consideration of the choices of varying control groups used in different studies, meta-analysis of outcomes related to depression measured by Symptom Checklist 90 (SCL-90) were performed on the remaining three RCTs of patients with type II diabetes [30–32]. Baseline characteristics were reasonably well balanced between the Qigong group and the control group for the three trials. At endpoint, there were a significant differences between the two groups on obsessive-compulsive, depression, anxiety and anger-hostility in Wang's study, on somatization in Lin's study, and on phobic anxiety in Zhang's study ($P < 0.05$). Results of the individual trials for SCL-90 are presented in Table 4.

We found significant differences between groups (ES = −0.29, 95% CI, −0.58–0.00), with $I^2 = 0\%$ (Figure 2(e)). Meta-analysis of outcomes related to anxiety were also performed in the same three studies [30–32]. We found significant differences between groups (ES = −0.37; 95% CI, −0.66 −0.08), with $I^2 = 0\%$ (Figure 2(f)).

Besides depression and anxiety, meta-analysis of other symptoms of SCL-90 were also performed in the same three studies. We found significant differences between groups in total SCL-90 score (ES = −0.49; 95% CI, −0.78 to −0.20), somatization (ES =−0.52; 95% CI, −0.81 to −0.23), obsessive-compulsive (ES = −0.35; 95% CI, −0.64 to −0.06), interpersonal sensitivity (ES = −0.39; 95% CI, −0.68 to −0.10), anger-hostility (ES = −0.48; 95% CI, −0.80 to −0.17), phobic anxiety (ES = −0.30; 95% CI, −0.58 to −0.01), psychotism (ES = −0.53; 95% CI, −0.83 to −0.24) and paranoid ideation (ES = −0.33; 95% CI, −0.62 to −0.05). All the above outcomes were with $I^2 = 0\%$ (Figures 2(a)–2(d), 2(g)–2(j)).

Two RCTs were included in the meta-analysis of psychological health measured by Diabetes Specific Quality of Life Scale (DSQL) [29, 36]. Baseline characteristics were reasonably well balanced between the Qigong group and the control group for the two trials. At endpoint, there was a significant difference between the two groups on psychological health ($P < 0.05$). Results of the individual trials for DSQL are presented in Table 4.

We also found significant differences between groups (ES = −0.58, 95% CI, −0.91 −0.25), with $I^2 = 0\%$ (Figure 2(k)). Data synthesis showed that Qigong was effective in reducing depression and anxiety and improving psychological well-being among subjects with type II diabetes. Yet the quality of the outcomes measures used in these studies was low (Table 5).

4. Discussion

The studies in this paper demonstrated that Qigong may have beneficial effects for a variety of populations on a range of psychological well-being measures, including mood, anxiety, depression, general stress management, quality of life, and exercise self-efficacy. The movements of Qigong is relatively easy to learn, when compared to other mind body traditions [2, 4]. Hence, people from diverse backgrounds practice Qigong for a variety of reasons, including exercise, recreation, well-being, self-healing, meditation, self-cultivation, and training for martial arts. We see a great potential for Qigong to be integrated for the prevention and treatment of various chronic illnesses, including psychiatric disorders.

This systematic review highlights the mood and psychological effects of Qigong in addition to its physical effects. The outcomes of the three selected studies showed improvements in psychological well-being, especially when the control intervention does not include active interventions such as exercise. These studies used SCL-90 to measure the pre- and post-outcomes related to Qigong intervention. While SCL-90 is a widely used and well validated measure for

Table 4: Results of trials included in meta-analysis on symptoms of SCL-90 and psychological health of DSQL in subjects with chronic illnesses.

	Wang et al. 2008 [30]				Lin 2007 [32]				Zhang 2008 [31]			
	Baseline		Endpoint		Baseline		Endpoint		Baseline		Endpoint	
	G1 (n = 25)	G2 (n = 20)	G1 (n = 25)	G2 (n = 20)	G1 (n = 71)	G2 (n = 23)	G1 (n = 71)	G2 (n = 23)	G1 (n = 49)	G2 (n = 29)	G1 (n = 49)	G2 (n = 29)
SCL-90												
Total score	131.0 (32.2)	142.3 (50.1)	121.4 (38.3)	143.4 (34.7)	139.2 (43.4)	145.1 (45.7)	126.8 (33.4)	145.1 (45.7)	50.7 (7.7)	48.6 (7.2)	51.1 (8.0)	55.0 (10.5)
Somatization	0.7 (0.5)	0.7 (0.8)	0.6 (0.6)	0.7 (0.5)	1.7 (0.7)	2.0 (0.7)	1.6 (0.5)*	2.0 (0.7)	41.3 (12.4)	40.8 (14.4)	33.6 (9.5)	39.9 (15.1)
Obsessive-compulsive	0.7 (0.4)	0.7 (0.7)	0.5 (0.5)*	0.8 (0.5)	1.9 (0.6)	1.8 (0.5)	1.7 (0.5)	1.8 (0.5)	38.9 (11.5)	36.5 (11.6)	35.9 (8.7)	38.5 (10.4)
Interpersonal sensitivity	0.4 (0.4)	0.4 (0.6)	0.3 (0.6)	0.5 (0.5)	1.5 (0.6)	1.6 (0.5)	1.4 (0.5)	1.6 (0.5)	31.7 (14.5)	29.8 (10.3)	27.6 (8.6)	30.6 (10.2)
Depression	0.5 (0.4)	0.4 (0.6)	0.4 (0.5)*	0.7 (0.5)	1.7 (0.6)	1.6 (0.6)	1.5 (0.5)	1.6 (0.6)	38.6 (12.0)	34.7 (8.2)	34.7 (7.4)	36.2 (8.7)
Anxiety	0.3 (0.4)	0.3 (0.7)	0.3 (0.4)*	0.5 (0.4)	1.4 (0.6)	1.5 (0.5)	1.4 (0.5)	1.5 (0.5)	33.0 (16.1)	29.7 (13.6)	26.2 (8.4)	30.1 (13.2)
Anger-hostility	0.6 (0.5)	0.7 (0.7)	0.3 (0.5)*	0.7 (0.6)	1.5 (0.5)	1.6 (0.7)	1.4 (0.4)	1.6 (0.7)	35.6 (10.2)	36.9 (14.7)	31.7 (7.5)	35.5 (9.9)
Phobic anxiety	0.2 (0.2)	0.5 (0.7)	0.2 (0.3)	0.4 (0.4)	1.3 (0.6)	1.4 (0.5)	1.2 (0.5)	1.4 (0.5)	29.3 (14.7)	26.8 (9.1)	25.4 (8.9)*	26.3 (7.9)
Psychotism	0.3 (0.4)	0.5 (0.6)	0.2 (0.4)	0.4 (0.5)	1.3 (0.5)	1.4 (0.3)	1.2 (0.4)	1.4 (0.3)	31.2 (13.8)	28.1 (8.7)	25.4 (9.0)	30.8 (9.9)
Paranoid ideation	0.3 (0.4)	0.4 (0.5)	0.2 (0.4)	0.4 (0.6)	1.3 (0.5)	1.4 (0.4)	1.3 (0.4)	1.4 (0.4)	31.8 (9.6)	29.1 (9.1)	30.7 (7.3)	33.0 (9.1)
DSQL												
Psychological health					35.0 (19.0)	35.2 (17.2)	30.6 (15.9)*	41.6 (19.3)	32.7 (19.0)	36.4 (19.3)	26.7 (17.0)*	36.5 (21.8)

Note: Qigong group (G1); control group (G2). Outcomes were reported by mean (SD). *The difference between the scores of the two groups was significant ($P < 0.05$).

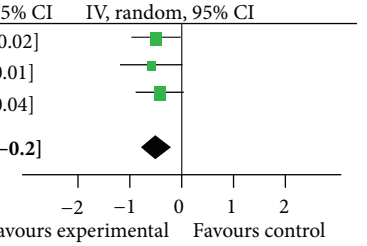
Table 5: Quality assessment of outcome measures in subjects with chronic illnesses.

Quality assessment							Summary of findings					
							No. of patients		Effect		Quality	Importance
No. of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Qigong	Control	Relative (95% CI)	Absolute		
Total score (measured with: total score of Symptom Checklist 90 at end of treatment; range of scores: 0–450; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.78 to −0.2)	⨁⨁◯◯ Low	Important[3]
Somatization (measured with: somatization score of Symptom Checklist 90 at end of treatment; range of scores: 0–48; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.81 to −0.23)	⨁⨁◯◯ Low	Important[3]
Obsessive-compulsive (measured with: obsessive-complusive score of Symptom Checklist 90 at end of treatment; range of scores: 0–40; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.64 to −0.06)	⨁⨁◯◯ Low	Important[3]
Interpersonal sensitivity (measured with: interpersonal sensitivity score of Symptom Checklist 90 at end of treatment; range of scores: 0–36; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.68 to −0.1)	⨁⨁◯◯ Low	Important[3]
Depression (measured with: depression score of Symptom Checklist 90 at end of treatment; range of scores: 0–52; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.58 to 0)	⨁⨁◯◯ Low	Important[3]
Anxiety (measured with: anxiety score of Symptom Checklist 90 at end of treatment; range of scores: 0–40; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.66 to −0.08)	⨁⨁◯◯ Low	Important[3]
Anger-hostility (measured with: anger-hostility score of Symptom Checklist 90 at end of treatment; range of scores: 0–24; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.8 to −0.17)	⨁⨁◯◯ Low	Important[3]
Phobic anxiety (measured with: phobic anxiety score of Symptom Checklist 90 at end of treatment; range of scores: 0–28; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.58 to −0.01)	⨁⨁◯◯ Low	Important[3]
Psychotism (measured with: psychotism score of Symptom Checklist 90 at end of treatment; range of scores: 0–40; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.83 to −0.24)	⨁⨁◯◯ Low	Important[3]
Paranoid ideation (measured with: paranoid ideation score of Symptom Checklist 90 at end of treatment; range of scores: 0–24; better indicated by less)												
3	Randomised trial	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[2]	145	72	—	MD 0 (−0.62 to −0.05)	⨁⨁◯◯ Low	Important[3]
Psychological health (measured with: psychological score of Diabetes Specific Quality of Life Scale at end of treatment; range of scores: 0–40; better indicated by less)												
3	Randomised trial	Serious[4]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias[5]	120	52	—	MD 0 (−0.91 to −0.25)	⨁⨁◯◯ Low	Important[3]

[1]Wang et al. 2008 [30]: lack of allocation concealment and blinding, and failure to adhere to intention to treat principle when indicated; Lin 2007 [32]: lack of blinding; Zhang 2008 [31]: lack of blinding and reporting of some outcomes and not others on the basis of the results, [2]Only three small studies were included, [3]Further research is very much needed, [4]Lin 2007 [32]: lack of blinding; Zhang 2008 [31]: lack of blinding and reporting of some outcomes and not others on the basis of the results, [5]Only two small studies were included.

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Lin 2007	126.83	33.37	71	145.1	45.7	23	37.4%	−0.49 [−0.97, −0.02]
Wang 2008	121.4	38.34	25	143.4	34.71	20	23.4%	−0.59 [−1.19, 0.01]
Zhang 2008	51.14	8.01	49	55	10.53	29	39.2%	−0.42 [−0.89, 0.04]
Total (95% CI)			**145**			**72**	**100%**	**−0.49 [−0.78, −0.2]**

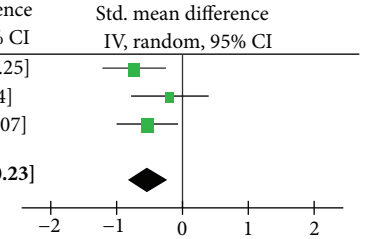
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.18$, df = 2 ($P = 0.91$); $I^2 = 0\%$
Test for overall effect: $Z = 3.29$ ($P = 0.001$)



(a)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Lin 2007	1.58	0.52	71	2	0.7	23	36.6%	−0.73 [−1.22, −0.25]
Wang 2008	0.6	0.56	25	0.7	0.45	20	24.5%	−0.19 [−0.78, 0.4]
Zhang 2008	33.55	9.46	49	39.93	15.06	29	39%	−0.53 [−1.00, −0.07]
Total (95% CI)			**145**			**72**	**100%**	**−0.52 [−0.81, −0.23]**

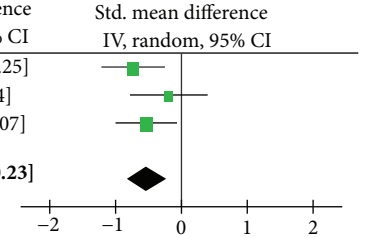
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 1.95$, df = 2 ($P = 0.38$); $I^2 = 0\%$
Test for overall effect: $Z = 3.51$ ($P = 0.0004$)



(b)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Lin 2007	1.58	0.52	71	2	0.7	23	36.6%	−0.73 [−1.22, −0.25]
Wang 2008	0.6	0.56	25	0.7	0.45	20	24.5%	−0.19 [−0.78, 0.4]
Zhang 2008	33.55	9.46	49	39.93	15.06	29	39%	−0.53 [−1.00, −0.07]
Total (95% CI)			**145**			**72**	**100%**	**−0.52 [−0.81, −0.23]**

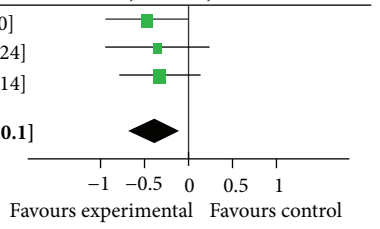
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.87$, df = 2 ($P = 0.65$); $I^2 = 0\%$
Test for overall effect: $Z = 2.35$ ($P = 0.02$)



(c)

Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Lin 2007	1.37	0.48	71	1.6	0.5	23	37%	−0.47 [−0.95, 0]
Wang 2008	0.3	0.62	25	0.5	0.46	20	23.8%	−0.35 [−0.95, 0.24]
Zhang 2008	27.57	8.53	49	30.59	10.23	29	39.2%	−0.33 [−0.79, 0.14]
Total (95% CI)			**145**			**72**	**100%**	**−0.39 [−0.68, −0.1]**

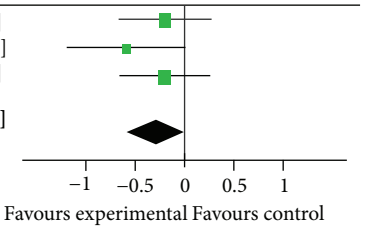
Heterogeneity: $\tau^2 = 0$; $\chi^2 = 0.2$, df = 2 ($P = 0.91$); $I^2 = 0\%$
Test for overall effect: $Z = 2.61$ ($P = 0.009$)



(d)

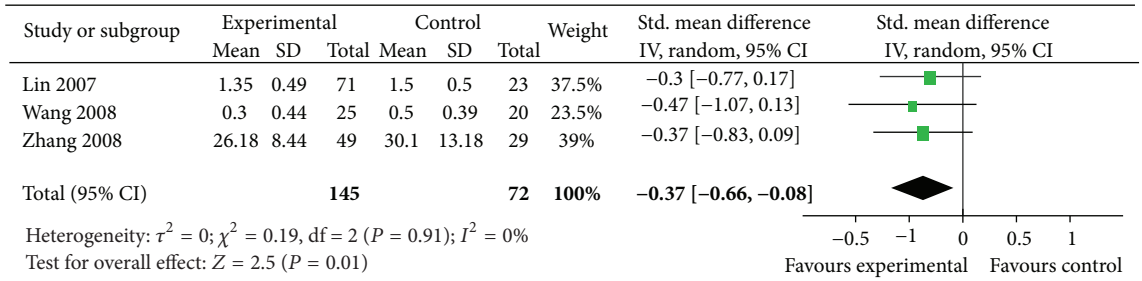
Study or subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. mean difference IV, random, 95% CI
Lin 2007	1.5	0.47	71	1.6	0.6	23	37.6%	−0.2 [−0.67, 0.27]
Wang 2008	0.4	0.47	25	0.7	0.53	20	23%	−0.59 [−1.19, 0.01]
Zhang 2008	34.65	7.35	49	36.24	8.72	29	39.4%	−0.2 [−0.66, 0.26]
Total (95% CI)			**145**			**72**	**100%**	**−0.29 [−0.58, −0]**

Heterogeneity: $\tau^2 = 0$; $\chi^2 = 1.27$, df = 2 ($P = 0.53$); $I^2 = 0\%$
Test for overall effect: $Z = 1.96$ ($P = 0.05$)

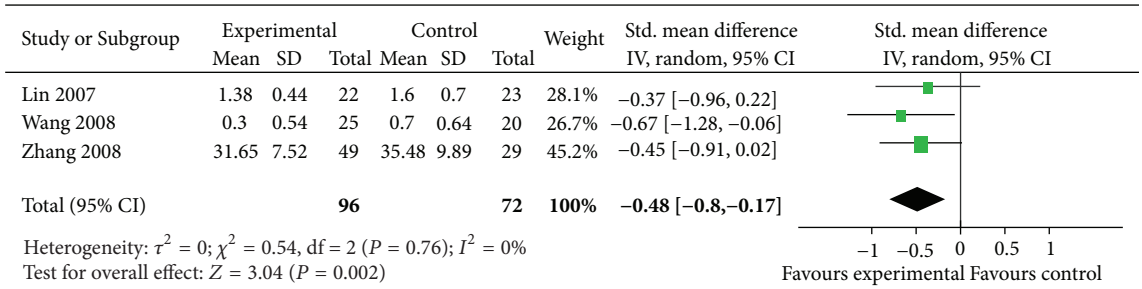


(e)

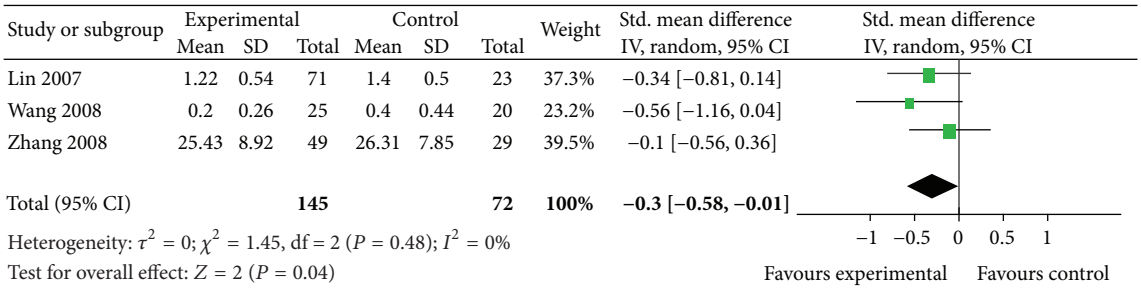
Figure 2: Continued.



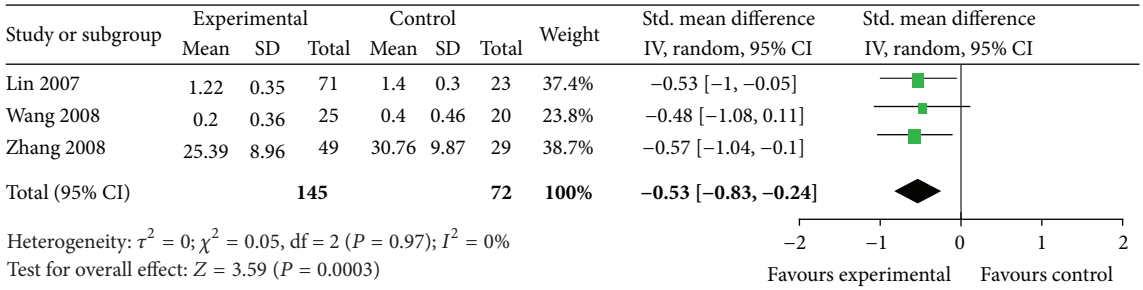
(f)



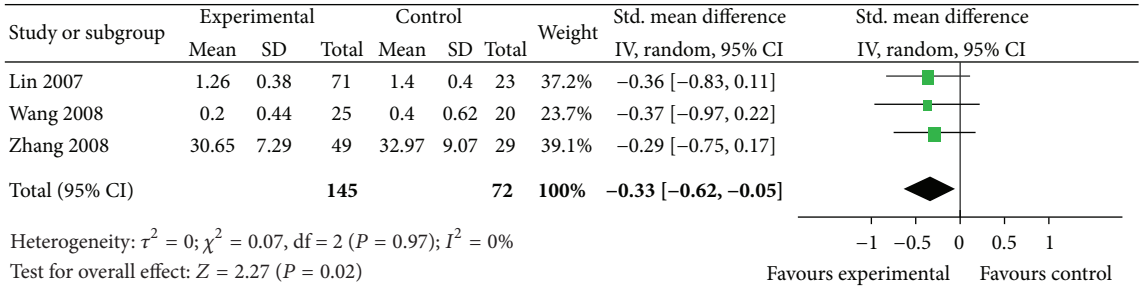
(g)



(h)

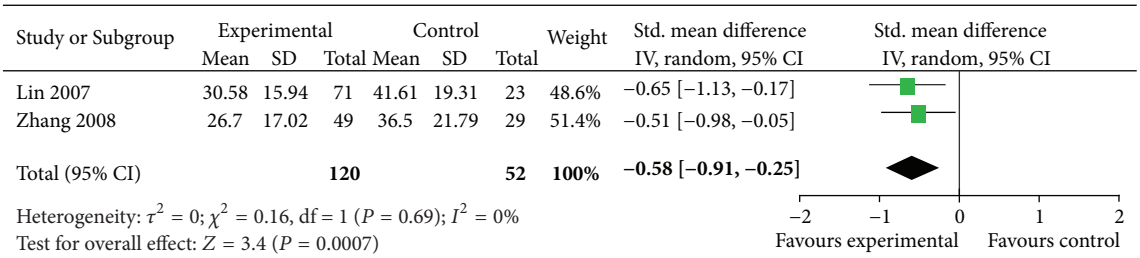


(i)



(j)

Figure 2: Continued.



(k)

Figure 2: Effects of Qigong on symptoms of SCL-90 and psychological health of DSQL in subjects with chronic illnesses.

psychological outcomes, it is important to point out that it does not provide information on clinical diagnoses of anxiety of depressive disorders. Due to the small number of studies available in this area, and the diverse outcomes used, we limited meta-analysis on patients with diabetes. With more relevant studies in the future, it will be informative to review separately, the anxiety and depressive outcomes among healthy subjects, patients with specific chronic illness (e.g., fibromyalgia, tension headache, etc.), and for patients with specific psychiatric disorders (e.g., generalized anxiety disorder, panic disorder, major depressive disorder, etc.).

Qigong practice usually involves doing Qigong (movements with breathing exercises and visualization), plus peer learning, social support, and positive expectation. All these could have beneficial effects to psychological well being and so all these are encouraged in Qigong practice. We have acknowledged that the outcomes of studying such Qigong practices will not provide us with the information on the question whether Qigong (movements with breathing exercise and visualization) alone is beneficial to psychological well being. Positive expectations or social interactions may add to effects related to the Qigong intervention, to form a multi-component mind-body practices instead of a single (Qigong) intervention.

In this paper, we included studies both from the Chinese and in English databases. We consider this approach a strength as many Qigong studies continue to be originated in China and published in Chinese language. While only one researcher performed literature search in Chinese which may lead to some biases, early Qigong research findings published before 2003 (in English), respectively, 2000 (in Chinese) have not been considered. This approach has substantially limited the literature base for the present review and consequently also its findings. The findings of this study should be interpreted in light of the methodological limitations of the studies reviewed. In both of the English and Chinese studies included in the review, most of them used treatment as usual (and one used a waitlist) for the control group. This may lead to bias since positive outcomes from the study could be due to positive expectations or social interactions rather than to the Qigong intervention. A sham treatment which offers social interaction and positive expectations from receiving an intervention could be a better control for these studies. It will also be important in future studies to control for what has been called the frustrebo effect (i.e., negative effects emanating from subject frustration in not receiving the kind of intervention they feel they need) [42].

The majority of these RCTs were pilot studies on patients with chronic illnesses conducted to collect preliminary data on the efficacy of a group intervention to estimate the effect size needed for a larger, more definitive study. While the studies provided valuable data regarding feasibility and clinical efficacy, the use of a small sample could lead to instability of the outcomes, making it harder to generalize to other populations. In addition, many studies used inadequate blinding of the intervention, which could lead to more favorable responses among the Qigong intervention groups. Most of the cited studies did not provide data on whether participants continued to practice Qigong after the intervention period. Subsequently, long-term psychological effects of Qigong are unclear.

Generally, Qigong practices are considered safe, and there have been few published adverse events [2, 4]. While Qigong induced psychosis has been reported The prevalence has been very low [43, 44]. However, there have been no systematic reviews of its risks either. The potential risks of this practice may have been underestimated, reflecting underreporting of adverse events in studies and in practice. In sum, preliminary evidence from the current literature suggests that Qigong may have positive psychological effects for the chronically ill individuals with symptoms of depression and/or anxiety. However, the studies reviewed generally had significant methodological limitations. Future RCTs with rigorous research design based upon the CONSORT statements [45] are needed to establish the efficacy of Qigong in improving psychological well-being and its potential to be used as interventions for populations with various clinical conditions.

Disclosure

The authors declare that they have no competing interests and no financial benefits to the authors. Each author's contribution to this paper is as follows: H. Benson and G. Fricchione obtained funding from the U.S. Centers for Disease Control and Prevention for the study. W. Wang obtained funding from the Ministry of Science and Technology of the People' Republic of China for the study. A. S. Yeung designed the study. F. Wang, J. K. M. Man, and E. Lee conducted the

research. F. Wang conducted the meta-analysis. E. Lee, F. Wang, J. K. M. Man, and A. S. Yeung wrote the first draft of the paper. F. Wang, J. K. M. Man, E. Lee, T. Wu, and A. S. Yeung participated in the revision of subsequent drafts. All authors read and approved the final paper.

Acknowledgments

The research was partly funded by the following two projects: (1) U.S. Centers for Disease Control and Prevention: Grant no. 5R01DP000339. (2) The Ministry of Science and Technology of the People' Republic of China: Grant no. 2008DFA32010. F. Wang and J. K. M. Man are cofirst authors; W. Wang and A. S. Yeung are cosenior authors.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 647896, 10 pages
doi:10.1155/2012/647896

Research Article

The Flexner Report of 1910 and Its Impact on Complementary and Alternative Medicine and Psychiatry in North America in the 20th Century

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Received 17 September 2012; Accepted 28 November 2012

Academic Editor: Melzer Jörg

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America experienced a genuinely vast development of biomedical science in the early decades of the twentieth century, which in turn impacted the community of academic psychiatry and changed the way in which clinical and basic research approaches in psychiatry were conceptualized. This development was largely based on the restructuring of research universities in both of the USA and Canada following the influential report of Johns Hopkins-trained science administrator and politician Abraham Flexner (1866–1959). Flexner's report written in commission for the Carnegie Foundation for the Advancement of Teaching in Washington, DC, also had a major influence on complementary and alternative medicine (CAM) in psychiatry throughout the 20th century. This paper explores the lasting impact of Flexner's research published on modern medicine and particularly on what he interpreted as the various forms of health care and psychiatric treatment that appeared to compete with the paradigm of biomedicine. We will particularly draw attention to the serious effects of the closing of so many CAM-oriented hospitals, colleges, and medical teaching programs following to the publication of the Flexner Report in 1910.

1. Introduction

Between 1900 and 1930, the United States of America and Canada witnessed a major expansion of research activities in the field of biomedicine (most notably impacting academic psychiatry, clinical research in internal medicine, and the integration of laboratory-based pathology), a process which became strongly connected with the great and lasting transformation of modern universities, colleges, and hospitals [1]. This development was at the same time flanked by an influential strategic report, which US science administrator and politician Abraham Flexner (1866–1959) had written in 1909, subsequently published by the Carnegie Foundation for the Advancement of Teaching in 1910 [2]. Flexner himself (Figure 1) was trained in the natural sciences at the preeminent Johns Hopkins University in Baltimore, MD (USA), where he received a German-style, research education which was grounded in intensive laboratory work and the active pursuit of scientific experimentation on both graduate and undergraduate levels. Since its inception by founding dean William Henry Welsh (1850–1934), in 1884, the medical school had focused on bedside teaching, concise, and standardized clinical observations and the early introduction of laboratory experimentation and research work. This science-based form of academic education had a lasting effect on Flexner's views about the status of modern medicine, who incessantly promoted this new scientific paradigm of medical education and research. To him, illegitimate "nonscientific" approaches in the medical marketplace (such as the offerings of folk psychologists, naturopaths, homoeopaths, chiropractors, and osteopaths) were actively competing with the scientific paradigm of research and education represented at major American and Canadian universities at the time [3].

Figure 1: Abraham Flexner (1866–1959).

At the bottom of these events lays a superb growth in the state funding for biomedical research, new psychiatric hospitals, and asylums, along with increasing health care support through company-based plans and state welfare insurance corporations emerging in the "American Progressive Era" since the 1890s [4]. These initiatives also included additional monetary support for biomedical research and medical education, and they were made possible by philanthropic foundations such as the Rockefeller Foundation and the Carnegie Foundation for the Advancement of Teaching in New York City. American medical schools and academic psychiatric departments—most prominently represented in the Clinical Department of Psychiatry headed by the Swiss émigré psychiatrist Adolph Meyer (1866–1950)—benefitted greatly from the renewed and increased financial support from external sources after the end of WWI, when the number of scientific research publications reached an unprecedented level and for the first time compared favorably with former leading countries, such as France, Germany, and Britain [5, 6]. Flexner's report on "Medical Education in the United States and Canada" was written in the middle of the bourgeoning economic and social context following the turn of the century, and it exerted a significant impact on the growth of North American biomedicine, yet it also had a large deleterious effect on the later development of complementary and alternative medicine (CAM) in psychiatry during the 20th Century. Mediated through the commissions of the Carnegie Foundation for the Advancement of Teaching and its Carnegie Foundation Washington, D C Office, Flexner's Report subsequently led to shutting down the majority of CAM-oriented colleges and programs (e.g., medical schools, homoeopathic colleges, and some psychiatric institutions) before and after WWI [7].

Summarizing the context in which Flexner's report appeared, modern scientific medicine—as it had emerged particularly with the French experimental physiologists in the 19th Century—[8] had come to be challenged by a variety of competing contemporary approaches within the medical marketplace (such as naturopathy, traditional homoeopathy, chiropractic, osteopathic medicine, and eclectic forms of therapy) [9]. And while having himself been trained in the scientific paradigm at Johns Hopkins University, Flexner developed a great reservation against the reliability and value of other "nonconformist" approaches in medicine and psychiatry which he pejoratively attacked as "charlatanism" and "quackery," wanting to weed them out from the modern canon of North American medicine [10]. Flexner became adamant in his strive and polemics against all training facilities that offered education and postgraduate work in the above-mentioned fields and advocated for the closing of nearly eighty percent of all the contemporary programs in homeopathy, naturopathy, eclectic therapy, physical therapy, osteopathy, and chiropractic. He had listed these programs in his report under the pejorative titles of the "medical sects" and stated that he openly aimed to "antagonize" them through the publication of his report, since he saw no firm juridical way to discard these nonbiomedical approaches on the American medical and psychiatric market. Only very few institutions (approximately twenty percent of those mentioned in the Flexner Report) were subsequently able to comply with Flexner's constraints and prescriptions, while most had to shut their doors forever, particularly those in the already medically underserved large rural areas of the American Midwest and the Southern States [11].

In this paper, we will begin by outlining some of the basic assumptions of Abraham Flexner's report to the Carnegie Foundation and its continuing effects on the North American clinical and research landscape in CAM and psychiatry. We then explore some of the antagonisms between the "biomedical model" of health research and nonconventional approaches that Flexner had subsumed under the "medical sects" of the time (e.g., homoeopathy, naturopathy, and homoeopathy, etc.), while pointing to the schism in medicine that Flexner had introduced and further aggravated and which the Canadian medical historian Don G. Bates (1940–2001) has so intriguingly explored and analysed as follows:

> *Recently, and for slightly different reasons, this unusual modern, scientific form of medicine [as it had developed during the 19th century] has also given rise to another term: biomedicine. The bio, of course, is meant to point to its strong biological and therefore material and scientific orientation, but the term is frequently used in a critical, even mildly pejorative sense, in order to emphasize the ways in which this caricature fails to make adequate provision for the social and cultural complexities that form part of any medical practice [...]. [12].*

In the final part of our paper, we look at the more specific aftereffects of the Flexner Report on North American medicine and psychiatry, while keeping in mind that nearly fifty percent of CAM-treated patients today are suffering from psychiatric disorders and symptoms [13]—including, for example, anxiety disorders, depression, bipolar, and

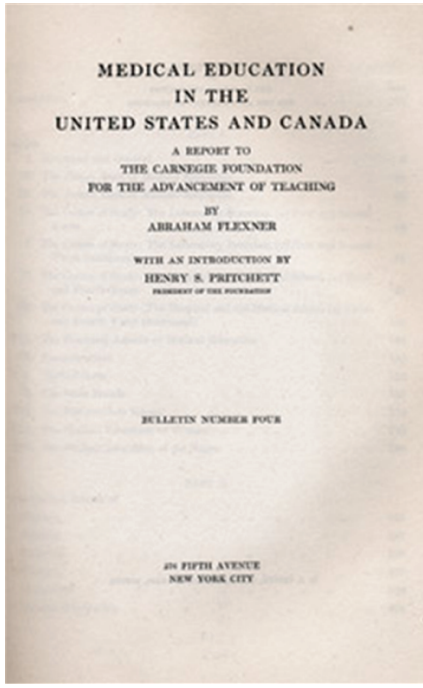
MEDICAL EDUCATION
IN THE
UNITED STATES AND CANADA
A REPORT TO
THE CARNEGIE FOUNDATION
FOR THE ADVANCEMENT OF TEACHING
BY
ABRAHAM FLEXNER
WITH AN INTRODUCTION BY
HENRY S. PRITCHETT
BULLETIN NUMBER FOUR

Figure 2: Front page of the Flexner Report of 1910.

personality disorders—not rarely treated in conjunction with traditional psychiatric approaches from biological psychiatry, psychoanalysis, and behavioural therapies.

2. Methods

Our historiographical research in this paper is based on an analysis of Flexner's *Medical Education in the United States and Canada: A Report to the Carnegie Foundation for the Advancement of Teaching* (1910) (Figure 2) and the available secondary scholarly, medical, and psychiatric literature on the subject. By way of an introduction, textbooks and journal articles on Complementary and Alternative Medicine and Psychiatry are also briefly discussed. Finally, we will scrutinize gray literature and pamphlets published by both the American National Institutes of Health (NIH) and the Canadian Institutes of Health Research (CIHR), as these pertained to the relationship between the biomedical paradigm and CAM-related approaches after the publication of the Flexner Report and, in particular, the inclusion of complementary and alternative therapies and approaches in psychiatry during the second half of the 20th century. This perspective will allow the impact of the Flexner Report to be placed within a contemporary context and its long-lasting effects analyzed.

3. Results

3.1. The Period Ensuing from the Flexner Report from 1910s to 1940s. The decades following the publication of the Flexner Report witnessed considerable pressure on all nontraditional forms of medical and health care training, which would nowadays be associated with CAM, as "a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine" [14]. In his report, Flexner had made the following claims about the new "standardization" of American medical education:

> *Scientific medicine therefore brushes aside all historic dogma. It gets down to details immediately. No man is asked in whose name he comes—whether that of [Samuel] Hahnemann [1755–1843], [Benjamin] Rush [1746–1813], or of some more recent prophet. But all are required to undergo rigorous cross-examination. [...] There is no need, just as there is no logical justification, for the invocation of names or creeds, for the segregation from the larger body of established truth of any particular set of truths or supposed truths as especially precious. [...] The tendency to build a system out of a few partially apprehended facts, deductive inference filling in the rest, has not indeed been limited to medicine, but it has nowhere had more calamitous consequences [...]. (The original text can be found in: Flexner, 1910 [2]).*

Rejecting historical forms of knowledge because of their traditional renown and medical educators' authority—including that of the acclaimed "father of American psychiatry" and, signatory of the Declaration of Independence, Benjamin Rush, who worked at the first academic hospital in Pennsylvania and who wrote a pioneering American textbook on mental disease, entitled *Observations and Inquiries upon the Diseases of the Mind* (1812)—was a major part of Flexner's general criticisms of contemporary medical programs. In particular, he dispensed with the continued use of bloodletting, leeches, and purging, as advocated for by Rush, in American psychiatric wards throughout the 19th and the early years of the 20th century. Flexner especially disapproved that such treatments were experimentally unproven nor statistically assessed. Following to his reasoning, these treatments did not adhere to the "gold standard" of modern medical education in biomedicine, that is, the laboratory-based and bedside-oriented Johns Hopkins model of medical research. He particularly criticized that many of the teaching programs in the traditional medical colleges and psychiatric hospitals had no experimental physiological, experimental physiological laboratories, calling them "filthy" and "unhygienic" institutions [2] . His rhetoric would of course stir massive public criticisms in North America, at the time, when rather more than less medical and psychiatric care facilities and training programs were needed, especially in the underserved states of the American Midwest and South and the Canadian Atlantic and Prairie Provinces [15]:

> *Of complete [M.D. granting] homeopathic schools, Boston University, the New York Homeopathic College, and the Hahnemann of Philadelphia alone possess the equipment necessary for the effective routine teaching of the fundamental*

branches. [...] Of the remaining homeopathic schools, four are weak and uneven: the Hahnemann of San Francisco and the Hahnemann of Chicago have small, but not altogether inadequate, equipment for the teaching of chemistry, elementary pathology and bacteriology; the Cleveland school offers an active course in experimental physiology. Beyond ordinary dissection and elementary chemistry, they offer little else. [...] Six schools remain—all utterly hopeless: [Hering-Chicago, Southwestern, Cincinnati, Atlantic-Baltimore, Detroit & Kansas City]. The buildings are filthy and neglected. At Louisville no branch is properly equipped; in one room, the outfit is limited to a dirty and tattered manikin; in another, a single guinea pig awaits his fate in a cage. (The original text can be found in: Flexner, 1910 [2]).

By also alluding to medical luminary of Sir William Osler [1849–1919] and the latter's preceding criticisms of homoeopathy, Flexner integrated a local aim with a general political one in order to promote modern biomedical and reductionist strategies in medical and psychiatric education. Canadian icon of medicine, the internist and pathologist William Osler belonged to the founding fathers of the Johns Hopkins University Medical School—together with the American pathologist William H. Welch, the gynaecologist Howard Kelly (1858–1943), and the surgeon William Stewart Halsted (1852–1922). Their program for restructuring American medical education was likewise based on the modern natural sciences, which aligned well with Flexner's strategy and Johns Hopkins' strive for preeminence among major American medical schools [16]:

Logically, no other outcome is possible. The ebbing vitality of homeopathic [medical] schools is a striking demonstration of the incompatibility of science and dogma. [...] Science, once embraced, will conquer the whole. Homeopathy has two options: one to withdraw into the isolation in which alone any peculiar tenet can maintain itself; the other to put that tenet into the melting-pot. Historically it undoubtedly played an important part in discrediting empirical allopathy. But laboratories of physiology and pharmacology are now doing that work far more effectively than homeopathy; and they are at the same time performing a constructive task for which homeopathy, as such, is unfitted. It will be clear, then, why, when outlining a system of schools for the training of physicians on scientific lines, no specific provision is made for homeopathy. [...] "A new school of [medical] practitioners has arisen," says Dr. [William] Osler, "which cares nothing for homeopathy [...]. (The original text can be found in: Flexner, 1910 [2])."

The process of introducing graduate schools for the purpose of scientific research—following the example of the German universities during the latter half of the 19th century—would also change the hierarchies in medicine, since science-based faculties claimed themselves that they had a better understanding of pathophysiology, pharmacology, and treatment options than any other institutions. This even included leading traditional medical colleges, such as some of the oldest homeopathic schools, for example, The Pennsylvania Hospital in Philadelphia and Palmer's Chiropractic School in Davenport, NH, USA. They had been established on pre-18th century styles of medical education—inaugurated, for example, in the spirit of Samuel Hahnemann (Figure 3)—and were primarily patient centered, often humanistically oriented and aligned with community medicine and mental health perspectives (Figure 4) [17].

It is not a difficult task to determine how Flexner's observations and criticisms came to influence the development of Complementary and Alternative Medicine and Psychiatry in North America, since this process can be described as

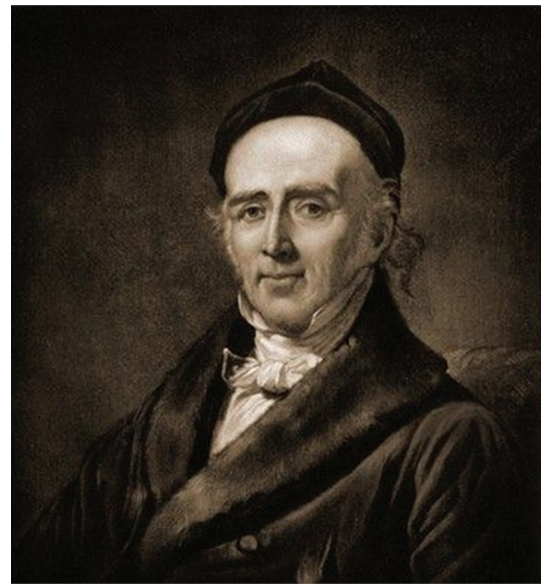

Figure 3: Samuel Hahnemann (1755–1843).

Figure 4: Community health provisions through homoeopathic neighborhood and district hospitals.

a major hindrance for the field to develop further. Among the recommendations of the Flexner Report were, for example, that the admission to a medical school should require, at minimum, a high school diploma and at least two years of college or university study, primarily devoted to basic science. The length of medical education was estimated to be four years, on top of basic science education and primary college graduation, a requirement which the Committee on Continuous Medical Education (CME) of the American Medical Association (AMA) had already agreed upon in 1905.

Furthermore, medical schools should be part of larger research universities, since a proper stand-alone medical school would have to charge fees that were too high for both of its patients and the students in its educational programs and thus would not allow the school to break even. In addition, Flexner envisioned clinical teaching in academically oriented hospitals, where thoughtful physicians and psychiatrists would pursue research stimulated by the questions that arose in the course of patient care and teach their students to do the same. In general, the report triggered a much-needed reform in the standards, organization, and curriculum of North American medical schools and also resulted in a strong emphasis on formal analytic reasoning and positivism in medical science.

A mediating position, one could argue, was taken by the Swiss-American psychiatrist Adolph Meyer, who, as mentioned above, directed the most influential clinical department of psychiatry in North America for more than forty years, and as a clinical professor at Johns Hopkins' School of Medicine, he balanced the Flexnerian demands for rigorous laboratory-based training in medicine with certain nonreductionist views inherent to psychiatry and mental health care. In fact, part of Meyer's academic success and full acceptance in the psychiatric community in the USA and Canada was in line with his reception at Johns Hopkins University of the thorough research program that Emil Kraeplin (1856–1926) had developed at the Clinical Department of Psychiatry at the University of Munich in 1910, while likewise promoting psychohygiene and facilitating the development of psychosomatic medicine—which for Meyer, similar to Flexner, was also a form of following the academic example of the German-speaking universities [18]. Despite the important role ascribed to the Flexner Report, for example, the increase of medical professionalism, closure of medical and psychiatric facilities, reduction of CAM-related educational programs at the existing medical schools—, it also reflected broader social and political trends, such as an increasing utilitarianism in American society, the necessity to economize social subsidiaries in the health care system, and the strengthening of the performance of science and medicine in the USA for applications in industry, the agricultural sector, and the military. Quite intriguing in this regard is a comparison with the situation in Germany, Austria, and the Netherlands, which did not experience such strong antagonisms and forms of social regulation as the USA and Canada with the Flexner Report [19]. This difference can be explained by referring to the considerable cultural differences in the acceptance of CAM-oriented research, health care, and education between the German- and English-speaking medical and scientific communities [20].

3.2. Comparison with the Reorganization of the CAM Field in Europe from 1960s to 1980s. Professors and chairs of the "1968 generation"—on the academic level—had introduced very different interests (such as research, teaching, and political aims) into university-based medicine in the following two decades, which were often founded on traditional "holistic ideals" (such as psychosomatic medicine, plurality of therapeutic methods, or the broadening of the curative dimension to disease prevention on larger societal scales) [21]. Among current themes, themes, "1968ers" featured an explicit critique of the somatic and organ concentration of the scientific paradigm in medicine as it had originated in the 19th century (among many medical students of the 1970s, the contemporary catchword for example was: "My first patient at medical school was a dead body"), leading to the creation of communication groups for the recording of medical history and for the breaking of bad news ("On the way to communicative medicine"); homoeopathy circles and discussion groups on Complementary and Alternative Medicine ("Nature, not Chemistry") [22]; political discussion circles on the role of medicine in the global community (such as in local chapters of the "International Physicians for the Prevention of a Nuclear War" and the "*Médecins sans frontières*"); psychosocial psychiatry groups [23]. All of these developments shared a profound criticism of scientific reductionism in medicine, which had gained so much ground since the advent of medical modernity and was also made responsible for many digressions and atrocities of research with human patients in medicine and health care in the 19th and 20th centuries [24, 25].

From the perspective of modern medicine, it had become necessary to understand and control bodily phenomena—and for the sake of argument one would need to abstract from the recent approaches in CAM—[27], clinical thinking, and scientific practices in functional frameworks. At the same time, modern medicine had barely found ways of receiving nonreductionist views in both the medical and psychiatric clinical communities, probably with the exception of psychosomatic physicians, psychoanalysts, and behavioural therapists, who continued to be involved in philosophical considerations about the status of their theories and changes in their practice as a response to the organ-centred and scientific paradigm in medicine and (biological) psychiatry.

In his introductory lectures to psychosomatics, Gerhard Danzer (b. 1956) of the Charité Medical School in Berlin, during the 1990s, particularly emphasized the roots of modern psychosomatics in late 19th and early 20th century publications of the Baden-Baden psychoanalytical physician Georg Groddeck (1866–1934) [28]. Groddeck's supervisor at the University of Berlin, Ernst Schweninger (1850–1924), who was the personal physician of the German Reich's Chancellor Otto von Bismarck (1815–1889), did not prioritize one medical system over any other. He rather developed a holistic approach integrated with elements of

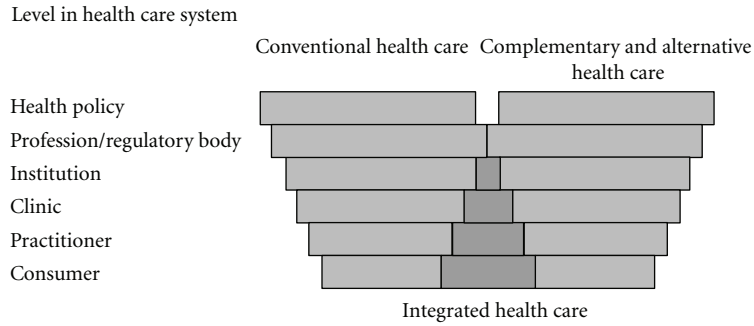

Figure 5: Level in health care systems [26].

deep psychology, psychoanalysis, psychiatry, narrative literature, and physical therapy, which he argued that would avoid the theoretical and practical pitfalls and limitations that 19th century experimental physiology had introduced into contemporary medicine. As in the case of Danzer, the critical works of the foundations of medical science and practice by Georg Groddeck also stimulated a larger group, particularly of German-speaking émigré-psychosomatic physicians in Britain and North America, to focus on additional CAM methods in both the practice of internal medicine and clinical psychiatry [29, 30]. Through the process of forced migration many, leading psychosomatic psychiatrists in the 1930s, such as Franz Alexander (1891–1964) from Budapest and Karl Stern (1906–1975) from Berlin, also introduced Schweniger's and Groddeck's concepts in the American and Canadian psychiatric communities [31]. In particular, psychiatric milieu therapy has advocated for this type of psychotherapy model, by focusing on the total environment in the treatment of mental and behavioral disorders or maladjustments by making substantial changes in a patient's immediate life circumstances, as this was historically advocated for and integrated into the therapeutic approaches of the American child psychiatrist Emmy Sylvester (b. 1910) and the Austro-American psychoanalyst Bruno Bettelheim (1903–1990). A further integration of early CAM approaches with psychiatry was achieved through the advocacy of mind-body-medicine precursors like the Chicago-based psychiatrist and the psychologist Edmund Jacobson (1888–1983) with his introduction of progessive muscle relaxation (PMR) therapy in the 1930s and 1940s ("You must relax") for mood and anxiety disorders as well as depression [32].

However, such an integration of holistic and psychosomatic approaches with CAM remained the exception rather than the rule until the 1990s, since traditional medical departments had scarcely addressed "integrative perspectives" on "the healing experience" in Central Europe and North America [33]. In this respect, some intriguing comments by German historian of medicine and physiology, Karl Eduard Rothschuh (1908–1984) should be allowed here, when he asked the question "What is and to what end does one study historical medicine?" in a lecture at the Westphalian Wilhelms University of Muenster in 1980 [34]. The lecture plastically summarized the incomplete picture of modern education in "physicianship," as taught by many medical faculties in the western world, *vis-à-vis* the fragmented body of medical knowledge founded on training in anatomy, physiology, and biochemistry:

> *The large weight, which is undoubtedly placed on the natural sciences with regard to the pursuit of medicine's healing tasks, does not mean, however, that medicine itself would be a natural science. Medicine is neither a natural science, nor a humanist discipline. Medicine is not a scientific discipline at all, but is based on scientific disciplines. [...] [Medical History, in addition,] develops and represents a set of values; without Medicina Historica this set of values would not at all be introduced into the medical canon. (The original text can be found in: Rothschuh, 1986 [34]).*

3.3. Impact of the Social Movements of the 1960s and the Opening of the NIH in the US. Differences in philosophical views about the scientific paradigm in medicine, medical reductionism, the place of the patient, and diverging interpretations of medical holism led to intense disputes between physicians, psychiatrists, and alternative practitioners [35]. A time of change had been brought about with the rise of the 1960s, increasing the uses of CAM and widespread discussions about the practice and role of medicine and psychiatry in Western societies and cultures, as is intriguingly represented in the influential criticisms of the Austrian philosopher, theologian, and social scientist Ivan Illich (1926–2002):

> *Physical sickness is confined to the body, and it lies in an anatomical, physiological, and genetic context. The "real" existence of these conditions can be confirmed by measurement and experiment, without any reference to a value-system. None of this applies to mental sickness: its status as a "sickness" depends entirely on psychiatric judgment. The psychiatrist acts as the agent of a social, ethical, and political milieu. Measurements and experiments on these "mental" conditions can be conducted only within an ideological framework which derives its consistency from the general social prejudice of the psychiatrist. The prevalence*

> *of sickness is blamed on life in an alienated society, but while political reconstruction might eliminate much psychic sickness, it would merely provide better and more equitable technical treatment for those who are physically ill. (The original text can be found in: Illich, 1976) [36].*

Of course, these criticisms of the scientific paradigm in medicine were by no means a homogenous trend, but rather triggered through a heterogeneous mixture of social, medical, and psychiatric movements, events, and developments that impacted the changes towards auxiliary and increased use of Complementary and Alternative Medicine and Psychiatry in places where modern medicine had little if nothing to offer (e.g., chronic pain management, oncology and palliative care, therapy of complex psychiatric disorders with compliance problems, etc.).

The "hippie movement"—on the broader level of society—was certainly one important strand among these heterogenous criticisms, in which virtues of a simple, natural life, tolerance of diverse lifestyles, consumption of natural and organic foods, and the social use of psychoactive drugs were promoted [37]. Also, the human potential movement is worth mentioning as they advocated for therapeutic approaches such as vegetarianism, natural birthing, transcendental meditation, yoga, and biofeedback. Its participants were concerned with the quality of both personal life and social life in the modern world, such as the preceding protagonists of psychosomatic medicine, wellness, movement, and humanistic medicine. In North America, this movement was centered around the foundation of the Academy of Psychoanalytic Medicine (APM), in 1954, and the address by Halpert L. Dunn (1896–1975) from the US Public Health Service on the concept of wellness in the early 1960s, which broke with earlier disease-based models that had developed during the 19th century scientific paradigm of medicine. Dunn introduced a new integrated concept of health and wellbeing, "which is oriented toward maximizing the potential of which the individual is capable, within the environment where he is functioning" [38].

Socially, the tradition of postmodernism, feminism and environmentalism were also crucial for the reaction to the previous era of modernism, characterized by the belief in the existence of truth, objectivity, determinacy, causality and impartial observation and with an emphasis on individuality, complexity, and personal experience. These changes became further integrated into the social construction of curricula and values in the medical system in the 20th century [39].

The development of Complementary and Alternative Medicine and Psychiatry after the publication of Flexner's 1910 Report to the American Carnegie Foundation was manifold and in certain respects was also fruitful. On the one hand, Flexner's work led to the closure of colleges, hospitals, and programs in which "unconscionable quacks" were working who had been "a disgrace to the State," as the author of the report wrote. The political and disciplinary crackdown on alternative and nonconventional forms of research and education in medicine and psychiatry, on the other hand, did not reach the general population, nor did its beliefs about the doctor-patient relationship and other forms of healing and medical support. Largely due to such outside developments, plans for integrative forms of medical practice that selectively incorporated elements of CAM evolved into comprehensive treatment plans alongside solidly orthodox methods of diagnosis and health care [40]:

> *Integrative Medicine is 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. (Consortium of Academic Health Centers for Integrated Medicine) [41].*

However, in many ways the current status of "integrative medicine" (IM) in medical and psychiatric institutions in North America is still (and importantly) future oriented in its thinking—although problematic in vision—, as relatively few schools have really integrated conventional medicine with Complementary and Alternative Medicine and Psychiatry, at least not until recently.

3.4. The Recent Chronology—Increasing International CAM and IM Platforms. The creation of the National Center for Complementary and Alternative Medicine (NCCAM) in the USA in 1991—even though it was given only a comparatively small budget below one percent of NIH's expenditures at the time, brought about by the US Senator Tom Harkin (b. 1939), proved to be a landmark event in the renewed support of CAM in North America [42]. Large scale research could now be pursued under the leadership of the NIH, by combining mainstream medical therapies and CAM approaches, while investigating scientific evidence, safety, and efficacy:

> *CAM is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine. Conventional medicine is medicine as practiced by holders of M.D. (medical doctor) or D.O. (doctor of osteopathy) degrees and by their allied health professionals, such as physical therapists, psychologists, and registered nurses. Some health care providers practice both CAM and conventional medicine. While some scientific evidence exists regarding some CAM therapies, for most there are key questions that are yet to be answered through well-designed scientific studies—questions such as whether these therapies are safe and whether they work for the diseases or medical conditions for which they are used. The list of what is considered to be CAM changes continually, as those therapies that are proven to be safe and effective become adopted into conventional health care and as new approaches to health care emerge. (NCCAM, 2007) [43].*

In its inaugural year of 2004, the international Consortium of Academic Health Centers for Integrated Medicine (CAHCIM) expressed the future hope that integrative medicine would become the cornerstone of the urgently needed reconstruction of what was perceived as a dysfunctional healthcare system, including both the somatic and the psychiatric fields. The development of new frameworks of CAM has also realized that genetic and translational aspects of modern biomedical and psychiatric research had their place in such a new health care paradigm [44]. In fact, psychiatrists and psychologists today display an increasing intellectual openness towards the use of CAM and integrative approaches in their therapeutic practice, as well as the growing evidence base for specific CAM modalities in both the treatment and prevention of mental illness and disease [45]. These major changes have largely occurred in the USA, or in countries that have adopted the US model. While the federal organization of Health Canada has also played an important role in Canada, quantitatively there has been only a minor level of involvement, especially when compared to the USA.

With the creation of the International Network of Integrative Mental Health (INIMH) in 2010, there now exists an important institutional platform which furthers the development of a biopsychosocio-spiritual model in integrative mental health that is evidence based. Some of these promising changes, which are taking place in mental health care in Western countries, are represented, for example, in the growing use of homoeopathy in mood and mild anxiety disorders and the increasing role of traditional Chinese acupuncture therapies in the management of chronic pain conditions, depression, and anxiety disorders, as well as folate and other substitutional nutritional factors in depression and bipolar disorders [46].

4. Conclusions

For some, the real trend in CAM medicine and psychiatry has become evidence-based medicine (EBM), not complementary and alternative medicine itself. This observation further aligned with the fact that medical, and increasingly also psychiatric education, has changed considerably over the past decade along with new trends in CAM education [47], while EBM is now infiltrating medical school curricula on both the basic science and clinical care ends [48]. While this paper has looked back from a history of medicine perspective at the publication of the Flexner Report one century ago, it should also be emphasized that the Flexner Report was revolutionary and and is even today even today widely celebrated as a seminal document that subsequently raised the standards for general education in medicine and psychiatry. However, the last decades have also seen a disturbing trend away from Flexner's prescriptions, since medical schools are reverting to many of the pre-Flexnerian standards by uncritically adding many pseudoscientific health claims to their course materials as "IM," without rigorous tests, studying CAM practice or asking trained physicians for their experiences (Figure 5). Certainly, Flexner himself would have "approved" of a new evidence-oriented direction in medical and psychiatric education:

> *Unfortunately, Flexner may be rotating all too rapidly. [...] medical schools are teaching and promoting what is often called CAM, despite the lack of logic or evidence supporting many CAM practices. Meanwhile, the same schools seem to give only lip service to the application of logic and evidence to healthcare, as exemplified by the formal processes of EBM. [49].*

We increasingly recognize today that treatment is not an isolated event in patients' lives, but it takes part in the patient's own bio-psycho-social context, which includes social networks, patients' subjective experiences, and their mental health status, along with the patient provider relationship (a system). These elements are crucial to testing an intervention, as a patient is not an average patient, with average beliefs, devoid from any contextual influences [50]. As CAM treatments in psychiatry become more and more efficient and safe, as well as increasingly supported by data from randomized controlled trials and other EBM methodologies in clinical epidemiology, new standards for an appropriate and reliable use of complementary and alternative medicine and psychiatry are emerging, which go hand in hand with recommendations for the monitored and evaluated use of CAM and integrative therapies in mental health care in the USA, Canada, and other developed countries [51].

In this context, INIMH aims at augmenting and adapting approaches in contemporary psychiatry, along with biomedical perspectives in health care and research and its attempts to work out a more adequate paradigm, one of which aims at transcending the boundaries of what Abraham Flexner had laid out a century ago in his influential Report on *Medical Education in the United States and Canada* [52].

Acknowledgments

F. W. Stahnisch gratefully acknowledges the support of the Mackie Family Collection in the History of Neuroscience, the Hotchkiss Brain Institute, and the Institute for Public Health (all: University of Calgary), as well as CIHR Open Operating Grant no. EOG-123690. M. J. Verhoef acknowledges CIHR support for a Canada Research Chair (CRC) award in complementary medicine. Both authors are grateful to Mikkel Dack, M.A. (Calgary), for the meticulous adjustment of the English language of this paper, as well as to the anonymous referees for their very constructive criticisms on an earlier version of this paper.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 260301, 10 pages
doi:10.1155/2012/260301

Research Article

Dose-Dependent Effects of the *Cimicifuga racemosa* Extract Ze 450 in the Treatment of Climacteric Complaints: A Randomized, Placebo-Controlled Study

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Received 10 August 2012; Accepted 7 October 2012

Academic Editor: Bernhard Uehleke

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Extracts from *Cimicifuga racemosa* (CR, synonym *Actaea racemosa*) have shown efficacy in trials in women with menopausal symptoms. Yet, dose dependency remains unclear. Therefore, 180 female outpatients with climacteric complaints were treated for 12 weeks in a randomized, double-blind, placebo-controlled, 3-armed trial (CR extract Ze 450 in 6.5 mg or 13.0 mg, or placebo). Primary outcome was the difference in menopausal symptoms (vasomotor, psychological, and somatic), assessed by the Kupperman Menopausal Index between baseline and week 12. Secondary efficacy variables were patients' self-assessments of general quality of life (QoL), responder rates, and safety. Compared to placebo, patients receiving Ze 450 showed a significant reduction in the severity of menopausal symptoms in a dose-dependent manner from baseline to endpoint (mean absolute differences 17.0 (95% CI 14.65–19.35) score points, $P < 0.0001$ for 13.0 mg; mean absolute differences 8.47 (95% CI 5.55–11.39) score points, $P = 0.0003$ for 6.5 mg). QoL and responder rates corresponded with the main endpoint. Changes in menopausal symptoms and QoL were inversely correlated. Reported adverse events and clinical laboratory testing did not raise safety concerns. The CR extract Ze 450 is an effective and well-tolerated nonhormonal alternative to hormone treatment for symptom relief in menopausal women.

1. Introduction

On the one hand, menopause is a normal biological process marking the transition of the lives of mature women from a reproductive into a postreproductive phase. On the other hand the profound physiological changes in the peri- and postmenopausal period can provoke complaints. Menopausal changes can lead to vasomotor (e.g., hot flushes, sweating), psychological/vegetative (e.g., insomnia, nervousness/irritability, depressive event, and palpitation), somatic (e.g., joint pain), and urogenital/sexual (e.g., libido changes, dyspareunia, and vaginal dryness) symptoms. They vary in frequency and severity, are related to lifestyle, demographics and sociocultural circumstances, and have been well characterized [1–3]. Hot flushes and night sweating are the cardinal symptoms with highly varying prevalence between 24 to 93% [3–6]. However, the interrelationship of hot flushes and sweating with other neuropsychological symptoms seems to diminish QoL in symptomatic menopausal women [7, 8].

Although the role of estrogen appears to be critical and is underlined by the clinical effects of estrogen or estrogen/progestin therapy [9, 10], the mechanisms leading to the development of hot flushes have not been fully elucidated [11]. Since large epidemiological studies with long-term hormonal replacement therapy (HRT), such as the Women's Health Initiative and the Million Women Study

[12–15], have shown a small but significantly increased risk for the development of invasive breast cancer, there is an increasing interest in nonhormonal treatment modalities for patients with climacteric symptoms.

Cimicifuga racemosa L. (synonym *Actaea racemosa* L., black cohosh) is a perennial medicinal plant native to North America where it has been used for centuries in indigenous medicine for the treatment of various conditions. However, today's sole accepted indications are menopause-related neurovegetative and emotional symptoms. *Cimicifuga racemosa* (CR) extracts are described in a 2003 monograph of the European Scientific Cooperative on Phytotherapy (ESCOP) as a pharmacologically active treatment of climacteric symptoms [16] and in the 2010 community herbal monograph of the Committee on Herbal Medicinal Products of the European Medicines Agency [17]; a well-established use status was granted.

The precise mechanism of action of CR is controversial, with some studies suggesting that it has no estrogenic effect while others indicate a selective estrogen modulating effect on some tissues, such as bone [18–20]. In addition, serotonin-binding properties in the brain may contribute to its mechanism of action [21, 22]. If indeed CR lacks estrogenic effects, it would have a beneficial influence on climacteric vasomotor and psychiatric symptoms without adversely affecting the development of breast or uterine tissue tumors or increasing the cardiovascular risk.

Randomized, controlled clinical trials (RCTs) have shown clinically significant effects of extracts from CR [20, 23–26]; but the results have not been consistent in systematic reviews [27–29]. The comparability of the trials is difficult because of differences in dosing, outcome parameters, rating scales, and different CR extracts used [30]. Nevertheless, a meta-analysis performed showed the efficacy of extracts from CR in vasomotor symptoms; but the authors pointed out the heterogeneity of the trials [31].

Dose-dependent effects of an isopropanolic aqueous CR extract have been previously investigated by Liske et al. [25]. Though no placebo or active control treatment was used in this study, both the low- and high-dose improved climacteric symptoms compared to baseline values, and no differences between the treatments could be demonstrated in the Kupperman Menopausal Index (KMI) [32]. For the present study, therefore, placebo treatment was compared to the dose-dependent effects of the CR extract Ze 450 on climacteric symptoms.

2. Patients and Methods

For this multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, 180 female outpatients with menopausal complaints were included. The study took place in four outpatient clinics. Patients were randomized to receive either 13.0 mg Ze 450, 6.5 mg Ze 450 or placebo for 12 weeks.

The study was performed between March 19, 2002 and July 23, 2003.

2.1. Ethics. The study protocol was approved by the Ethics Committee of the Medical Association (Ethik-Kommission Landesärztekammer Hessen), Frankfurt, Germany, and the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)) was informed prior to its start. Conduct was in accordance with the ICH Guidelines for Good Clinical Practice and the Declaration of Helsinki. A written informed consent was obtained from all patients prior to screening/baseline visit.

2.2. Inclusion/Main Exclusion Criteria. Females (age $\geq$ 40 years) suffering from menopausal syndrome with neurovegetative components, which have been stable anamnestically during the last 2 weeks, and who consulted a physician for the treatment of symptoms were included. The diagnosis of menopausal complaints was confirmed by a Climax Score according to M. Metka and F. H. Fischl. The Climax Score includes neurovegetative, psychical, and atrophic symptoms. By using this tool, the diagnosis of menopausal syndrome was confirmed by the physician. In addition, the baseline Kupperman Menopausal Index (KMI) was recorded by the investigator. Patients were excluded due to previous or current psychological disease that could interfere with their ability to participate in the study; anamnestic or current alcohol or drug abuse; concomitant treatment with psychotropic (in particular benzodiazepines, antidepressants, hypnotics or neuroleptics, tamoxifen, clomifen, and danazol) or hormonally acting drugs such as hormone replacement therapy (HRT); hyperthyroidism; malignant tumors; continuous climacteric bleeding and complaints related to myomas; patients who have taken another experimental drug within a 4-week period prior to the trail; pregnancy/lactation; serious internal disease; previous organ transplantation; premenopausal women with insufficient contraceptive protection; hypersensitivity to one of the ingredients of the trial medication; a body mass index >30.

2.3. Study Medication. A 6.5 mg tablet of the (60% v/v) ethanolic CR extract Ze 450 (from rhizomes and roots of CR; drug-extract ratio 4.5–8.5 : 1; Max Zeller Söhne AG, Romanshorn, Switzerland) was used. Placebo was identical looking.

The treatment schedule for the double-dummy, parallel group design was 2 tablets/once a day given with a meal in the morning: (a) placebo (PLA) + PLA, (b) PLA + 6.5 mg Ze 450, (low dose; LD), and (c) 6.5 mg Ze 450 + 6.5 mg Ze 450 (high dose; HD). Treatment compliance was assessed by a pill count of the returned medication (return of $\leq$25% was considered compliant).

2.4. Outcome Measures. All assessments were done at baseline (visit 1), optionally 6 weeks later (visit 2), and 12 weeks later (visit 3). The severity of menopausal symptoms was assessed at each visit using a modified total KMI score [24, 32–34]. Subitems of this index focused on the neurovegetative symptoms: a 10-item questionnaire of single symptoms

whose severity ranged from 0 to 3 (none, mild, moderate, and severe). Score values were multiplied by weighting factors: hot flushes (×4), sweating (×2), insomnia (×2), nervousness/irritability (×2), depressive events/melancholy (×1), vertigo (×1), concentration weakness (×1), joint pain (×1), headache (×1), and palpitations (×1). For this study, the total KMI equalled the sum of the multiplied subitem scores (maximum = 48) and was classified as mild (KMI ≤ 20), moderate (KMI = 21–35), or severe (KMI > 35) [32].

The general quality of life (QoL) was assessed by the visual analog scale (VAS). Using a 100 mm printed line, patients checked off how they evaluated their status (0 mm = "best possible quality of life due to health condition"; 100 mm = "worst possible quality of life due to health condition").

At all visits, routine hematological and clinical-chemical laboratory tests were performed. Thyroid hormones (T3, T4), thyroid-stimulating hormone (TSH), follicle-stimulating (FSH), luteinizing hormone (LH) and estradiol (E2), pregnancy test, and urinalysis were performed only at baseline.

The *primary endpoint* was the difference in the total KMI between both verum groups (HD and LD) and PLA at the end of therapy (week 12), stratified by individual baseline scores in an intention-to-treat (ITT) analysis (patients treated with study medication and with at least one efficacy assessment after baseline). *Secondary endpoints* were (1) the analysis for each subitem of the KMI; (2) analysis of treatment responders (patients with a reduction of ≥50% of the total KMI); (3) a QoL analysis; (4) safety assessment.

2.5. Statistical Analysis. Within each clinical site involved the allocation of the randomised treatment was sequential. The random code was supplied by an external provider, using a validated random program (Mathematica, Wolfram Research). Randomization was provided in blocks of six to assure balanced allocation of treatments. Each of the study centres received their own randomization list according to which patients were allocated to the treatment groups.

Responsible for all statistical aspects, regarding design and analysis of the study, was the Department of Medical Information Technology, University of Giessen, Germany.

Data management was done by Brunner and Hess, Zurich, Switzerland. Data were entered in duplicate and independently by suitably trained personnel at a statistical institute, who were blinded with respect of treatment group allocation.

Based on KMI data from previous clinical trials, sample size was conservatively estimated as $n = 60$ patients/group. Assuming an alpha-error = 0.05, mean KMI scores (SD) of 27(15) and 18(15) in the placebo and verum groups, respectively, an anticipated 10% drop-out rate and using the two-sided Mann-Whitney test, a power $(1-\beta)$ of >90% could be expected (G*Power software, University of Duesseldorf, Germany). A predefined hierarchical statistical design was used. Hierarchically sequenced null hypotheses were that the medians between treatment groups at the end of treatment would be the same, stratified by individual baseline scores: H01 : PLA versus HD; H02 : PLA versus LD; H03 : LD versus HD. The respective alternative hypotheses (HA1 to HA3) stated that the medians would be different. Comparisons were performed by the stratified non-parametric Wilcoxon-Mann-Whitney test ($\alpha = 0.05$, 2-sided, StatXact, Version 9) to test the hypotheses with the following hierarchical-sequentially rejecting procedure: Step 1: H01 versus HA1; Step 2: H02 versus HA2; Step 3: H03 versus HA3. The test procedure was terminated once a null hypothesis could not be rejected. This hierarchical statistical design was used as a method to control type I error for multiple comparisons. Therefore, there was no need to adjust P values for multiple comparisons for the 3-step testing. Responder analysis (for total KMI) was done using the same hierarchical sequence by Pearson's Chi-square test. For patients terminating participation prematurely at the interim visit, all available efficacy data were treated according to the principle of last observation carried forward (LOCF).

3. Results

Of the 232 patients originally referred to the clinics, 52 failed the selection criteria. A total of 180 patients were randomized. Their mean age was 51.7 years and mean BMI (Body Mass Index) was 25.2 kg/m^2 when entering the study. Safety and ITT populations comprised $n = 177$ and $n = 166$ patients, respectively (Figure 1). The majority of patients in the ITT population ($n = 85$, 51.2%) were in the early postmenopausal stage (less than 5 years since last menstruation); fewer patients ($n = 43$, 25.9%) were in the late postmenopausal (more than 5 years since last menstruation) or premenopausal stage ($n = 38$, 22.9%). A similar categorization was obtained when threshold FSH concentration of 40 mIU/mL was used. Smoking habits did not differ between the treatment groups (Table 1). Severity of symptoms (total KMI) ranged from mild ($n = 29$, 17.5%) to moderate ($n = 109$, 65.7%) to severe ($n = 28$, 16.9%). There were no significant differences between the treatment groups in any of the demographic parameters or for baseline levels of T3, T4, TSH, FSH, LH, and E2.

Concerning the primary endpoint verum was superior to placebo in reducing the total KMI score in a dose-dependent manner (Table 2, Figure 2). Regarding KMI sub-items, a significant reduction in each item was seen only with the HD group. The clinical relevance was the strongest for vasomotor subitems (e.g., hot flushes, sweating), less for psychological/vegetative sub-items (e.g., insomnia, nervousness/irritability, and depressive events/melancholy) and the smallest for somatic symptoms (joint pain), although significant (Table 3).

Treatment effect size at the end of study (week 12) was dependent on the baseline symptom severity (Table 4). For patients with initially mild (total KMI ≤ 20) and moderate symptoms (20 < total KMI ≤ 35), average KMI scores decreased from baseline values significantly and in a dose-dependent manner by 5.4 (8.3 SD) and 9.6 (11.5 SD) score points in the LD group and by 10.5 (4.4 SD) and 17.8 (8.6 SD) score points in the HD group. This contrasts to the average KMI scores in the PLA group that even

Table 1: Demographic details: mean (SD), ITT population.

	n	Placebo	n	Low dose	n	High dose	P value[1]
Age (years)	54	50.5 (7.0)	57	52.0 (6.3)	55	52.8 (6.0)	0.168
Weight (kg)	54	67.7 (11.6)	57	70.5 (13.0)	55	68.3 (12.2)	0.433
BMI (kg/m^2)	54	24.9 (4.3)	57	25.6 (5.1)	55	25.0 (3.9)	0.634
Height (cm)	54	164.9 (5.1)	57	166.3 (7.1)	55	165.2 (7.4)	0.537
KMI (points)	54	27.3 (6.5)	57	28.1 (6.9)	55	28.4 (8.0)	0.692
QoL (mm)	54	37.2 (15.6)	57	31.2 (15.9)	55	34.7 (17.6)	0.150
Premenopausal (n)	54	15	57	12	55	11	
Early postmenopausal (n)	54	27	57	28	55	30	0.803[2]
Late postmenopausal (n)	54	12	57	17	55	14	
Baseline FSH $\leq$ 40 mIU/mL (n)	54	21	57	22	55	15	
Baseline FSH > 40 mIU/mL (n)	54	22	57	26	55	33	0.333[2]
Baseline FSH unknown	54	11	57	9	55	7	
Baseline KMI $\leq$ 20	54	9	57	10	55	10	
Baseline KMI 21–35	54	36	57	41	55	32	0.454[2]
Baseline KMI > 35	54	9	57	6	55	13	
Nonsmoker (n)	54	41	57	44	55	39	
Occasional smoker (n)	54	3	57	0	55	4	0.575[3]
Moderate smoker (n)	54	6	57	7	55	7	
Heavy smoker (n)	54	4	57	6	55	5	

[1]Analysis of variance, [2]Chi-square test, [3]Fisher's exact test.

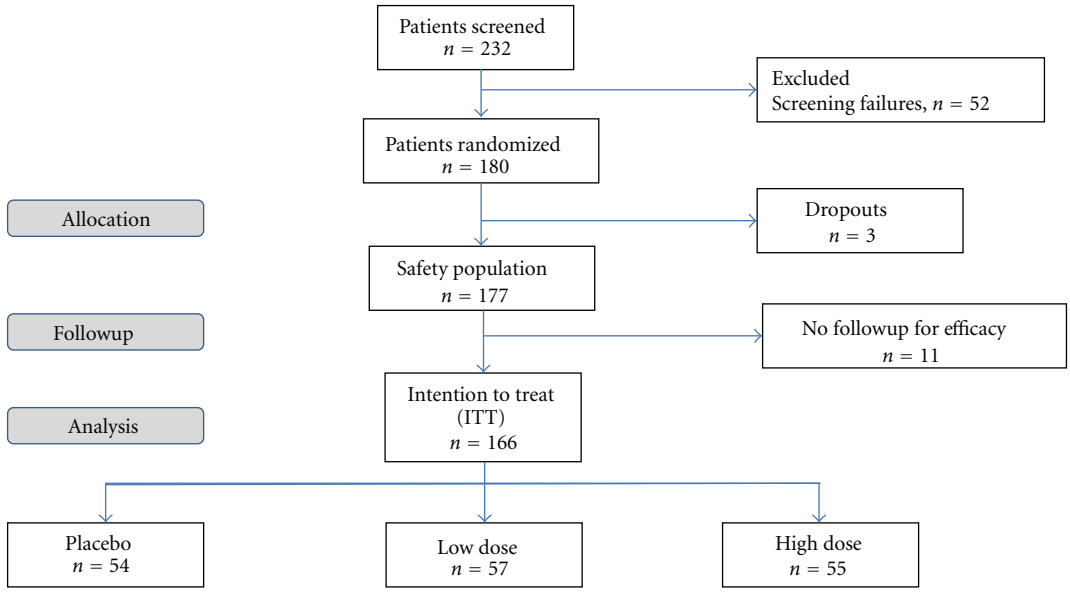

Figure 1: CONSORT diagram of the disposition of participants.

increased from baseline values by 12.2 (4.7 SD) (initially mild symptoms) and 0.6 (7.8 SD) (initially moderate symptoms) score points. For patients with initially severe symptoms (total KMI > 35), average scores decreased by 4.8 (8.5 SD) (PLA), 5.8 (12.0 SD) (LD), and 20.1 (9.5) (HD) score points. However, only for the HD group could a significant difference versus the PLA group be demonstrated.

For premenopausal patients, only the HD showed a significant ($P < 0.001$) decrease in average total KMI scores compared to the PLA group (20.9 (7.6 SD) versus 1.1 (7.8 SD) score points, resp.). In patients in the early and late postmenopausal states, comparable magnitudes of effects of Ze 450 treatments were observed: LD and HD treatments in early postmenopausal women decreased KMI by 11.0 (11.2 SD) and 17.2 (9.7 SD) score points, respectively, whereas PLA increased KMI by 3.3 (7.9 SD) score points. In late postmenopausal women, LD and HD treatment decreased KMI by 10.2 (11.2 SD) and 13.6 (5.8 SD)

Table 2: Intention to treat analysis: total KMI after 12 weeks of treatment ($n = 166$).

Treatment	n	Baseline		End of study		Absolute differences		Hierarchical test procedure*		
		Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Step 1	Step 2	Step 3
Placebo	54	27.30 (6.5)	25.53–29.06	28.94 (7.6)	26.87–31.02	1.65 (9.0)	−0.80–4.10	Reference	Reference	
Low dose	57	28.12 (6.9)	26.28–29.96	19.65 (13.1)	16.17–23.13	−8.47 (11.0)	−11.39 to −5.55		$P = 0.0003$	Reference
High dose	55	28.44 (8.0)	26.28–30.60	11.44 (9.1)	8.98–13.90	−17.00 (8.7)	−19.35 to −14.65	$P < 0.0001$		$P = 0.0057$

* According to two-sided Mann-Whitney test stratified to individual baseline scores; 95% CI: 95% confidence interval; SD: standard deviation; n: number of patients.

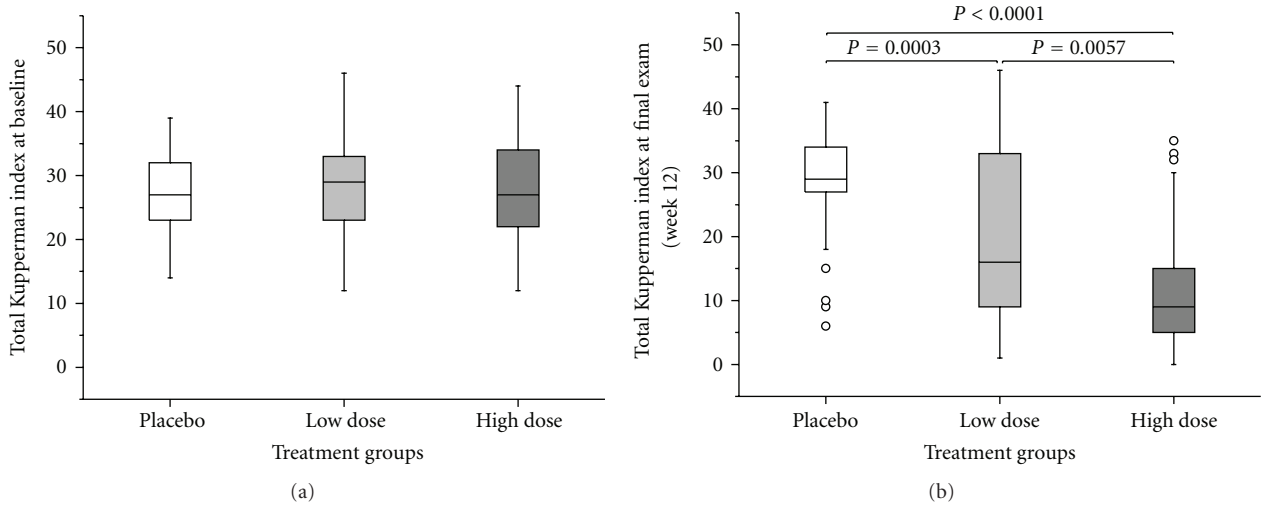

Figure 2: Total KMI (a) at baseline and (b) after 12 weeks of treatment (ITT population, $n = 166$) with PLA, LD, and HD. Circles denote outliers. Two-sided Mann-Whitney test stratified to baseline scores.

score points, respectively, whereas PLA increased KMI by 1.5 (12.1 SD) score points. However, in contrast to the early postmenopausal subgroup, in the late postmenopausal subgroup no superiority for the HD over the LD group could be established.

With respect to the secondary endpoints, the responder rate for ≥50% reduction in total KMI increased from 7.4% in the PLA group to 40.4% in the LD group ($P < 0.001$) and increased further to 69.1% in the HD group. The latter was significantly higher than in the PLA group ($P < 0.001$) or the LD group ($P = 0.002$).

Corresponding to the reduction in symptom severity, the QoL VAS increased dose-dependently (Figure 3). Changes in menopausal symptoms and QoL were inversely correlated.

As to safety no serious, but 21 nonserious adverse events (AE) occurred in 20 patients: 9 of which were possibly treatment related (5 PLA, 2 LD, and 2 HD group), five were unlikely or not related to the study medication, and the relationship was assessed as unknown for seven. Among the nine possibly study-related AEs, five were of a gastrointestinal nature, a known AE of Ze 450. The frequency of possibly related AEs was higher in the placebo group. Laboratory assessments revealed no clinically significant changes, except for three patients (one from each group) with elevated liver enzyme values. Two were likely caused by excessive alcohol consumption, while the third remained undefined. These three AEs were not clustered in one specific treatment group; but they were equally distributed among the three groups. No safety concerns were raised based on the monitoring of vital signs, physical examination, and laboratory values from the beginning to the end of the study.

4. Discussion

Our study demonstrated that the CR extract administered for 12 weeks decreased significantly, and in a dose-dependent manner, the severity of climacteric symptoms in the total KMI. This was predominantly seen in single subitems especially for vasomotor as well as for some psychological symptoms. Furthermore, the administration of CR extract over 12 weeks improved general QoL and was safe.

The strengths of the current trial are as follows. (a) It analysed one of the unanswered questions in the nonhormonal treatment of menopausal complaints with extracts from CR—the dose-dependency. This was done in a suitable methodological manner with the high internal validity of the 3-arm RCT. Blinding was achieved by applying a double-blind, double-dummy setting in order to avoid any unblinding bias.

(b) A subgroup analysis showed that both the LD and HD demonstrated, in a dose-dependent manner, a significantly larger effect than placebo in patients with mild and moderate symptom severity. For patients with severe symptoms, however, only the high dose (13.0 mg) of Ze 450 was effective. Compared to the placebo and LD groups, only

Table 3: Change in symptom severity of KMI sub-items after treatment during 12 weeks (ITT population).

Subitem	Treatment group	Baseline			Final examination (12 weeks)			Absolute differences			Hierarchial test procedure*		
		Valid *n*	Mean (SD)	95% CI	Valid *N*	Mean (SD)	95% CI	Valid *N*	Mean (SD)	95% CI	Step 1	Step 2	Step 3
Hot flushes	Placebo	54	8.37 (3.83)	7.33–9.42	54	9.93 (3.27)	9.03–10.82	54	1.56 (3.60)	0.57–2.54	Ref.	Ref.	
	Low dose	57	8.56 (3.25)	7.70–9.42	57	6.32 (4.34)	5.16–7.47	57	−2.25 (4.47)	−3.43 to −1.06		$P < 0.0001$	Ref.
	High dose	55	8.65 (3.83)	7.62–9.69	55	3.20 (3.48)	2.26–4.14	55	−5.45 (4.17)	−6.58 to −4.33	$P < 0.0001$		$P = 0.0001$
Sweating	Placebo	54	3.85 (2.05)	3.29–4.41	54	4.70 (1.61)	4.26–5.14	54	0.85 (2.08)	0.28–1.42	Ref.	Ref.	
	Low dose	57	4.14 (1.77)	3.67–4.61	57	2.74 (2.26)	2.14–3.34	57	−1.40 (2.20)	−1.99 to −0.82		$P < 0.0001$	Ref.
	High dose	55	4.18 (1.82)	3.69–4.67	55	1.60 (1.70)	1.14–2.06	55	−2.58 (2.02)	−3.13 to −2.03	$P < 0.0001$		$P = 0.0064$
Insomnia	Placebo	54	4.00 (1.90)	3.48–4.52	54	4.19 (1.87)	3.67–4.70	54	0.19 (2.31)	−0.44–0.81	Ref.	Ref.	
	Low dose	57	4.04 (1.98)	3.51–4.56	57	2.91 (2.27)	2.31–3.51	57	−1.12 (2.11)	−1.68 to −0.56		$P = 0.0015$	Ref.
	High dose	55	3.93 (2.07)	3.37–4.49	55	1.75 (1.81)	1.26–2.23	55	−2.18 (2.32)	−2.81 to −1.56	$P < 0.0001$		$P = 0.0044$
Nervousness, irritability	Placebo	54	4.11 (1.71)	3.64–4.58	54	4.00 (2.02)	3.45–4.55	54	−0.11 (2.11)	−0.69–0.46	Ref.	Ref.	
	Low dose	57	4.14 (1.64)	3.70–4.58	57	2.70 (2.12)	2.14–3.26	57	−1.44 (1.96)	−1.96 to −0.92		$P = 0.0005$	Ref.
	High dose	55	3.67 (2.03)	3.12–4.22	55	1.64 (1.54)	1.22–2.05	55	−2.04 (2.13)	−2.61 to −1.46	$P < 0.0001$		$P = 0.0100$
Depressive events, melancholy	Placebo	54	1.59 (1.11)	1.29–1.89	54	1.54 (0.97)	1.27–1.80	54	−0.06 (1.11)	−0.36–0.25	Ref.	Ref.	
	Low dose	57	1.77 (1.09)	1.48–2.06	57	1.26 (1.09)	0.97–1.55	57	−0.51 (0.98)	−0.77 to −0.25		$P = 0.0308$	Ref.
	High dose	55	1.80 (1.06)	1.51–2.09	55	0.71 (0.76)	0.50–0.92	55	−1.09 (1.02)	−1.37 to −0.81	$P < 0.0001$		$P = 0.0020$
Vertigo	Placebo	54	0.67 (0.89)	0.42–0.91	54	0.74 (0.87)	0.50–0.98	54	0.07 (1.01)	−0.20–0.35	Ref.	Ref.	
	Low dose	57	0.65 (0.86)	0.42–0.88	57	0.49 (0.83)	0.27–0.71	57	−0.16 (0.56)	−0.31 to −0.01		$P = 0.0390$	Ref.
	High dose	55	0.84 (0.94)	0.58–1.09	55	0.42 (0.63)	0.25–0.59	55	−0.42 (0.81)	−0.64 to −0.20	$P = 0.0103$		NS
Concentration weakness	Placebo	54	1.31 (0.97)	1.05–1.58	54	1.02 (1.00)	0.75–1.29	54	−0.30 (1.02)	−0.58 to −0.02	Ref.	Ref.	
	Low dose	57	1.42 (1.03)	1.15–1.70	57	1.02 (1.09)	0.73–1.31	57	−0.40 (0.90)	−0.64 to −0.16		NS	Ref.
	High dose	55	1.56 (0.94)	1.31–1.82	55	0.76 (0.86)	0.53–1.00	55	−0.80 (0.91)	−1.05 to −0.55	$P = 0.0350$		NS**
Joint pain	Placebo	54	1.26 (1.17)	0.94 (1.58)	54	1.06 (1.14)	0.74–1.37	54	−0.20 (0.94)	−0.46–0.05	Ref.	Ref.	
	Low dose	57	1.49 (1.20)	1.17–1.81	57	1.04 (1.20)	0.72–1.35	57	−0.46 (0.95)	−0.71 to −0.21		NS	Ref.
	High dose	55	1.53 (1.18)	1.21–1.85	55	0.58 (0.81)	0.36–0.80	55	−0.95 (0.95)	−1.20 to −0.69	$P = 0.0006$		$P = 0.0191$**
Headache	Placebo	54	0.89 (0.92)	0.64–1.14	54	0.93 (0.80)	0.71–1.14	54	0.04 (1.05)	−0.25–0.32	Ref.	Ref.	
	Low dose	57	0.81 (0.91)	0.56–1.05	57	0.54 (0.85)	0.32–0.77	57	−0.26 (0.61)	−0.43 to −0.10		$P = 0.0030$	Ref.
	High dose	55	0.96 (0.96)	0.70–1.22	55	0.38 (0.56)	0.23–0.53	55	−0.58 (0.85)	−0.81 to −0.35	$P < 0.0001$		NS
Palpitations	Placebo	54	1.24 (0.80)	1.02–1.46	54	0.85 (0.90)	0.61–1.10	54	−0.39 (0.83)	−0.62 to −0.16	Ref.	Ref.	
	Low dose	57	1.11 (0.90)	0.87–1.34	57	0.63 (0.88)	0.40–0.86	57	−0.47 (0.93)	−0.72 to −0.23		NS	Ref.
	High dose	55	1.31 (1.10)	1.01–1.61	55	0.40 (0.68)	0.22–0.58	55	−0.91 (0.99)	−1.18 to −0.64	$P = 0.0005$		NS**

*Two-sided Mann-Whitney test stratified to baseline values; Ref.: reference.

**Not applicable due to hierarchical design; NS: not significant; 95% CI: 95% confidence interval; *n*: number of patients.

Table 4: Change in symptom severity as assessed by total KMI in patient subgroups.

Treatment	n	Baseline	End of study	Absolute differences		Hierarchical test procedure*		
		Mean (SD)	Mean	Mean (SD)	95% CI	Step 1	Step 2	Step 3
Baseline KMI ≤ 20								
Placebo	9	17.7 (2.2)	29.9 (4.3)	12.2 (4.7)	8.58–15.86	Ref.	Ref.	
Low dose	10	18.4 (2.7)	13.0 (8.5)	−5.4 (8.3)	−11.35 to −0.55		$P < 0.001$	Ref.
High dose	10	17.3 (3.0)	6.8 (5.0)	−10.5 (4.4)	−13.65 to −7.35	$P < 0.001$		NS
21 ≤ baseline KMI ≤ 35								
Placebo	36	27.2 (3.6)	27.8 (8.1)	0.6 (7.8)	−2.01–3.23	Ref.	Ref.	
Low dose	41	28.7 (4.1)	19.1 (12.6)	−9.6 (11.5)	−13.23 to −5.99		$P < 0.001$	Ref.
High dose	32	27.5 (4.0)	9.7 (7.6)	−17.8 (8.6)	−20.87 to −14.70	$P < 0.001$		$P = 0.004$
Baseline KMI > 35								
Placebo	9	37.2 (1.1)	32.4 (7.7)	−4.8 (8.5)	−11.27–1.72	Ref.	Ref.	
Low dose	6	40.5 (3.5)	34.7 (13.0)	−5.8 (12.0)	−18.38–6.71		NS	Ref.
High dose	13	39.3 (2.4)	19.2 (10.7)	−20.1 (9.5)	−25.83 to −14.33	$P = 0.001$		$P = 0.022$**
Premenopausal								
Placebo	15	29.5 (6.4)	28.4 (8.9)	−1.1 (7.8)	−5.43–3.16	Ref.	Ref.	
Low dose	12	25.5 (8.6)	25.3 (12.3)	−0.2 (5.4)	−3.62–3.29		NS	Ref.
High dose	11	27.6 (9.5)	6.7 (6.3)	−20.9 (7.6)	−26.00 to −15.82	$P < 0.001$		$P = 0.001$**
Early postmenopausal								
Placebo	27	26.4 (6.8)	29.6 (6.7)	3.3 (7.9)	0.13–6.39	Ref.	Ref.	
Low dose	28	27.5 (6.0)	16.6 (12.7)	−11.0 (11.2)	−15.31 to −6.62		$P < 0.001$	Ref.
High dose	30	28.4 (7.2)	11.2 (9.0)	−17.2 (9.7)	−20.81 to −13.53	$P < 0.001$		$P = 0.039$
Late postmenopausal								
Placebo	12	26.6 (5.6)	28.1 (8.3)	1.5 (12.1)	−6.21–9.21	Ref.	Ref.	
Low dose	17	30.9 (6.5)	20.7 (13.6)	−10.2 (11.2)	−15.99 to −4.48		$P = 0.006$	Ref.
High dose	14	29.2 (8.9)	15.6 (9.8)	−13.6 (5.8)	−16.91 to −10.24	$P = 0.001$		NS

*Two-sided Mann-Whitney test stratified to baseline values; Ref.: reference; descriptive P values.
**Not applicable due to hierarchical design; NS: not significant; SD: standard deviation; 95% CI: 95% confidence interval; n: number of patients.

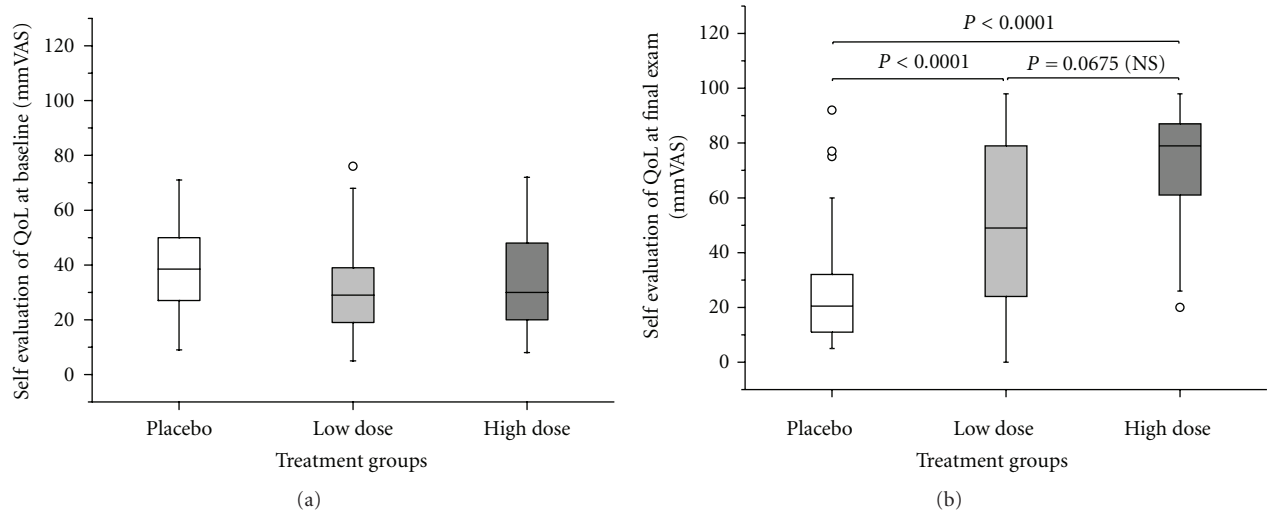

Figure 3: QoL assessment by VAS (a) at baseline and (b) after 12 weeks of treatment (ITT population, $n = 166$) with PLA, LD, and HD. Circles denote outliers. Two-sided Mann-Whitney test stratified to baseline scores.

the high dose reduced significantly the symptom score in patients at all menopausal stages; the LD was superior to placebo only in the early and late postmenopausal stage.

Nonetheless, there are some limitations. (a) Although the study duration was 3 months, a longer duration of 6–12 months would better meet the necessary long-term treatment of most women. This will be the subject of a future trial. (b) The question which menopause scale should be administered is an ongoing discussion. Although the comparison of the Menopause Rating Scale (MRS) with the KMI produced a high correlation of raw scores, the MRS, especially in its second version (MRS-II), is somehow favoured today [35, 36]. This might be due to its better appropriateness for factor analysis of symptom clusters and QoL measurements. Nonetheless, it is known that CR extracts are most effective for vasomotor symptoms therefore it seemed appropriate to use the KMI [28, 31]. Additionally, we tried to overcome this shortcoming with analysing the single symptoms next to total KMI score, giving a subgroup analysis and rating general QoL with the VAS.

The placebo response might have been low in the present study. However, also in other clinical trials in postmenopausal women, with a small number of visits, no reduction of the KMI was observed with placebo treatment [36, 37] as it was the case in the present study. On the other hand, higher placebo effects were observed in trials, where more patients visits had been performed (such as in [34]). This suggests that the study design might influence the placebo response.

The results of our current study partly confirm previous studies with other CR extracts [20, 23–26]. The age and BMI distribution of the patients are comparable to several previously conducted clinical studies with extracts from CR. Nevertheless, the study population is still small and may give predictions at best for middle-European women without heavy overweight. However, Liske et al. [25] have shown that two doses of an isopropanolic aqueous CR extract given for 24 weeks reduced significantly the symptom severity as assessed by KMI to a similar extent. In both treatment groups, total KMI decreased by about 50% from baseline scores of 30.5 (low dose) and 31 (high dose) to scores less than 15 in 70% and 72% of the patients, respectively. The responder rates were comparable to our study, where the rate of patients with at least a 50% decrease in total KMI was 69.1% in the HD group. In contrast to the study of Liske et al., however, we could clearly demonstrate for the first time a dose-dependent effect of a CR extract. The efficacy of other CR extracts was further shown by Osmers et al. [23] using a fixed dose of an isopropanolic extract and a placebo treatment during a 12-week period. In a further study of the same extract continued for 52 weeks, the effect on the number and intensity of hot flushes was confirmed [38] and, in addition, overall tolerability and endometrial safety were demonstrated. On the other hand, after a short-term, 4-week treatment in patients suffering from breast cancer, a similar CR extract demonstrated no superior effect when compared to placebo [39]. However, the extract used in the latter study was not sufficiently characterized and the duration of treatment was shorter than in previous studies [20, 23–26] that have demonstrated a significant reduction in the number and intensity of hot flushes. Additionally, the dose-effect relationship was not investigated. This underscores the difficulties in comparing clinical results between studies using different extracts with potentially different spectra of pharmacologically active constituents.

Whether the treatment effects of Ze 450 can be maintained for longer treatment periods is a subject for further research. Reported AEs did not raise safety concerns.

In conclusion, the CR extract, Ze 450, appears to be an effective and well-tolerated nonhormonal alternative to HRT for symptom relief in menopausal women.

Conflict of Interests

Juergen Drewe, Christian Zimmermann, and Catherine Zahner are employees of Max Zeller Söhne AG.

Acknowledgments

The authors thank the participating physicians for their valuable contributions: Ruediger Schellenberg, Wolf-Dietrich Kaiser, Roland Martin, and Ewald Schrader. The study was funded by Max Zeller Söhne AG.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 520198, 15 pages
doi:10.1155/2012/520198

Review Article

Traditional Oriental Herbal Medicine for Children and Adolescents with ADHD: A Systematic Review

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Received 23 July 2012; Revised 27 September 2012; Accepted 14 October 2012

Academic Editor: Jörg Melzer

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Objective. To evaluate the efficacy of traditional Oriental herbal medicines (TOHM) for children and adolescents with ADHD. *Methods*. Randomized clinical trials published from January 1, 1990, to December 31, 2010, in English, Chinese, Japanese, or Korean language which evaluated the use of TOHM on ADHD subjects of 18 years old or below, diagnosed based on DSM-IV, were searched from MEDLINE, EMBASE, PsyINFO, Cochrane Library, and 10 other databases. *Results*. Twelve studies involving 1189 subjects met the inclusion criteria. In general, the included studies claimed that TOHM has similar efficacy to methylphenidate and at the same time has fewer side effects compared to methylphenidate. Some studies also suggested that the effect of TOHM sustained better than methylphenidate. However, solid conclusions could not be drawn because the included studies were not of high quality. Risk of bias issues such as randomization, allocation, concealment and blinding were not addressed in most of the studies, and the risk of publication bias could not be ruled out. *Conclusion*. Currently, there is not strong evidence to say that TOHM is effective in treating the core symptoms of ADHD.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a behavioral disorder of which patients display persistent pattern of inattention and hyperactivity/impulsivity or a combination of the two at an abnormal level that their social, academic, or occupational functioning is impaired [1]. While the etiology of ADHD is not clearly known, studies have suggested that the abnormality of the frontal network and dysregulation of catecholamines are the underlying pathophysiology [2]. Frontal lobes are involved in decision making to convert impulse to action, attention, and concentration, and they are primarily activated by the catecholamines, dopamine, and norepinephrine [3]. When frontal lobes are not fully activated, or when there are changes in the levels of dopamine and norepinephrine, the symptoms of hyperactivity and inattention are likely.

When making a diagnosis of ADHD, clinicians should determine that the diagnostic criteria have been met by assessing information obtained from primarily parents, guardians, and teachers [4]. For adolescents, information from at least two teachers and other sources should be assessed because adolescents usually have multiple teachers and parents have little direct contact to observe their strengths and problems [4, 5]. Instruments such as the Revised Conners' Parent Rating Scale and Revised Conners' Teacher Rating Scale are useful for screening and assessing behavioral problems, and also helpful for assessing treatment effectiveness [6, 7].

Behavioral therapy and pharmacotherapy are two kinds of treatments commonly used in ADHD. Recommendation of treatment for ADHD varies depending on the patient's age. While evidence-based behavioral therapy is recommended as the first line of treatment for preschool-aged children (4-5 years of age), school-aged children (6–11 years of age) and adolescents (12–18 years of age) are recommended a combination of medication and behavioral therapy [4].

Stimulants are reported to be highly effective for most children in reducing the core symptoms of ADHD and thus are used as first line medication for ADHD patients [2, 4]. They are structurally similar to endogenous catecholamines

and are thought to work by enhancing dopaminergic and noradrenergic neurotransmission [2, 8].

Methylphenidate (Ritalin) is the most commonly used stimulant for the treatment of ADHD [2, 9]. Around 70% of ADHD patients who receive stimulant treatment are given methylphenidate [10]. It is shown to be effective, at least in short term, on improving the core symptoms of ADHD such as attention, distractibility, and impulsivity (effect size 0.75–0.84, mean 0.78). Methylphenidate has observable effects on improving social and classroom behavior (effect size 0.63–0.85, mean 0.8) [9]. Pemoline (Cylert) is a stimulant that is longer acting than methylphenidate, but due to its potential for hepatotoxicity, it is regarded as a third line treatment [2]. In some cases, nonstimulants are also used in the treatment of ADHD such as the norepinephrine specific reuptake inhibitors atomoxetine, and antidepressants such as Imipramine, Phenelzine, and Bupropion [2, 11] but have been found to have significant differences in terms of efficacy compared to stimulants [8].

While stimulants are effective for many children with ADHD, they may cause side effects, with the most common ones being decreased appetite, insomnia, and headache (Cohen's d 0.67, 0.40, and 0.33 resp.) [12]. Other side effects such as motor tics, abdominal pain, irritability, nausea, and fatigue are also reported [9]. Therefore, many parents of ADHD children try to search for more natural and safe treatment options [13, 14], which has resulted in a growing interest in complementary and alternative therapies (CAM), such as herbal remedies, dietary supplements, dietary modification, neurofeedback, homeopathic therapy, and chiropactic, in treatment of ADHD. Several surveys conducted on the use of CAM in ADHD showed over 50% of ADHD sufferers have used CAM [13, 15].

Herbal medicine is a treatment measure used in traditional Oriental medicine. Although herb usually refers to materials from plant sources, in respect of traditional Oriental medicine, herbal materials can be originated from plants, animals, or minerals. In this review, traditional Oriental herbal medicine (TOHM) is defined as medicine made by materials used under traditional Oriental medical theory. Herbal materials that are not documented in the Korean Pharmacopoeia, the Japanese Pharmacopoeia, Pharmacopoeia of the People's Republic of China, Zhong Hua Ben Cao, and Zhong Yao Da Ci Dian (Chinese Medical Great Dictionary) are considered outside the context of TOHM. TOHM should be taken orally and studies employing other route of administration, such as intravenous or transdermal, are excluded from this review.

Even though ADHD was not described in literature of traditional Oriental medicine, in traditional Oriental medical theory, ADHD is related to congenital deficiency or insufficient postnatal nourishment that leads to imbalances in the body. It is suggested that the disorder is related to the heart, the liver, the spleen, and the kidneys [16]. TOHM is believed to work by adjusting the inner imbalances of ADHD patients and thereby relieving the symptoms.

A study on ADHD using an animal model of spontaneous hypertensive rat treated with an Oriental herbal decoction comprised of Caulis Polygoni Multiflori (stem of *Polygonum multiflorum* Thunb.), Radix Rehmanniae Preparata (processed Rehmannia root), Carapax et Plastrum Testudinis (Carapace and plastron of *Chinemys reevsii* (Gray)), Os Draconis (fossilized bones), Radix Polygalae (Polygala root), and Rhizoma Acori Tatarinowii (Grassleaf Sweetflag Rhizome) showed that the decoction increased the amount of dopamine at the frontal cortex and corpus striatum [17], suggesting that its possible mechanism in ADHD is to increase dopamine level and thereby enhance catecholaminergic neurotransmission.

This review aims to evaluate the efficacy of TOHM as a treatment for ADHD in patients under the age of 18. TOHM is natural and often perceived to have fewer side effects than conventional ADHD pharmacotherapy. Various research and clinical studies have been conducted on TOHM's efficacy on ADHD, but very few articles review the evidence of efficacy of the treatment. A systematic review on complementary medicines for ADHD suggested that a Chinese herbal medicine may be effective for ADHD [18] however in the review only one study about Chinese herbal medicine was included and analyzed. Further compilation and analysis of currently available data about TOHM on ADHD may help to understand the true effect of the treatment on the disorders, and provide insight into the direction of future research.

2. Methods

2.1. Database Searching. English, Chinese, Korean and Japanese articles on randomized clinical trials (RCTs) of Oriental herbal treatment on ADHD published between January 1, 1990, and December 31, 2010, were searched from various databases. The details of search terms used in different databases are presented in the appendix. The following databases were searched:

(1) Cochrane Library,

(2) EMBASE,

(3) MEDLINE,

(4) AMED,

(5) CINAHL Plus,

(6) PsyINFO,

(7) SinoMed–CBM—Chinese Database,

(8) China Journal Net—Chinese Database,

(9) WanFang Data—Chinese Database,

(10) Oriental Medicine Advanced Searching Integrated System (OASIS)—Korean Database,

(11) Scholarly and Academic Information Navigator (CiNii)—Japanese Database,

(12) Database of Grants-in-Aid for Scientific Research (KAKEN)—Japanese Database,

(13) Japanese Institutional Repositories Online (JAIRO)—Japanese Database,

(14) Academic Research Database Repository (NII-DBR)—Japanese Database.

2.2. Reference List. Other than searching from databases, the reference lists of the included studies were referred to in order to identify more potential articles.

2.3. Criteria for Considering Studies for This Review

2.3.1. Type of Studies. Randomized clinical trials of TOHM. The efficacy of TOHM treatment should be compared to either a placebo or a conventional medication used for treating ADHD. If there was a baseline treatment, it had to be the same in both the treatment and control groups. Studies only comparing different TOHM formulae, or comparing TOHM with other traditional Oriental treatment such as acupuncture were excluded. Studies without indicating "randomized" were considered not randomized and excluded.

2.3.2. Type of Participants. Subjects under the age of 18 who were diagnosed with ADHD based on DSM-IV.

2.3.3. Type of Interventions. Traditional Oriental herbal medicine must be used. Herbs that are not documented in the Korean Pharmacopoeia, the Japanese Pharmacopoeia, Pharmacopoeia of the People's Republic of China, Zhonghua Bencao, and Zhongyao Dacidian were not considered. Other treatment measures of Oriental medicines such as acupuncture and moxibustion were excluded.

2.3.4. Types of Outcome Measures. The core symptoms of ADHD (hyperactivity, impulsivity, and inattention) were considered in this review. Core symptoms should be assessed by at least one of the following tools: Revised Conners' Parent Rating Scale, Revised Conners' Teacher Rating Scale, Conners' Hyperactivity Index, Conners' Abbreviated Symptoms Questionnaire, Conners' Global Index for Parents, and/or Conners' Global Index for Teachers.

2.4. Risk of Bias Assessment of Included Studies. The risk of bias of all the included studies was assessed according to Cochrane Handbook for Systematic Reviews of Invention version 5.1.0.

3. Results

The search came up with 1240 results, and 12 studies [16, 19–29] involving 1189 subjects were included in this review (see Figure 1 for included studies selection).

All of the studies included in this review were conducted in China as single-centre trials. Five results in Japanese and eighteen results in Korean were identified. Only one Japanese article was about a clinical trial; however the trial was not a randomized trial and was therefore not selected.

Among the twelve included studies, none included the information on how sample size was derived and whether the study was statistically powered. The length of study ranged from 4 weeks to 24 weeks. Six studies had follow-up observation on subjects, ranging from 2 weeks to 12 months after finishing treatment, to evaluate whether the intervention sustained effectiveness after treatment is stopped while the other six studies did not report if follow-up observations were conducted. Ten of the included studies reported homogeneity of baseline characteristics, but only seven [20, 22, 24, 26–29] showed relevant descriptive statistical data. Two studies [16, 19] did not report if baseline characteristics of subjects were homogenous. Only one of the studies [27] specified the subtype of ADHD subjects included in the study. Characteristics of included studies are summarized in Table 1.

3.1. Assessment of Risk of Bias. In general, the risk of bias in the included articles is unclear. Very limited information was revealed in the studies to enable the reviewers to tell if the included studies were at risk of bias.

Only one of the included studies [16] described how randomization was done, but the study used two randomization methods where part of the subjects were randomized using a random number table while part were allocated to the treatment or control groups by their patient record numbers. The allocation concealment issue was not addressed in any of the included studies.

The blinding method was also not addressed in most of the studies, and only two of the included studies [22, 26] claimed to be a double-blind trial. Li et al. (1999) described the blinding method, which was to include a placebo resembling methylphenidate in the treatment group and a placebo that looked like the corresponding TOHM in the control group. Wang et al. (2003) did not describe how blinding was done.

Most of the studies indicated no missing data. However, Ma et al. (2007) [25] did not specify the initial number of subjects so it could not be determined if there was any participant drop-out. Ma et al. (2007) [16] reported seven drop-outs but no explanations were provided, and it was unclear whether the drop-outs were from the treatment group or the control group. In another study [23], three subjects were excluded and there were five drop-outs, but the reasons were not sufficiently provided. Among those eight subjects, it is only known that four of the drop-outs were reported to have terminated the study due to adverse effect of methylphenidate. Those three studies were considered to have unknown risk of bias on incomplete outcome data.

Study protocols were not available for any of the included studies, therefore it could not be discerned whether all pre-specified outcomes were reported. Lai and Li (2006) [21] did not report the baseline score before treatment and score after treatment. Xu (2005) [27] did not report the baseline score of rating. The two studies were considered to have high risk of reporting bias.

The risk of bias graph and summary are presented in Figures 2 and 3, respectively.

3.2. Diagnosis and Assessment of the Disorder. Although all included studies specified the diagnostic criteria and method to assess treatment effect, only one study [16] specified who completed the rating questionnaire or did the rating assessment. None of the studies addressed under which setting the assessment was done. Also, the language of

Table 1: Selected studies characteristics.

Study	Method	Participants	Intervention	Outcomes
Cheng et al. 2006 [19]	Randomized Control Trial	*Treatment group* Number: 50, male/female: 39/11 Age range: mean 8.7 ± 1.5 *Control group* Number: 50, male/female: 40/10 Age range: mean 8.9 ± 1.4 Country: China Diagnostic criteria: DSM-IV Baseline characteristic: not described	*Treatment group* Yizhiyidong decoction 30 mL each time, 3 times a day for 12 weeks *Control group* Ritalin 5 mg–10 mg each time, twice a day for 12 weeks	The study defined treatment effect as follows: (i) Showing effectiveness—disappearance of symptoms, Conners index decrease ≥80%: treatment/control: 16/23 (ii) Showing improvement—improvement of symptoms, Conners index decrease 80%–50%: treatment/control: 21/18 (iii) Ineffective—no improvement or worsening in core symptoms, Conners index and studying: treatment/control: 13/9
Kong et al. 2007 [20]	Randomized Control Trial	*Treatment group* Number: 60, male/female: 44/16 Age range: mean 8.4 ± 1.42 *Control group* Number: 60, male/female: 48/12 Age range: mean 8.40 ± 1.40 Country: China Diagnostic criteria: DSM-IV Baseline characteristic: homogeneity for gender, age, and IQ	*Treatment group* Qijudihuang pill, 3 pills, 3 times a day for 3 months *Control group* Ritalin starting from 5mg and adjusted to 10 mg–20 mg for 3 months	There was no significant difference of treatment effectiveness between treatment group and control group. Followup 6 months and 12 months after treatment indicated that treatment had significantly more sustainable effect than control, and statistics showed that treatment group has significantly less side effects compared to control group.
Lai and Li 2006 [21]	Randomized Control Trial	Treatment/control: 21/19 Male/female: 24/16 Age range: 6–14 (mean 8.437 ± 2.061) Country: China Diagnostic criteria: DSM-IV Baseline characteristic: homogeneity for gender, age, and course of disease	*Treatment group* Oriental herbal medicine decoction 150 mL a day, 5 days a week for 8 weeks *Control group* Ritalin 0.3–0.5 mg/kg a day, 5 days a week for 8 weeks	The study defined treatment effect as follows: (i) Recovery—disappearance of core symptoms, Conners index decrease >80%, obvious improvement in studying, effectiveness sustains after stopping medication for 6 months: treatment/control: 2/1 (ii) Showing effectiveness—obvious alleviation of core symptoms, Conners index decrease >50%, improvement in studying: treatment/control: 10/9 (iii) Showing improvement—improvement of core symptoms, Conners index decrease >30%, improvement in studying but not stable: treatment/control: 7/6 (iv) Ineffective—no improvement or worsening in core symptoms, Conners index and studying: treatment/control: 3/3

Table 1: Continued.

Study	Method	Participants	Intervention	Outcomes
Li and Chen 1999 [22]	Randomized Control Trial	*Treatment group* Number: 37, male/female: 37/0 Age range: mean 10.7 ± 4.2 *Control group* Number: 33, male/female: 33/0 Age range: mean 10.3 ± 3.9 Country: China Diagnostic criteria: DSM-IV and Conners Rating Scale Baseline characteristic: Homogeneity for gender, age, course of disease, and IQ	*Treatment group* Duodongning granule 3 g for age <8, 6 g for age ≥8 daily with placebo that resembles Ritalin, 1 tablet each day, 6 days a week for 4 weeks *Control group* Ritalin 10 mg daily, with placebo that resembles Duodongning granule and same dosage as treatment group, 6 days a week for 4 weeks	The study defined treatment effect as follows: (i) Showing effectiveness—disappearance of core symptoms, Conners index <1.2, obvious improvement in studying, normal social function: treatment/control: 17/15 (ii) Showing improvement—improvement of core symptoms, Conners index decrease but still >1.5, improvement in studying and social function but not stable: treatment/control: 16/14 (iii) Ineffective—no evident improvement in core symptoms, Conners index, studying, and social function: treatment/control: 4/4 3 subjects in treatment group reported mild loss of appetite, while 7 subjects in control group reported evident loss of appetite and 1 subject reported sleeplessness.
Li et al. 2004 [23]	Randomized Control Trial	Treatment/control: 58/48 Male/female: 84/22 Age range: 7–15 Country: China Diagnostic criteria: DSM-IV Baseline characteristic: Homogeneity for age, gender, and course of disease There were 114 subjects originally, 3 excluded and 5 attrited. 4 were attrited due to adverse effect caused by methylphenidate but attrition/exclusion reason for other subjects was not indicated.	*Treatment group* Yizhiningshen granules 1 dose for age 7–10, 2 doses for age 10–15, twice a day for 6 weeks *Control group* Ritalin 5 mg per day for age 7–8, 10 mg per days for age 8–15, twice a day, 5 days a week for 6 weeks	The study defined treatment effect as follows: (i) Recovery—disappearance of core symptoms, Conners index decrease >80%, obvious improvement in studying, effectiveness sustains after stopping medication for 6 months, Chinese medicine therapeutic index ≥90%: treatment/control: 6/2 (ii) Showing effectiveness—obvious alleviation of core symptoms, Conners index decrease ≤80% and >50%, improvement in studying, Chinese medicine therapeutic index <90% and ≥60%: treatment/control: 20/18 (iii) Showing improvement—improvement of core symptoms, Conners index decrease ≤50% and >30%, improvement in studying but not stable, Chinese medicine therapeutic index <60% and ≥10%: treatment/control: 26/22 (iv) Ineffective—no improvement or worsening in core symptoms and studying, Conners index decrease ≤30%, Chinese medicine therapeutic index <10%: treatment/control: 6/6

Table 1: Continued.

Study	Method	Participants	Intervention	Outcomes
Lin et al. 2007 [24]	Randomized Control Trial	*Treatment group* Number: 40, male/female: 32/8 Age range: 6.5–13, mean 8.7 ± 2.7 *Control group 1* (*Ritalin*) Number: 40, male/female: 31/9 Age range: 7–12, mean 8.5 ± 2.5 *Control group 2* (*treatment + Ritalin*) Number: 40, male/female: 32/8 Age range: 7–11, mean 8.2 ± 2.1 Country: China Diagnostic criteria: DSM-IV Baseline characteristic: Homogeneity for gender, age, and course of disease	*Treatment group* Ningshen oral liquid 30–60 mL per day for 12 weeks *Control group 1* Ritalin 5 mg–40 mg per day for 12 weeks *Control group 2* Ningshen oral liquid 30–60 mL plus Ritalin 5 mg–40 mg per day for 12 weeks	The study defined treatment effect as follows: (i) Near recovery—disappearance of core symptoms, Conners index decrease >80%, obvious improvement in studying: treatment/control 1/control 2: 4/3/7 (ii) Showing effectiveness—obvious alleviation of core symptoms, Conners index decrease ≤80% and >50%, improvement in studying: treatment/control 1/control 2: 7/7/10 (iii) Showing improvement—improvement of core symptoms, Conners index decrease ≤50% and >30%, improvement in studying but not stable: treatment/control 1/control 2: 16/19/17 (iv) Ineffective—no improvement or worsening in core symptoms and studying, Conners index decrease ≤30%: treatment/control 1/control 2: 13/11/6 Assessment of Conners index 12 weeks after stopping medication reported that there was significant drop in effectiveness in Ritalin control group but not in treatment group and combined treatment group.
Ma 2007 [16]	Randomized Control Trial	*Treatment group* Number: 22, male/female: 15/7 *Control group* Number: 20, male/female: 20/16 Age range: 6–13 Country: China Diagnostic criteria: DSM-IV Baseline characteristic: not described There were originally 49 subjects in the study and 7 cases were attrited, but there was no indication of whether they belonged to treatment group and control group. Reasons for attrition were also not sufficiently presented	*Treatment group* Duodongting decoction 150 mL each time for age 4–7, 200 mL each time for age 8–12, twice a day for 28 days, and break for 2 days (1 treatment cycle) before starting another treatment cycle, for 2 cycles + behavioral therapy *Control group* Ritalin 0.45 mg/kg for 28 days and break for 2 days (1 treatment cycle) before starting another treatment cycle, for 2 cycles + behavioral therapy	The study defined treatment effect as follows: (i) Showing effectiveness—hyperactivity, and inattention alleviated by 2/3: treatment/control: 7/6 (ii) Showing improvement—obvious symptomatic improvement, hyperactivity and inattention alleviated by 1/2: treatment/control: 11/10 (iii) Ineffective—no symptomatic relief after 2 treatment cycles treatment/control: 4/4

Table 1: Continued.

Study	Method	Participants	Intervention	Outcomes
Ma et al. 2007 [25]	Randomized Control Trial	Treatment group/control group-Chinese medicine/control group-Ritalin: 55/53/51 Country: China Diagnostic criteria: DSM-IV Baseline characteristic: homogeneity for age, gender, and course of disease Attrition criteria was mentioned but there was no indication if any subject was attrited because initial number of subjects randomized was not stated	*Treatment group* YIzhiningshen granules 10 g each time for age 6–10, 15 g each time for age 11–18, twice a day for 24 weeks *Control group 1-Chinese medicine* Jingning oral liquid 10 mL each time, twice a day, 5 days per week for 24 weeks *Control group 2-Ritalin* Ritalin 5 mg each time for age 6–8, and 10 mg each time for age 9–18, twice a day, 5 days per week for 24 weeks	The study defined treatment effect as follows: (i) Recovery—disappearance of core symptoms, Conners index decrease >80%, obvious improvement in studying and social function, Chinese medicine therapeutic index ≥90%: treatment/control 1/control 2: 6/3/3 (ii) Showing effectiveness—obvious alleviation of core symptoms, Conners index decrease ≤80% and >50%, improvement in studying and social function, Chinese medicine therapeutic index <90% and ≥60%: treatment/control 1/control 2: 29/18/19 (iii) Showing improvement—improvement of core symptoms, Conners index decrease ≤50% and >30%, improvement in studying but not stable, Chinese medicine therapeutic index <60% and ≥10%: treatment/control 1/control 2: 15/27/22 (iv) Ineffective—no improvement or worsening in core symptoms and studying, Conners index decrease ≤30%, Chinese medicine therapeutic index <10%: treatment/control 1/control 2: 5/5/7
Wang and Shi 2003 [26]	Randomized Control Trial	*Treatment group* Number: 58, male/female: 49/9 Age range: mean 9.3 ± 2.9 *Control group* Number: 50, male/female: 42/8 Age range: mean 9.5 ± 3.2 Country: China Diagnostic criteria: DSM-IV and Conners index >1.5 Baseline characteristic: homogeneity for age, gender, course of disease, and IQ	*Treatment group* Jingning oral liquid 10 mL each time, twice a day for 4 weeks *Control group* Ritalin 10 mg in the morning and 5 mg at night for 4 weeks	The study defined treatment effect as follows: (i) Showing effectiveness—disappearance of symptoms, obvious improvement in social function and studying, Conners index < 1.2: treatment/control: 27/23 (ii) Showing improvement—improvement of symptoms, improvement in social function and studying but improvement not stable, decrease in Conners index but still >1.5: treatment/control: 26/22 (iii) Ineffective—no improvement or worsening in symptoms, Conners index and studying: treatment/control: 5/5 No side effects observed in treatment group but 10 subjects in control group reported nausea and loss in appetite, 2 subjects reported dizziness, and 1 subject reported sleeplessness.

Table 1: Continued.

Study	Method	Participants	Intervention	Outcomes
Xu 2005 [27]	Randomized Control Trial	*Treatment group* Number: 100, male/female: 87/13 Age range: mean 9.3 ± 2.4 *Control group* Number: 50, male/female: 43/7 Age range: mean 9.1 ± 2.3 Country: China Diagnostic criteria: DSM-IV criteria of combined type ADHD Baseline characteristic: homogeneity for age, gender, course of disease, and IQ	*Treatment group* Jingningzhidong granules 1 g/kg/day, maximum 50 g, for 12 weeks *Control group* Ritalin 0.3 mg/kg/day, increase dosage gradually to maximum 0.6 mg/kg/day, for 12 weeks	The study defined treatment effect as follows: (i) Showing effectiveness—decrease in Conners index by ≥66%: treatment/control: 56/26 (ii) Showing improvement—decrease in Conners index ≥33% and <66%: treatment/control: 22/14 (iii) Ineffective—decrease in Conners index < 33%: treatment/control: 22/10 There was almost no side effect reported in treatment group but subjects in control group reported more obvious and persistent side effects. Assessment of Conners index 4 weeks after stopping medication reported that there was significant drop in effectiveness in control group but not in treatment group.
L. Yang and J. Yang 2005 [28]	Randomized Control Trial	*Treatment group* Number: 48, male/female: 40/8 Age range: 6–12 (mean 8.3) *Control group* Number: 38, male/female: 31/7 Age range: 6.5–13 (mean 8.6) Country: China Diagnostic criteria: DSM-IV Baseline characteristic: Homogeneity for gender, age, course of disease, and coexisting symptoms	*Treatment group* Yizhiningshen oral liquid 2 × 10 mL, 3 times a day for 3 months + behavioral therapy *Control group* Ritalin 10 mg, once per day for 3 months, no medication during weekend and holiday + behavioral therapy	The study defined treatment effect as follows: (i) Recovery—disappearance of core symptoms, Conners index decrease >80%, obvious improvement in studying, effectiveness sustains after stopping medication for 6 months: treatment/control: 6/2 (ii) Showing effectiveness—obvious alleviation of core symptoms, Conners index decrease >50%, improvement in studying: treatment/control: 16/15 (iii) Showing improvement—improvement of core symptoms, Conners index decrease >30%, improvement in studying but not stable: treatment/control: 20/17 (iv) Ineffective—no improvement or worsening in core symptoms, Conners index and studying: treatment/control: 6/4 Treatment group showed improvements in co-existing symptoms such as loss in appetite, recurrent flu, but no evident improvement in control group.

Table 1: Continued.

Study	Method	Participants	Intervention	Outcomes
Yu and Wang 2005 [29]	Randomized Control Trial	*Treatment group* Number: 68, male/female: 54/14 Age range: mean 9.1 ± 2.8 *Control group* Number: 20, male/female: 15/5 Age range: mean 9.3 ± 2.7 Country: China Diagnostic criteria: DSM-IV and Conners index > 1.5 Baseline characteristic: homogeneity for age, gender, and course of disease	*Treatment group* Jingning decoction one dose per day for 3 months *Control group* Ritalin 0.2–0.5 mg/kg/day for 3 months	The study defined treatment effect as follows: (i) Showing effectiveness—disappearance of symptoms, obvious improvement in social function and studying, Conners index < 1.2: treatment/control: 42/15 (ii) Showing improvement—improvement of symptoms, improvement in social function and studying but improvement not stable, decrease in Conners index but still >1.5: treatment/control: 19/3 (iii) Ineffective—no improvement in symptoms, Conners index and studying: treatment/control: 7/2

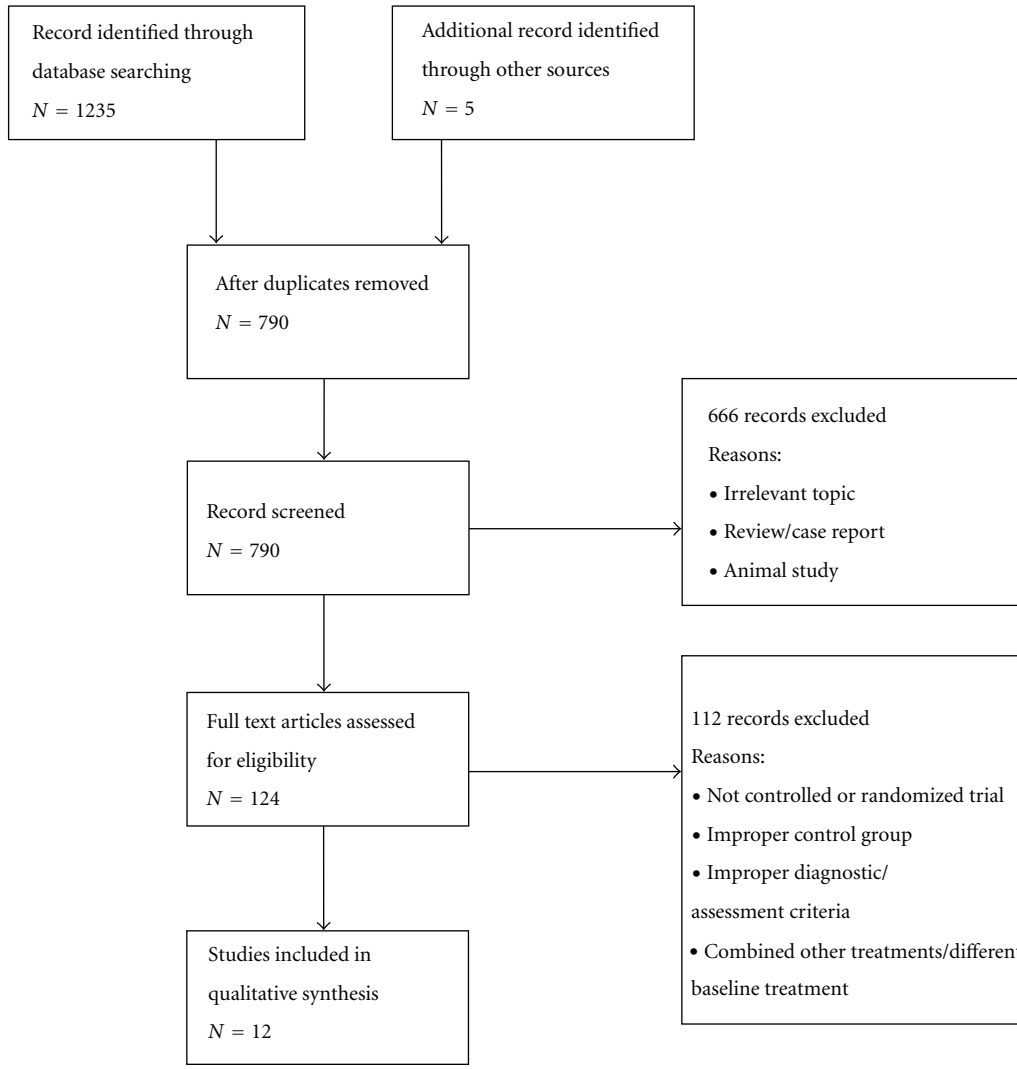

Figure 1: Selection of studies flowchart.

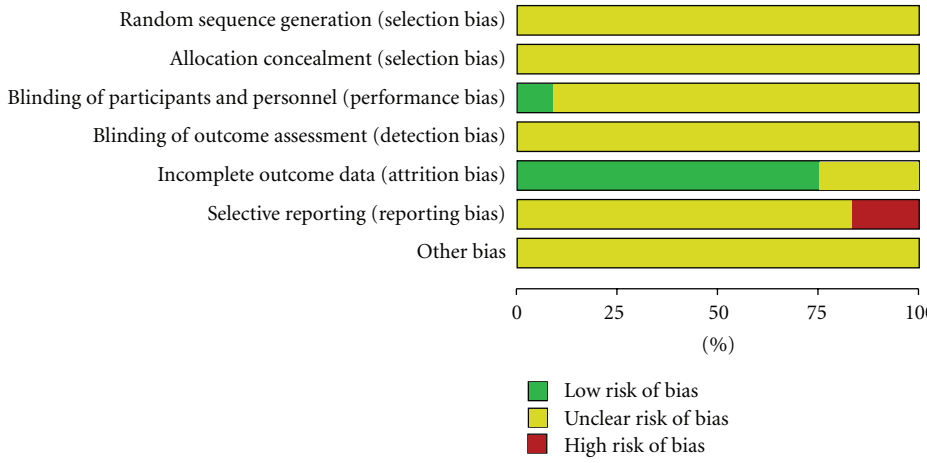

Figure 2: Risk of bias graph of the included studies.

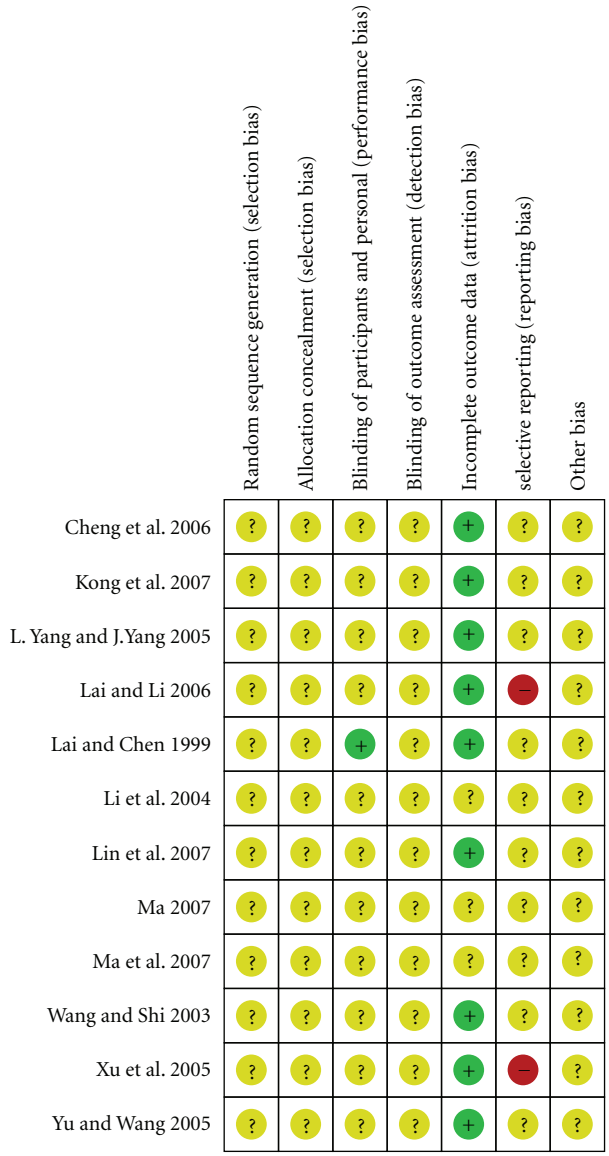

Figure 3: Risk of bias summary of the included studies. −: high risk of bias, +: low risk of bias, ?: unknown risk of bias.

assessment tools was not specified. It was not clear if the assessment tools were validated in cases where they were translated into another language.

3.3. Treatment Effectiveness. The herbal formulae used in the included twelve studies varied, and dosage forms of decoction, granules, oral liquids, pill, and so forth were used. Nine studies [16, 19–22, 25, 27–29] provided the ingredients of the formulae, but among them five [22, 25, 27–29] did not specify the amount of each herb used in the formula, and therefore there was very little information on drug to extract ratio. Three studies [23, 24, 26] did not provide the formula at all. None of the studies mentioned how the herbal medicines used were standardized. The details of the herbal ingredients used in the included studies, their dosage form, and daily dose are presented in Table 2.

Among the twelve studies, there were ten 2-arm studies [16, 19–23, 26–29] that compared the effectiveness of TOHM to methylphenidate, and one 3-arm study [24] which included a TOHM treatment group, a TOHM control group, and methylphenidate control group. These studies claimed that TOHM had no significant difference on effectiveness compared to methylphenidate. However, seven of them [16, 21, 22, 26–29] did not conduct statistical analyses to demonstrate whether there was significant efficacy compared to the baseline.

The remaining one of the twelve included studies [24] evaluated the net effect of TOHM by having a combined treatment group of TOHM and methylphenidate, and a methylphenidate control group. The study reported that TOHM and methylphenidate worked better in combination than methylphenidate alone, with statistically significant differences when comparing the rate of effectiveness of the two groups.

3.4. Follow-Up Observation on Effectiveness. Among the included studies, six had follow-up observations to evaluate the sustainability of treatment effect of core symptom after stopping medication, while the other six studies did not specify if follow-up observation was done. The follow-up period varied from 2 weeks to 12 months after stopping the treatment. For the six studies with follow-up observation, five [20, 23, 24, 27, 28] compared the treatment effect of TOHM and methylphenidate after stopping medication and all reported the effect of TOHM sustained better compared to methylphenidate. The remaining one [25] only followed up on the effect of the TOHM treatment group.

3.5. Safety and Side Effects. In general, TOHM was claimed to have fewer side effects than methylphenidate. Eight of the included studies [19–24, 27, 28] discussed side effects. In general, more cases of side effect were reported in the methylphenidate control group than the TOHM treatment group. Two studies [26, 28] reported no cases of side effect in the TOHM treatment group. Cheng et al. (2006) reported that among the side effect cases in their study, dry mouth, sweating, nausea, weight loss, loss of appetite, and headache were significantly fewer in the TOHM treatment group compared to the methylphenidate control group ($P < 0.05$) [19]. Lai and Li (2006) reported that cases of loss of appetite and drowsiness were significantly fewer ($P < 0.05$) [21]. Lin et al. (2007) reported that cases of sleeplessness, dizziness/headache, sweating, dry mouth, nausea, loss of appetite, weight loss, and constipation were significantly fewer in the treatment group than the control group ($P < 0.01$) [24]. Xu (2005) compared the average score of Treatment Emergent Symptoms Scale (TESS) in the treatment group and the control group, and reported that the average score was significantly higher in the control group ($P < 0.01$) [27]. Four other studies [19, 20, 22, 26] also claimed to have used TESS to evaluate side effects but scores were not reported.

Three studies [16, 25, 28] performed liver function tests, renal function tests, and/or ECGs on subjects after treatment

Table 2: Details of the herbal treatments used in the included studies.

Cheng et al. 2006 [19]	*Ingredients and amount*: Radix Rehmanniae Preparata 6 g, Carapax et Plastrum Testudinis 5 g, Cervi Cornu Degelatinatum 5 g, Rhizoma Acori Tatarinowii 10 g, Radix Polygalae 10 g, Radix et Rhizoma Salviae Miltiorrhizae 10 g, Fructus Schisandrae Chinensis 5 g *Dosage form*: Decoction. The above amount of ingredients are boiled with water to yield 90 mL of decoction. *Daily dose*: 90 mL *Standardization*: not known
Kong et al. 2007 [20]	*Ingredients and amount*: Fructus Lycii 9 g, Flos Chrysanthemi 9 g, Radix Rehmanniae Preparata 24 g, Fructus Corni 12 g, Rhizoma Dioscoreae 12 g, Rhizoma Alismatis 9 g, Cortex Moutan 9 g, Poria 9 g *Dosage form*: Pills. It was not clear how many pills were made out of the above amount of herbs. *Daily dose*: 9 pills *Drug to extract ratio*: not known *Standardization*: not known
Lai and Li 2006 [21]	*Ingredients and amount*: Os Draconis 20 g, Carapax et Plastrum Testudinis 10 g, Radix Polygalae 5 g, Rhizoma Acori Tatarinowii 10 g, Fructus Tritici Levis 20 g, Radix Ophiopogonis 10 g, Caulis Polygoni Multiflori 15 g, Radix *Codonopsis* 15 g, Poria 15 g, Radix Rehmanniae Preparata 15 g, Fructus Schisandrae Chinensis 4 g, Radix et Rhizoma Glycyrrhizae 4 g. Depending on the symptoms of different patients, other herbs might be added but the amount was not specified. *Dosage form*: Decoction. 150 mL of decoction was made from the above ingredients. *Daily dose*: 150 mL *Standardization*: not known
Li and Chen 1999 [22]	*Ingredients and amount*: Fructus Lycii, Radix Rehmanniae Preparata, Fructus Schisandrae Chinensis, Radix et Rhizoma Ginseng, Poria, Radix et Rhizoma Glycyrrhizae. Amount was not specified. *Dosage form*: Granules *Daily dose*: 3 g or 6 g depending on the age of subject *Drug to extract ratio*: not known *Standardization*: not known
Li et al. 2004 [23]	*Ingredients and amount*: not known *Dosage form*: Granules *Daily dose*: 2 doses or 4 doses depending on the age of subject. Amount of granules contained in 1 dose was not specified. *Drug to extract ratio*: not known *Standardization*: not known
Lin et al. 2007 [24]	*Ingredients and amount*: not known *Dosage form*: oral liquid *Daily dose*: 30–60 mL *Drug to extract ratio*: not known *Standardization*: not known
Ma 2007 [16]	*Ingredients and amount*: Flos Magnoliae 10 g, Radix Paeoniae Alba (parched) 30 g, Rhizoma Gastrodiae 8 g, Radix Isatidis 15 g, Radix Scrophulariae 15 g, Massa Medicata Fermentata 6 g, Fructus Crataegi 6 g *Dosage form*: Decoction. The amount of decoction yielded from the above ingredients was not specified. *Daily dose*: 150 mL or 200 mL depending on the age of subject *Drug to extract ratio*: not known *Standardization*: not known
Ma et al. 2007 [25]	*Ingredients and amount*: Homonis Placenta, Radix Rehmanniae Preparata, Rhizoma Acori Tatarinowii, Radix Polygalae, Rhizoma Alismatis, Rhizoma Coptidis, and so forth. Amount was not specified. *Dosage form*: Granules *Daily dose*: 20 g or 30 g depending on the age of subject *Drug to extract ratio*: not known *Standardization*: not known
Wang and Shi 2003 [26]	*Ingredients and amount*: not known *Dosage form*: Oral liquid *Daily dose*: 20 mL *Drug to extract ratio*: not known *Standardization*: not known
Xu 2005 [27]	*Ingredients and amount*: Radix Bupleuri, Radix Peoniae Alba, Ramulus cum Uncis Uncariae, Os Draconis, Margaritifera Concha, Radix Pseudostellariae, Fructus Alpiniae Oxyphyllae, Radix Polygalae, Rhizoma Acori Tatarinowii, Fructus Schisandrae Chinensis, Poria, Radix et Rhizoma Glycyrrhizae Preparata. Amount was not specified. *Dosage form*: Granules. 1 g of granules is equivalent to 5 g of herbs. *Daily dose*: up to 50 g depending on the body weight of subject *Standardization*: not known

Table 2: Continued.

L. Yang and J. Yang 2005 [28]	*Ingredients and amount*: Radix Rehmanniae Preparata, Radix Astragali, Radix Peoniae Alba, Os Draconis, Radix Polygalae, Rhizoma Acori Tatarinowii, Fructus Schisandrae Chinensis, Rhizoma Atractylodis Macrocephalae. Amount not specified. *Dosage form*: Oral liquid *Daily dose*: 60 mL *Standardization*: not known
Yu and Wang 2005 [29]	*Ingredients and amount*: Rhizoma Coptidis, Pericarpium Citri Reticulatae, Rhizoma Pinelliae Preparatum, Poria, Rhizoma Atractylodis Macrocephalae, Radix Peoniae Alba, Ramulus cum Uncis Uncariae, Flos Chrysanthemi, Radix Polygalae, Fructus Alpiniae Oxyphyllae, Fructus Corni. Amount was not specified. Other herbs might be added depending on the symptoms of individual subject but the exact ingredients and amount were not given. *Dosage form*: Decoction *Daily dose*: 1 dose. The amount of 1 dose was not specified. *Drug to extract ratio*: not known *Standardization*: not known

and results showed that subjects had no impairment on liver function, renal function, and/or cardiac function after treatment with TOHM and methylphenidate, suggesting that both TOHM and methylphenidate do not cause any significant safety concern on treatment of ADHD, at least in the short term.

4. Discussion

This review included twelve studies, and though findings of this review suggested that the herbal preparations covered under the term TOHM may be effective in treating the core symptoms of ADHD; the overall evidence is not strong enough to draw solid conclusions, because in general the clinical trials were not of high quality and the herbal preparations far too different. Additionally, it cannot be ruled out that there is possibility of publication bias.

The included studies that discussed side effect issues all suggested that TOHM had fewer side effects compared to methylphenidate. However, such result should be interpreted with caution, because first of all it was not clear whether the side effect cases, both in the TOHM group and the methylphenidate group, were investigated to find out if they were related to the intervention. Secondly, it was not addressed in most studies whether blinding was done. As mentioned, since TOHM is indigenous to the study population, and is often perceived as natural with fewer side effects, if measures are not properly done to blind subjects from knowing what treatment they are getting, it may cause bias in reporting side effects.

In the future, should more clinical trials on ADHD using TOHM as treatment be conducted, clinical investigators should consider to address the issues discussed below in order to improve the robustness of data.

In the diagnosis of ADHD and assessment of treatment efficacy, tools such as rating scales are often used. In order to make precise assessment, information should be obtained from different parties including parents, guardians, and teachers under different settings, such as home and school [4]. However, among the included studies, eleven of them did not specify who completed the questionnaires for assessment or under which setting the assessment was done. It was difficult to tell whether sufficient information was obtained to facilitate an accurate assessment of the treatment effect. Also, since the studies were done in Chinese population, it was possible the questionnaires used were in Chinese, but no information was available to tell whether the questionnaires, in case written in another language, were validated or not. Investigators did not indicate whether the tool of assessment has been modified to suit the study purpose as well. Such information should be described in the study methods.

Among the included studies, the herbal medicines themselves varied. Some of the studies did not tell what herbs were used, some did not specify the amount of herbs used, and the treatment dosage was not clear in some studies. Also, the treatment period varied for each study. Due to such heterogeneity, it is not possible to deduce from the data which herbal formulae or ingredients may be effective for ADHD, nor to conclude that TOHM is effective for ADHD in children and adolescents. Although it is inevitable that different studies may use different herbs and have different treatment periods, the materials used and the amount should be stated clearly in the publication of clinical trial results. As various herbal treatments are used in different clinical studies the results even of the positive studies cannot be compared. Clinical investigators may have to consider repeating a study with the same herbal treatment, or to conduct a clinical trial in multiple sites.

Due to the complex nature of herbs, how the consistency of herbal treatment is maintained throughout a clinical study is often an issue to consider. Most of the studies included in this review used the herbal treatment substances in form of decoctions or other preparations such as granules or oral liquid prepared by the clinical sites. It was not addressed how the consistency of treatment substances was kept throughout the studies, or how the treatment substances were standardized to ensure quality. In addition, in three of the studies [16, 21, 29], prescriptions given to subjects varied according to their symptoms. Although one of the characteristics of traditional Oriental medicine is tailor-made treatment according to the patient's condition, in a clinical study setting, this may introduce confounding variables. Investigators should make an effort to ensure the herbal treatment used in a study is of consistent quality

throughout the study period. One of the possible ways to address this problem is to use herbal medicines prepared by qualified pharmaceutical manufacturers, and the treatment preparation should also be standardized.

4.1. Strength of This Review . In this review, the reviewers performed a thorough search in various databases. Other than major databases that have information of articles published mostly in English, additional Chinese, Korean, and Japanese databases were searched to identify potential studies. Articles written in English, Chinese, Korean, and Japanese languages were screened in order to include as many suitable studies in the review as possible.

4.2. Limitation of This Review. Due to limited resources, the reviewers could only seek published studies. For a robust review, nonpublished data should also be sought. Also, the reviewers were not able to contact the authors of included studies for clarification and further information on their studies.

Even though the reviewers did a thorough search of published studies, the included studies were all conducted on Chinese population. Little could be told about the effect of TOHM on ADHD on populations of other countries .

5. Conclusion

This review included twelve studies on different herbal preparations from TOHM as a treatment for children and adolescents with ADHD. Findings suggest that some of them may have similar efficacy to methylphenidate, but solid conclusions could not be drawn due to quality problems of the clinical trials. In conclusion, currently there is no strong evidence to suggest that TOHM is effective in treating the core symptoms of ADHD. More studies with low risk of bias and using the same herbal preparation are required before further conclusions can be drawn.

Appendix

Search Terms Used in Different Databases

Cochrane Library, EMBASE, MEDLINE, AMED, CINAHL Plus, PsyINFO. ADHD (or attention-deficit/hyperactivity disorder or hyperkinetic disorder or minimal brain dysfunction) and alternative medicine (or complementary medicine or Chinese medicine or kampo or Korean medicine or Oriental medicine or phytotherapy or herbal).

SinoMed (CBM), China Journal Net, WanFang Data—Chinese Databases

(1) ADHD and Chinese medicine (in Chinese).

(2) Attention-deficit/hyperactivity disorder (in Chinese) and Chinese medicine (in Chinese).

(3) Hyperactivity (in Chinese) and Chinese medicine (in Chinese).

(4) Minimal brain dysfunction (in Chinese) and Chinese medicine (in Chinese).

(5) Hyperkinetic disorder (in Chinese) and Chinese medicine (in Chinese).

Oriental Medicine Advanced Searching Integrated System (OASIS)—Korean Database

(1) ADHD.

(2) Attention-deficit/hyperactivity disorder (in Korean).

Scholarly and Academic Information Navigator (CiNii), Database of Grants-in-Aid for Scientific Research (KAKEN), Japanese Institutional Repositories Online (JAIRO), Academic Research Database Repository (NII-DBR)—Japanese Databases

(1) ADHD and Kampo (in Japanese).

(2) Attention-deficit/hyperactivity disorder (in Japanese) and Kampo (in Japanese).

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 508623, 8 pages
doi:10.1155/2012/508623

Research Article

Depression, Comorbidities, and Prescriptions of Antidepressants in a German Network of GPs and Specialists with Subspecialisation in Anthroposophic Medicine: A LongitudinalObservational Study

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Received 12 July 2012; Accepted 8 October 2012

Academic Editor: Jörg Melzer

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Background. Depression is a major reason for counselling in primary care. Our study aims at evaluating pharmacological treatment strategies among physicians specialised in anthroposophic medicine (AM). *Methods*. From 2004 to 2008, twenty-two German primary care AM-physicians participated in this prospective, multicentre observational study. Multiple logistic regression was used to determine factors associated with a prescription of any antidepressant medication. *Results*. A total of 2444 patients with depression were included (mean age: 49.1 years (SD: 15.4); 77.3% female). 2645 prescriptions of antidepressants for 833 patients were reported. Phytotherapeutic preparations from *Hypericum perforatum* were the most frequently prescribed antidepressants over all (44.6% of all antidepressants), followed by amitriptyline (16.1%). The likelihood of receiving an antidepressant medication did not depend on comorbidity after controlling for age, gender, physician specialisation, and type of depression (adjusted OR (AOR) = 1.01; CI: 0.81–1.26). Patients who had cancer were significantly less likely to be prescribed an antidepressant medication than those who had no cancer (AOR = 0.75; CI: 0.57–0.97). *Conclusion*. This study provides a comprehensive analysis of everyday practice for the treatment of depression in AM -physicians. Further analysis regarding the occurrence of critical combinations is of high interest to health services research.

1. Background

Depression is one of the three leading causes of disease burden worldwide strongly correlated with increased morbidity and a major reason for counselling and primary patient care [1, 2]. Depending on the study origin and setting, the prevalence of depression in the general population is estimated between 10% and 25% in females and 5–12% in males with a one-year incidence rate of approximately 2% [3–5]. Thus, early detection and treatment of depression is a major task for health care policy makers. Due to increasing patient numbers and the development of new antidepressive drugs, family physicians today play an important role in the treatment of depressed patients [6, 7]. Although approximately 40% of patients with depression still remain untreated, those patients who decide to consult a therapist are more likely to see a family physician than a psychiatric specialist for both diagnosis and treatment. This is quite important as knowledge and accuracy of nonpsychiatric physicians in treating depression have a great influence the outcome of the illness.

Although research has significantly advanced in the last years, and depression is now generally more acknowledged as an important factor in primary care, patients, relatives,

and physicians still have reservations and prejudices against pharmaco- or psychotherapy, which may aggravate a sufficient and individualized treatment of depression in primary care and may account for insufficient treatment of depressive symptoms [7]. Studies have shown that only a small amount of primary care patients diagnosed with depression receive appropriate care, which may further lead to poor treatment outcome and increased mortality [4, 7].

Accordingly, national guidelines about depression treatment in primary care are a key area of public policy. In Germany that is, the development of a German National Disease Management Guideline (DM-CPG) for depression was induced to increase transparency and improve patient care [6, 8, 9].

With respect to complementary and alternative medicine (CAM), guidelines from Germany, Canada, and Switzerland have listed the phytopharmaceutical preparation of *Hypericum perforatum* [6, 10, 11] which is traditionally used quite frequently for mild and moderate depressions. Moreover its effectiveness for unipolar depressive episodes was shown in systematic reviews and meta-analyses [12, 13]. But also other drugs from phytotherapy or homoeopathy may have a potential in the treatment of depression [14, 15]. However, the prescribing of antidepressants is influenced by physician—as well as patient–related factors, and less is known about prescribing habits of physicians in primary care particularly of those being specialized in CAM.

The present study, thus, aims to analyse prescribing patterns in a network of GPs and specialists with subspecialisation in anthroposophic medicine (AM) for patients who experienced a new episode of depression and to investigate conformity and variations in antidepressant prescriptions. It was hypothesized that (a) *Hypericum perforatum* was the most frequently prescribed antidepressant and (b) that patients with co-morbidities were more likely prescribed any antidepressant medication.

2. Methods

Physicians for the EvaMed Network were recruited through the German National Association of Anthroposophic Physicians (GAÄD) in 2004 [16]. At that time, 118,085 primary care physicians were practising in Germany. Of those, 626 (0.5%) primary care physicians were members of the GAÄD. For a physician to be eligible to participate in the study, his or her medical practice had to meet a number of technical requirements, including the presence of a special computerized patient documentation system (DocExpert, DocConcept, TurboMed, Duria, PDE-Top, and Medistar), a local area network (LAN) connection, and Microsoft Windows and Internet Explorer (i.e., as client software). From the 626 physicians of the GAÄD, 362 (57.8%) met these criteria based on self-reported information and were contacted. Physicians were required to give their informed consent to participate in the EvaMed Network and to report all detected serious ADRs (definition provided below "data collection and classification of ADRs") to the EvaMed Network. A total of 38 physicians from 12 of the 16 federal German states finally agreed to participate in EvaMed, covering 6.1% of the overall primary care physicians of the GAÄD [17]. They all had practised for at least five years in primary care in addition to completing training in anthroposophic medicine.

For our study, 16 physicians specialized in paediatrics, dermatology, and gynaecology were excluded from the study which led to 22 physicians who participated in this study.

The present study is based on secondary data provided by the physicians. As such, the recommendations for good practice in secondary data analysis (e.g., anonymization of data on prescriptions and diagnoses) were developed by the German Working Group on the Collection and Use of Secondary Data were applied in full [18].

Patients were included if they had at least one diagnosis of depression according to the 10th revision of the International Classification of Diseases (ICD10: F32 or F33) during a 5-year study period (01·01·2004–01·01·2009). Patients were excluded if patients were <18 years of age. Patients were also excluded if there was no new diagnosis of depression during the study period. "New diagnosis" of depression was operationally defined as having no diagnosis of depression before and no prescription of any antidepressant medication during the 6 months preceding the index diagnosis. Patients who had no office visit before the index depression diagnosis were also excluded because it was not able to distinguish, whether the index diagnosis represented either a new diagnosis of depression or the entry of an established diagnosis of depression for a new patient. Finally, we also excluded patients with a recorded diagnosis of mania (F30), bipolar disorder (F31), or schizophrenia (F20) because it was thought that these patients would be treated differently.

During the study, physicians continued to follow their routine documentation procedures, recording diagnoses, and all prescriptions for each consecutive patient using their existing computerized patient documentation system. These data were exported to the QuaDoSta postgreSQL database hosted in each practice [19]. Physicians used a browser-based interface to match individual diagnoses with the corresponding drugs or remedies that had been prescribed. Prescribed drugs were documented using the German National Drug Code. Diagnoses were coded according to the 10th revision of the International Classification of Diseases (ICD-10).

Depression was classified as "depressive episode" (ICD10: F32) or "recurrent depressive disorder" (ICD10: F33). Co-morbidities were classified as coronary heart disease (ICD10: I20-I25), cerebrovascular disease (ICD10: I60-I69), diabetes mellitus (ICD10: E10-E14), cancer (ICD10: C00-C97), congestive heart failure (ICD10: I50), and chronic obstructive pulmonary disease (COPD; ICD10: J44). Multi-morbidity was considered if a patient had at least two co-morbidities.

Study investigators identified all drugs and remedies prescribed for depression. Each substance was classified using the Anatomical Therapeutic Chemical Index German version (ATC). Antidepressant medication was clustered into non-selective monoamine reuptake inhibitors (NSMRIs; ATC: N06AA), selective serotonin reuptake inhibitors (SSRIs; ATC: N06AB), monoamine oxidase inhibitors (MAOIs; ATC: N06AF), non-selective monoamine oxidase A inhibitors (ATCs: N06AG), other antidepressants (e.g., bupropion,

mirtazapine, and nefazodone; ATC: N06AX), and phytotherapeutic antidepressants (N06APs).

Statistical analysis was performed with SPSS 18.0 for Windows. Descriptive analysis was used to determine prescription rates. Means and standard deviations (SDs) were calculated for continuous data. In cases where data were not normally distributed, medians and interquartile ranges (IQRs) were reported. Subgroup analyses of prescribing rates were performed for patient age (18–39 years, 40–59 years, and 60 years and older), gender, and co-morbidities. The two-tailed chi-square test was used to analyse differences in prescription rates. A P value of less than 0.05 was regarded as indicating a statistically significant difference.

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multiple logistic regression with any antidepressant being prescribed medication as the outcome variable. For each outcome ORs were calculated for patients who had and did not have each of the co-morbidities as well as for who had and did not have any of the 6 co-morbidities. After calculating unadjusted OR, two models including potential confounders were determined. Model 1 was controlled for patient age and gender, and model 2 was controlled for patient age, gender as well as for physicians' gender and specialisation and type of depression. Patient age was introduced in the model as a continuous variable.

3. Results

Of the 22 physicians, 17 were GPs (77%) and 5 were specialists working as GPs (23%). The participating physicians did not differ significantly from the overall population of physicians certified in anthroposophy in Germany ($n = 362$) in terms of age (mean = 49.4; SD = 6.3 years versus mean = 47.5; SD = 6.1 years; $P = 0.709$) or gender (60.0% versus 62.2% men; $P = 0.917$) and were only slightly younger and consisted of a similar percentage of women compared to all office-based physicians in Germany (mean 52.0 years; 61.2% men) [20].

During the 5-year study period, a total of 2444 patients with depression were included. The inclusion process is shown in Figure 1. 73.4% of all patients were treated by a GP ($n = 1793$), 17.9% by an internist ($n = 437$), and the remaining 8.8% of the patients were treated by a neurologist ($n = 214$). 77.3% of the patients were female ($n = 1889$). The mean age of the patients was 49.1 years (SD = 15.4). Altogether, 26.8% of the patients were 18–39 years ($n = 656$), 49.8% were 40–59 years ($n = 1218$), and 23.3% were 60 years or older ($n = 570$). Depression was classified as depressive episode (88.3%) and recurrent depressive disorder (11.7%). There was no significant difference according to type of depression and age group ($P = 0.789$) or gender ($P = 0.658$).

In total, 8.3% of all patients ($n = 204$) had two or more co-morbidities and were, therefore, classified as multimorbid. The most frequent co-morbidities were cancer (14.4% of all patients), coronary heart disease (8.3%), and diabetes mellitus (7.1%). Table 1 provides a detailed overview of the co-morbidities of the participating patients according to patient age and gender.

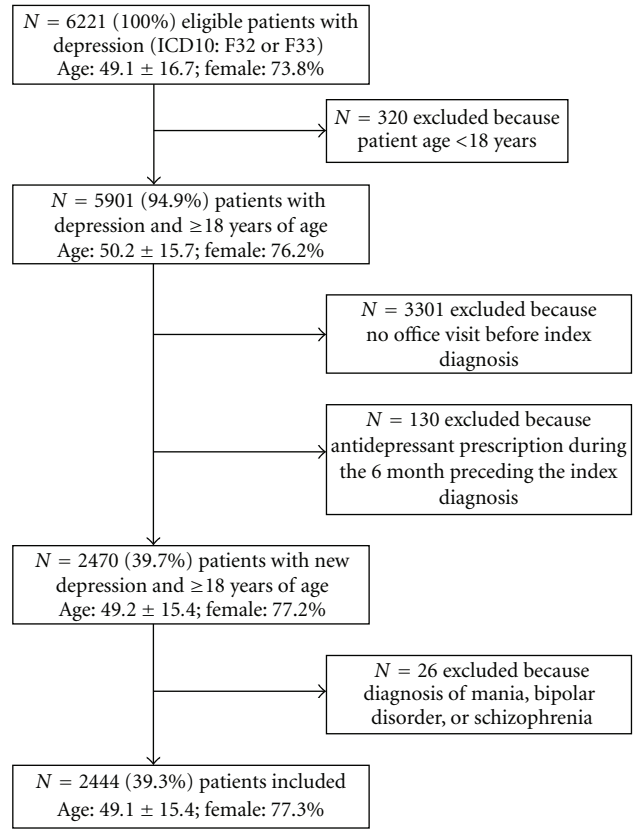

Figure 1: Flow chart of the inclusion process.

Overall, 833 patients were prescribed an antidepressant medication, representing 33.9% of patients who experienced a new episode of depression. In total, 2645 prescriptions of antidepressants for these patients were reported. They were nearly uniformly distributed over the four quarters (1st quarter: 630 (23.8%), 2nd quarter: 645 (24.4%), 3rd quarter: 616 (23.3%), and 4th quarter: 754 (28.5%)).

Table 2 gives an overview of the prescribed antidepressants. Phytotherapeutic preparations of *Hypericum perforatum* were the most frequently prescribed antidepressants over all (44.6% of all antidepressants). The most common class of conventional antidepressants prescribed was the NSMRI class, and amitriptyline was the most commonly prescribed individual medication.

Table 3 gives a detail overview of the included patients according to antidepressant medication. Phytotherapeutic preparations from *Hypericum perforatum* were prescribed to 539 of 833 patients with any antidepressant medication (64.7%), followed by NSMRI (28.2%), and SSRI (16.8%). The proportion of patients with antidepressant medication was especially high among neurologists (76.2%). The proportion of patients being prescribed any antidepressant medication increased with patient age from 27.7% of patients under 40 years to 44.4% of patients of 60 years or older. Patients with multi-morbidity were more likely to receive an antidepressant than patients without co-morbidity (47.1% versus 32.9%; $P = 0.016$ chi-square test). The differences

Table 1: Characteristics of the study population according to co-morbidities, age, and gender.

Comorbid condition	Patients	Age group [years]			Gender [%]	
		<40	40–59	≥ 60	Male	Female
	N (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Coronary heart disease	202	7 (3.5)	71 (35.1)	124 (61.4)	66 (32.7)	136 (67.3)
Cerebrovascular disease	99	—	21 (21.2)	78 (78.8)	26 (26.3)	73 (73.7)
Diabetes mellitus	174	9 (5.2)	54 (31.0)	111 (63.8)	66 (27.9)	108 (62.1)
Cancer	351	19 (5.4)	162 (46.2)	170 (48.4)	81 (23.1)	270 (76.9)
Congestive heart failure	113	1 (0.9)	12 (10.6)	100 (88.5)	23 (20.4)	90 (79.6)
Chronic obstructive pulmonary disease	68	8 (11.8)	25 (36.5)	35 (51.5)	19 (27.9)	49 (72.1)
Comorbidities						
0	1736	614 (35.4)	921 (53.1)	201 (11.6)	358 (20.6)	1378 (79.4)
1	504	40 (7.9)	257 (51.0)	207 (41.1)	142 (28.2)	362 (71.8)
≥2	204	2 (1.0)	40 (19.6)	162 (79.4)	55 (27.0)	149 (73.0)
Total	2444	656 (26.8)	1218 (49.8)	570 (23.3)	555 (22.7)	1889 (77.3)

Table 2: Top 10 of prescribed antidepressants.

Rank	Substance	ATC	Type	*N*	%	Cum %
1	*Hypericum perforatum*	N06AP	Phytoceutical[1]	1180	44.6	44.6
2	Amitriptyline	N06AA09	NSMRI	426	16.1	60.7
3	Mirtazapine	N06AX11	NaSSA	200	7.6	68.3
4	Citalopram	N06AB04	SSRI	197	7.4	75.7
5	Doxepin	N06AA12	NSMRI	140	5.3	81.0
6	Opipramol	N06AA05	TCAs[2]	104	3.9	85.0
7	Venlafaxine	N06AX16	SSNRI	69	2.6	87.6
8	Trimipramine	N06AA06	NSMRI	52	2.0	89.5
9	Fluoxetine	N06AB03	SSRI	51	1.9	91.5
10	Paroxetine	N06AB05	SSRI	46	1.7	93.2
11–28	Other < 1.7%[3]			138	9.4	100.0
Total				2645	100.0	100.0

MAOIs: nonselective, monoamine oxidase A inhibitors; NaSSAs: noradrenergic and specific serotonergic antidepressants; NSMRIs: non-selective monoamine reuptake inhibitors; TCAs: tricyclic antidepressants; SSRIs: selective serotonin reuptake inhibitors; SSNRIs: selective serotonin and noradrenergic reuptake inhibitors.

[1]Two of the primary active constituents of *Hypericum perforatum* are hyperforin and adhyperforin. Hyperforin and adhyperforin are wide-spectrum inhibitors of the reuptake of serotonin, noradrenaline, glutamate, dopamine, and GABA.

[2]Although opipramol is a member of the tricyclic antidepressants, today it is typically used in the treatment of generalized anxiety disorders (GAD).

[3]Others drugs: for example, Bupropion (NDRIs: noradrenergic and dopaminergic reuptake inhibitors) and nefazodone (DSAs: dual serotonergic antidepressants).

in age and co-morbidities were only due to conventional antidepressants, especially to NSMRI, whereas there was no difference in the prescription rates of phytotherapeutic preparations from *Hypericum perforatum*.

As shown in Table 4, the likelihood of being prescribed an antidepressant medication was not significantly different for persons who had a co-morbid condition compared with those who did not have a co-morbid medical condition after controlling for age and gender (model 1: adjusted OR = 0.88; CI: 0.71–1.09) and after controlling for further potential confounder (model 2: adjusted OR = 1.01; CI: 0.81–1.26). But there were significant differences according to the presence or absence of the individual co-morbidities. The adjusted OR for receiving any antidepressant medication was greater than 1 for the co-morbidity cerebrovascular disease (model 1: adjusted OR = 1.78; CI: 1.16–2.74; model 2: adjusted OR = 1.76; CI: 1.12–2.76). Patients who had cancer were significantly less likely to be prescribed an antidepressant medication than those who had no cancer (model 1: adjusted OR = 0.65; CI: 0.51–0.84; model 2: adjusted OR = 0.75; CI: 0.57–0.97). Finally model 2 also indicated OR < 1 for the co-morbidities heart failure and COPD.

Our data, however, suggest an increase in antidepressant medication over the time of the study period. While in 2004, a total of 579 patient were prescribed 360 antidepressant

Table 3: Sample of patients with depression subdivided according to antidepressants.

	Patients	Antidepressant[1]					
	N	Any [*n* (%)]	NSMRI [*n* (%)]	SSRI [*n* (%)]	MAOI [*n* (%)]	Hyp.-perf. [*n* (%)]	Other[2] [*n* (%)]
Gender							
Male	555	202 (36.4)	53 (9.5)	34 (6.1)	1 (0.2)	124 (22.3)	26 (4.7)
Female	1889	631 (33.4)	182 (9.6)	106 (5.6)	3 (0.2)	415 (22.0)	59 (3.1)
Age [years]							
<40	656	182 (27.7)	27 (4.1)	23 (3.5)	—	147 (22.4)	9 (1.4)
40–59	1218	398 (32.7)	109 (8.9)	73 (6.0)	2 (0.2)	260 (21.3)	41 (3.4)
≥60	570	253 (44.4)	99 (17.4)	44 (7.7)	2 (0.4)	132 (23.2)	35 (6.1)
Physician specialization							
GP	1793	522 (29.1)	124 (6.9)	83 (4.6)	2 (0.1)	355 (19.8)	44 (2.5)
Internist	437	148 (33.9)	27 (6.2)	26 (5.9)	1 (0.2)	110 (25.2)	6 (1.4)
Neurology	214	163 (76.2)	84 (39.3)	31 (14.5)	1 (0.5)	74 (34.6)	35 (16.4)
Type of depression							
Depressive episode	2158	762 (35.3)	219 (10.1)	120 (5.6)	4 (0.2)	497 (23.0)	78 (3.6)
Recurrent depressive disorder	286	71 (24.8)	16 (5.6)	20 (7.0)	—	42 (14.7)	7 (2.4)
Multi-comorbidity							
No	2240	737 (32.9)	202 (9.0)	122 (5.4)	3 (0.1)	492 (22.0)	69 (3.1)
Yes	204	96 (47.1)	33 (16.2)	18 (8.8)	1 (0.5)	47 (23.0)	16 (7.8)
Comorbidity							
Coronary heart disease	202	84 (41.6)	27 (13.4)	17 (8.4)	1 (0.5)	48 (23.8)	9 (4.5)
Cerebrovascular disease	99	56 (56.6)	27 (27.3)	13 (13.1)	—	23 (23.2)	12 (12.1)
Diabetes mellitus	174	82 (47.1)	23 (13.2)	15 (8.6)	1 (0.6)	46 (26.4)	10 (5.7)
Cancer	351	108 (30.8)	27 (7.7)	17 (4.8)	1 (0.3)	70 (19.9)	12 (3.4)
Congestive heart failure	113	59 (52.2)	22 (19.5)	11 (9.7)	1 (0.9)	30 (26.5)	6 (5.3)
Chronic obstructive pulmonary disease	68	34 (50.0)	11 (16.2)	3 (4.4)	1 (1.5)	19 (27.9)	8 (11.8)
Total	2444	833 (34.1)	235 (9.6)	140 (5.7)	4 (0.2)	539 (22.1)	85 (3.5)

[1] Double entries possible, [2] including bupropion, mirtazapine, and nefazodone.
MAOIs: non-selective monoamine oxidase A inhibitors.
NSMRI: non-selective monoamine reuptake inhibitors.
SSRIs: selective serotonin reuptake inhibitors.
Others: for example, bupropion, mirtazapine, and nefazodone.

drugs (mean 0.62), the amount of prescribed antidepressants almost doubled to a mean of 1.28 in 2008 (376 patients with 483 prescriptions).

4. Discussion

In this paper, we presented the results of a secondary data analysis of electronic health record data from the EvaMed-Network, a German network of physicians with a subspecialisation in anthroposophic medicine [16, 17, 19] which aims at improving clinical practice by collecting prescription and ADR data.

In the current study, 2444 patients with a first diagnosis of depression fitted the inclusion criteria. A proportion of 8.3% of them were multi-morbid with more than two diagnoses. 33.9% of the patients received an antidepressant medication. The proportion of patients with medications is much less compared to the findings of, for example, 51.9% by Robinson et al., 76.1%, and accordingly 77.4% by Gill and colleagues in 2008 and 2010 respectively 2010 [21–23]. This is even more of relevance as our patients received more complementary drug medication with phytotherapeutic preparations from *Hypericum perforatum* being the most prescribed drug over all. Within our study period, the number of psychiatric diseases and in particular depressive disorders in Germany significantly rose which is reflected in the data of prescription costs of antidepressants which according to health insurance data rose from 5 Mio. Euro in 2000 up to 14.5 Mio. Euro in 2009 [24]. Published data also suggest a higher proportion of female patients receiving such medication [25, 26]. Both of these are strongly supported by our findings with three of four medicated patients being female and a doubling in the prescribed drugs per patient from 2004 to 2008.

To improve the situation of people with depression in Germany, a first measure was the implementation of the German Disease Management Guideline (DMG-CPG) for depression [6, 8, 9]. The increased prescriptions of new antidepressive pharmacotherapies like SSRIs nowadays is

Table 4: Likelihood of being prescribed any antidepressant medication by co-morbidity ($n = 2444$).

Co-morbid condition	Patients who were prescribed an antidepressant		Likelihood of being prescribed antidepressant		
	Patients with co-morbidity	Patients without co-morbidity	Unadjusted OR	Model 1 Adjusted OR[1] (95% CI)	Model 2 Adjusted OR[1] (95% CI)
	n/N (%)	*n/N* (%)			
Coronary heart disease	84/202 (41.6)	749/2242 (33.4)	1.419 (1.058–1.903)*	1.028 (0.753–1.404)	1.191 (0.864–1.643)
Cerebrovascular disease	56/99 (56.6)	777/2345 (33.1)	2.628 (1.750–3.947)*	1.781 (1.159–2.739)*	1.762 (1.124–2.762)*
Diabetes mellitus	82/174 (47.1)	751/2270 (33.1)	1.803 (1.322–2.459)*	1.342 (0.968–1.860)	1.317 (0.936–1.855)
Cancer	108/351 (30.8)	725/2093 (34.6)	0.829 (0.657–1.070)	0.652 (0.505–0.842)*	0.745 (0.572–0.969)*
Congestive heart failure	59/113 (52.2)	774/2331 (33.2)	2.198 (1.504–3.211)*	1.431 (0.951–2.154)	1.652 (1.082–2.521)*
Chronic obstructive Pulmonary disease	34/68 (50.0)	799/2376 (33.6)	1.974 (1.218–3.199)*	1.612 (0.986–2.638)	1.950 (1.188–3.200)*
Any comorbidity	267/708 (37.7)	566/1736 (32.6)	1.252 (1.043–1.502)*	0.878 (0.709–1.086)	1.007 (0.807–1.257)

[1] Odds ratio for patients who had a co-morbidity compared to patients who did not have co-morbidity.
Model 1: adjusted for patient age and gender.
Model 2: adjusted for patient age and gender, as well as for physician specialisation and type of depression.

critically discussed within the scientific community [26, 27]. One of their major concerns is the unjustified medication of mild and potentially self limiting depressive episodes with expensive medications with a high potential of adverse drug reactions.

Our study also gives data on the prescription of NSMRI (28.2%) and SSRI (16.8%) which is considerably below the German standard. One reason might be the compensation of such drug classes by the use of complementary drug therapies like *Hypericum perforatum*.

Several publication on prescriptions [24] state that citalopram, mirtazapin and amitriptylin are the most common and popular remedies for depression. We also found these three remedies to be the most often prescribed conventional drugs. However, we can not tell why the ranking in our study is the other way round (Amitriptylin, Mirtazapine followed by Citalopram). This may be due to the comparably longer time frame of our study or to the different sample of physicians. One explanation might also be that Amitriptylin is the "oldest" remedy and thus the most known.

In the treatment of depression, medication is only one issue; guidelines additionally focus on nonpharmacological treatments like psychotherapy, mind body techniques, or light therapy. These are also relevant therapeutic options which are very often underrepresented [23]. However, our data do not provide detailed information on such therapies.

With regards to comorbidities, studies have shown the prevalence of depression to be higher for persons with heart diseases, diabetes mellitus, stroke, COPD, and cancer [28]. This was also confirmed in the study of Gill et al. 2008 , which found depression to be more likely among patients with a significant number of medical comorbidities [21]. In our study, 504 (20.6%) had at least one comorbidity, while 204 patients (8.3%) had two or more comorbidities. This is nearly comparable to the proportions provided in the study of Gill et al. from 2010, who found 20.7% with one and 5.8% with two or more co-morbidities in their sample of 1513 patients [22]. They also found that after controlling for age and gender, patients with multiple comorbidities were less likely to be prescribed medication (adjusted odds ratio, 0.58; 95% CI, 0.35–0.96). In our first multivariate model, which equates the approach of Gill et al., we were also able to show this effect but were not able to reach significance (adjusted odds ratio 0.88; 95% CI, 0.71–1.09). A more detailed differentiation between the co-morbidities was not performed to guarantee the statistical model performance.

Although there is some comparability of our results with former studies, some discrepancies of our results with another German study of Jacobi et al. [29] have to be mentioned. Although the proportion for one comorbidity with 20.8% is quite similar, they found 39.9% of depressive patients with two or more comorbidities. This may be explained by the fact that all patients with one depressive episode form the basis of their study which is not comparable with our situation.

5. Limitations

The present study has several important limitations which should be taken into account when interpreting the results. Firstly, additional data on the depression diagnoses are lacking. We do not know to what extent the diagnoses were made, only clinically or with additional validated questionnaires, that is, as a functional evaluation with the WHO-5 or PHQ-D [30, 31]. We therefore are also not able to give detailed information on the severity of the depression.

Secondly, although physician prescribing data were subjected to an internal review, coding inaccuracies cannot be ruled out entirely.

Thirdly, our data do not provide more detailed information on the type and dosage of phytotherapeutic *Hypericum perforatum* preparations. For the same methodological boundaries, our data also do not allow a calculation of daily drug doses, which limits the comparability of our data with other studies.

Fourthly, data on subsequent medication use in patients who switched physicians were unavailable.

Fifthly, our data from the group of 22 participating physicians are not representative for physicians in general practice in Germany nor may be seen as such for the smaller subgroup of anthroposophical physicians. The same problem arises for the patients the data are based on. Although an earlier paper gives an estimate for the prevalence of mood and affective disorders (F00-F39) of about 10% in our patients between 40 and 70 years in 2005 which is comparable to the numbers given, that is, in [7], it is less than the prevalence of 19.8% reported in [29]. Thus generalisations from this data are somehow limited.

Finally, although there were no major differences to the studies of Gill et al., the present study lacks a direct comparison group and the options to carry out detailed subgroup analyses. Further research on this subject would benefit from including a comparison group of conventional primary care physicians.

6. Conclusion

This study provides a comprehensive analysis of everyday practice for treatment of depression in primary care in physicians with subspecialisation in anthroposophic medicine (AM). Although the administration of phytotherapeutic preparations from *Hypericum perforatum* was significantly higher, the prescribing frequency for conventional antidepressive drugs is partly comparable to those found in other studies.

Authors' Contribution

E. Jeschke participated in the design of the study and acquisition of data, performed the statistical analysis, and helped in drafting the paper. T. Ostermann drafted the manuscript and made substantial contributions to the interpretation of data and statistical analysis. H. C. Vollmar helped with the interpretation of the data and drafting and critical revision of the manuscript. M. Tabali helped in data acquisition and in drafting and critical revising the manuscript. H. Matthes conceived the study and participated in its design and coordination. All authors read and approved the final manuscript.

Acknowledgments

The EvaMed Network was supported by grants from the Software AG Foundation, Wala Heilmittel GmbH, and Weleda AG. The sponsors had no influence on the design, on implementation of the study, collection, management, or analysis of data or the preparation, review, or approval of the manuscript. The authors would also like to express their special gratitude to all participating physicians in the EvaMed Network.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 923925, 10 pages
doi:10.1155/2012/923925

Research Article

Tai-Chi for Residential Patients with Schizophrenia on Movement Coordination, Negative Symptoms, and Functioning: A Pilot Randomized Controlled Trial

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Received 18 April 2012; Accepted 7 August 2012

Academic Editor: Jörg Melzer

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Objective. Patients with schizophrenia residing at institutions often suffer from negative symptoms, motor, and functional impairments more severe than their noninstitutionalized counterparts. Tai-chi emphasizes body relaxation, alertness, and movement coordination with benefits to balance, focus, and stress relief. This pilot study explored the efficacy of Tai-chi on movement coordination, negative symptoms, and functioning disabilities towards schizophrenia. *Methods*. A randomized waitlist control design was adopted, where participants were randomized to receive either the 6-week Tai-chi program and standard residential care or only the latter. 30 Chinese patients with schizophrenia were recruited from a rehabilitation residency. All were assessed on movement coordination, negative symptoms, and functional disabilities at baseline, following intervention and 6 weeks after intervention. *Results*. Tai-chi buffered from deteriorations in movement coordination and interpersonal functioning, the latter with sustained effectiveness 6 weeks after the class was ended. Controls showed marked deteriorations in those areas. The Tai-chi group also experienced fewer disruptions to life activities at the 6-week maintenance. There was no significant improvement in negative symptoms after Tai-chi. *Conclusions*. This study demonstrated encouraging benefits of Tai-chi in preventing deteriorations in movement coordination and interpersonal functioning for residential patients with schizophrenia. The ease of implementation facilitates promotion at institutional psychiatric services.

1. Introduction

Schizophrenia affects about 24 million people worldwide. Despite a low incidence rate (3/10,000) [1, 2], its poor recovery prognosis and chronic nature renders it a highly prevalent disorder (0.4%–1%). Long-term care and symptoms management become crucial as symptoms may persist lifelong. While mild-graded patients under medication may live independently, others may benefit from residential care which prepares them for reentering the community when their symptoms and personal care, are well-managed.

Under the medical model, the primary focus of care and research on patients prioritizes illness management, self-care, and functioning abilities while physical or psychological well-being falls secondary. Patients with schizophrenia have comparatively shorter life expectancies due to poor physical health (higher incidence of cardiovascular and metabolic diseases) and psychological health (depression and suicide) [3–5]. However, this may be partially attributable to the side-effects of medication; poor lifestyles or a simple lack of exercise [6].

There are a number of known benefits of exercise to patients' psychosocial well-being and their symptoms of psychiatric disorders. Levin and Gimino [7] indicated that aerobic exercise reduces depression, anxiety, and obsessive-compulsive symptoms in hospitalized schizophrenic patients compared to no-exercise controls. Similar interventions improved mood, anxiety and depression, increased self-esteem, energy, concentration, quality of life, and social

interactions [8, 9]. Faulkner and Sparkes [10] investigated a 10-week exercise program which reduced auditory hallucinations, raised self-esteem, improved sleep patterns, and general behaviors. Randomized controlled trials established even stronger evidence of aerobic and strength exercises in lowering positive and negative symptoms, state anxiety, and psychological distress while improving quality of life [11]. More recent research noted anatomical changes associated with aerobic exercise particularly in increasing hippocampal volume [12] which potentially improves short-term memory among exercisers with schizophrenia. Besides symptom-related outcomes, a lack of physical activity was associated with worse health-related quality of life [13].

Exercises based upon Eastern health philosophy like Tai-chi stress the interrelated body and mind. Besides being a form of light-to-moderate intensity physical exercise [14, 15] which improves cardiovascular fitness, balance control, and flexibility [16], Tai-chi is also a cultivation of psychological focus and relaxation [17]. There is strong empirical evidence on the mind-body effects of Tai-chi for the elderly, depressed patients and those suffering from coronary heart diseases [18, 19]. Besides symptom-specific improvements, regular practice of Tai-chi can also effectively enhance physical and mental quality of life for various patient populations [20, 21]. Through a decrease in the neuroendocrinal stress response, it brings about psychological benefits for chronic patients through its antidepressant and antiolytic effects [22]. Tai-chi is principled upon body relaxation, mental alertness, movement sequencing, and coordination [23]. Targeting both the mind and body, Tai-chi holds promising benefits for patients with mental illnesses. A randomized-controlled trial [24] on a 12-week Tai-chi program for patients with chronic schizophrenia found reduced negative symptoms. Another form of mind-body intervention, yoga, which also stresses breathing, relaxation and stretching, was found effective in reducing positive and negative symptoms while enhancing health-related quality of life in a systematic review of randomized-controlled trials [25]. Emphasizing focus cultivation, relaxation, bodily coordination, and control, Tai-chi can potentially improve psychopathogical symptoms, movement coordination, and general functioning. However, little research investigated the potential benefits of Tai-chi for these clienteles.

The present study explored the effectiveness and implementation feasibility of Tai-chi (Wu-style Cheng form) on the movement coordination, negative schizophrenic symptoms, and general functioning disabilities for residential schizophrenic patients. This pilot trial was conducted for patients with schizophrenia residing at residential rehabilitation facilities. Halfway houses and long-stay care homes offer training on illness management and life skills so as to facilitate community reintegration [26]. This reflects a gradual departure from relying purely on medical treatment to incorporating adjuvant nonpharmalogical interventions. Yet, institutionalized patients with schizophrenia, particularly those in long-stay care homes, suffer from higher cognitive impairments, more serious negative symptoms and worse social functioning compared to their counterparts in other living conditions [27]. If the benefits of Tai-chi can be established, this can be a promising contribution to residential mental illness rehabilitation. Not only does it facilitate illness management, the mastery of a Tai-chi movement sequence may further promote independence and a sense of control over illness outcomes.

The primary aim of this pilot trial is to examine the effectiveness of a 6-week Tai chi program as an adjunctive intervention in a residential rehabilitation setting. The secondary objective is to explore the benefits and disadvantages of such intervention, thereby, informing the feasibility for promotion and areas for improvement.

2. Methods

2.1. Subjects. The pilot trial recruited thirty residential patients with chronic schizophrenia from the Sheng Kung Hui Providence Garden for Rehab, a mental health rehabilitation complex in Hong Kong providing both long-stay care and halfway house services to enhance the heterogeneity of the sample. Potential participants were invited to participate by their social workers based on the following inclusion and exclusion criteria. 30 participants were recruited so as to ensure an optimal group size of 12 after randomization [28] and a dropout rate of 20%.

The inclusion criteria included the following. (a) A diagnosis of schizophrenia according to the DSM IV-TR criteria. (b) Age between 18 to 65 years. (c) Ability to understand and speak Cantonese. (d) no prior experience in learning Tai-chi. Participants were excluded if (e) diagnosed with acute schizophrenia requiring hospitalization; (f) suffering from severe schizophrenic symptoms (e.g., persistent withdrawal) that would limit their ability to interact or participate in the class; (g) suffering from physical disabilities that would limit Tai-chi practice (including past or current serious spinal, hip or knee injury or pathology; severe pain limiting movement; or unsuitable for Tai-chi exercise as determined by their physicians); (h) Suffering from other severe illnesses which may impair cognitive or visuomotor functioning, cause physical pain or limit life expectancy to 10 years or less.

Ethical approval for this study was granted by the Human Research Ethics Committee for Non-Clinical Faculties at the University of Hong Kong. Written informed consent was solicited from all participants.

2.2. Intervention and Waitlist Randomization. This Tai-chi class was based on the Wu-style Cheng-form Tai-chi Chuan [29] led by mental health professionals. They were provided formal training in Tai-chi before going through a 12-session Tai-chi trainer's course at a professional Tai-chi institute. While movement is relatively standardized across various styles of Tai-chi, the unique strengths of the Wu-style (Cheng form) Tai-chi are its emphasis on movement rhythm, with potential benefits on movement coordination. It comprises of 22 simple movement forms (listed in Table 1) which are relatively easy and emphasizes attention and coordination in their basic philosophy [29]. One is required to name the movement form during practice which demands attention, concentration, memory and physical exertion inclusive in one simple exercise routine. One-hour classes were held

Table 1: The 22 movement forms of Wu-style Cheng form Tai-chi.

Tai-chi (Wu-style Cheng form) movements
(1) Ready style (預備式)
(2) Tai chi beginning style (太極起式)
(3) Seven stars style (七星勢)
(4) Grasping a bird's tail (攬雀尾)
(5) Single whip (單鞭)
(6) Gliding diagonally (斜飛勢)
(7) Raising hands and stepping up (提手上勢)
(8) Flapping wings (白鶴亮翅)
(9) Brush knee and twist step (摟膝拗步)
(10) The seven stars style (Left) (左七星勢)
(11) Brush knee and twist step (摟膝拗步)
(12) The seven stars style (Left) (左七星勢)
(13) Playing the lute (手揮琵琶)
(14) Step up, parry and punch (上步搬攔捶)
(15) Door shutting motion (如封似閉)
(16) Embrace tiger and return to mountain (抱虎歸山)
(17) Crossing hands (十字手)
(18) Diagonally brush knee and twist step (斜摟膝拗步)
(19) Turn body, brush knee, and twist step (轉身摟膝拗步)
(20) The seven stars style (七星勢)
(21) Grasping a Bird's tail (攬雀尾)
(22) Diagonal single whip (斜單鞭)

twice weekly for 6 weeks with 15 participants. Additional half-hour trainer-led practice sessions were held on a weekly basis throughout the 12-week study period, accumulating to a total of 2.5 hours of Tai-chi practice per week.

Randomization of participants was done using random numbers. The waitlist group received their standard residential care which includes a 30-minute daily morning stretching routine for both the Tai-chi and control participants.

2.3. Measurements. Both the Tai-chi and waitlist groups were assessed (i) before intervention (T1), (ii) within 1 week after the 6-week intervention (after intervention T2), and (iii) within the 6th week after the intervention (maintenance T3). Qualitative feedback on learning and practising Tai-chi were collected with a structured interview schedule at T3 on their perceived benefits and difficulties of practising Tai-chi. Responses were recorded on paper by the interviewer.

A series of patient assessments were administered by trained research assistants who were blinded to the group assignment of participants.

2.3.1. Movement Coordination Tests. Measurements of arm-hand dexterity and rapid eye-hand coordination were assessed using the Minnesota Rate of Manipulation Test (CMDT) [30], which is a collection of structured and well-established tests on motor disabilities used for occupational planning. It consists of five sub-tests: placing, turning, displacing, one-hand turning/placing, and two-hand turning/placing. Scoring is based on time needed to complete the tasks which involve the manipulation of cylindrical discs on two boards with perforated holes. A practice trial was given for all tests followed by two trials of which the average score was taken. Higher scores indicate longer time needed to complete the task, hence greater disabilities in movement coordination. The CMDT has good test-retest reliability for psychiatric patients (including schizophrenia) [31] and is currently being used as a formal motor assessment at the test site.

2.3.2. Scale for the Assessment of Negative Symptoms (SANSs). The SANS [32] was used for the assessment of negative symptoms in 5 dimensions including attention, anhedonia-asociality, avolition-apathy, alogia, and affective flattening or blunting. The scale is rated on a 6-point Likert scale where higher scores indicate greater severity of negative symptoms.

To ensure inter-rater reliability, the first 5 interviews were conducted with multiple interviewers and final ratings were given after deliberation by the team. The rated scores would subsequently be discussed with psychiatric social workers providing care to the participants to ensure that ratings given closely reflected their actual symptom levels.

2.3.3. World Health Organization Disability Assessment Schedule (WHODAS-II). The WHODAS-II [33] measures levels of health-induced disabilities in a number of life domains in the past 30 days. Domains include cognition, mobility, self-care, interpersonal interactions, life activities, and community participation. The internal consistency, test-retest reliability, and validities of this instrument were satisfactory for patients with schizophrenia [34, 35].

The interviewer-administered 36-item version was adopted. Items were translated and back-translated by the research team into Chinese to facilitate participants' understanding. Certain items including "staying by yourself for a few days" and "sexual activities" were dropped for a lack of relevance at the studied residential facility. Higher scores denote greater functioning disabilities.

2.3.4. Sociodemographic and Clinical Information. Patients' sociodemographic and clinical information were solicited from personal and medical records. This included their age, gender, education level, martial status, and employment. Their period of psychiatric diagnosis, medication, and consecutive lengths of stay at residential facilities were collected as clinical data.

2.3.5. Qualitative Feedback. Structured interview questions requiring participants to list their subjective advantages and disadvantages of Tai-chi were posed at the maintenance assessment.

2.4. Statistical Analyses. Intention-to-treat analysis was employed, such that participants with missed Tai-chi sessions or data were still included in the final analysis. Due to the small sample size, nonparametric techniques were adopted. Within and between-group comparisons were conducted with the Wilcoxon signed ranks the Mann-Whitney U tests, respectively, using the Statistical Package for Social

Sciences version 18.0. Analyses were conducted on all three time points for intervention and maintenance effects. All statistical significance tests are two-sided, at the level of significance of $P \leq 0.05$. Effects sizes were calculated according to [36], where medium and large effects sizes are indicated by $r = 0.3$ and $r = 0.5$, respectively. Missing variables were replaced with the median of the respective subscale if the number of missing variables did not exceed half of the subscale. Qualitative feedback was analyzed using theme analysis.

3. Results

3.1. Participants. 30 participants fulfilling the inclusion and exclusion criteria were invited to participate into the study (Figure 1).

Participants had a mean age of 53 years and were diagnosed for about 28 years. The average consecutive length of stay at rehabilitation residencies was 11.8 years. All participants were receiving antipsychotic medication.

On Chi-square and Mann-Whitney tests, the Tai-chi and the waitlist groups were comparable on their sociodemographic and clinical statues as well as the assessment variables (Table 2). The sole exception is a relatively higher ratio of females in the waitlist group as compared to the Tai-chi group.

Antipsychotic medication use at baseline (T1) did not differ significantly between the two groups which were assessed based on chlorpromazine equivalents which reflects medication dosage ($Z = -0.591$; $P = 0.555$) [37]. The average daily chlorpromazine equivalents of the Tai-chi and waitlist groups were 391 mg and 365 mg, respectively. Medication change at maintenance (T3) was minimal, where only two participants from the Tai-chi group and one from the waitlist group had their dosages altered during the study period. The average change in the chlorpromazine equivalents did not significantly differ between the groups ($Z = -0.537$; $P = 0.592$). Approximately 57% of the participants ($n = 17$) were taking atypical antipsychotics.

3.2. Movement Coordination. Motor dexterity and eye hand coordination (CMDT) after attending the Tai-chi class (T2) was not vastly different from baseline (T1). But the waitlist group experienced significant deterioration on 3 of the 5 tests of the CMDT, the turning test ($Z = 2.22$; $P = 0.026$; $r = 0.57$), the displacing test ($Z = 2.22$; $P = 0.026$; $r = 0.57$) and the one-hand test ($Z = -2.98$; $P = 0.003$; $r = 0.77$).

There is a significant difference in how the Tai-chi group and the waitlist group faired on the displacing test ($Z = -2.28$; $P = 0.023$; $r = 0.42$) and marginal significance the one-hand test ($Z = -1.95$; $P = 0.065$; $r = 0.36$). Therefore, the Tai-chi class buffered from deteriorations in movement coordination but effects were not sustained at maintenance (T3).

3.3. Negative Symptoms. Changes to negative symptoms were not statistically significant after the Tai-chi class or in the waitlist group. Between group comparison also failed to reach significance.

3.4. Functioning Disability. Fewer disruptions in life activities functioning was observed for the Tai-chi group at maintenance (T3) ($Z = -2.14$; $P = 0.03$; $r = 0.55$). The Tai-chi participants also found fewer difficulties with community participation at T2 ($Z = -2.73$; $P = 0.01$; $r = 0.70$). The waitlist group, however, experienced greater disruptions in interpersonal functioning at T2 ($Z = -2.22$; $P = 0.03$; $r = 0.57$) and sustained at T3 ($Z = -2.43$; $P = 0.02$; $r = 0.63$). Between group differences in interpersonal functioning were marginally significant between baseline and T2 ($Z = -2.56$; $P = 0.07$; $r = 0.47$) and significant between baseline and T3 ($Z = -2.56$; $P = 0.01$; $r = 0.47$). Performance outcomes of the two groups are detailed in Table 3.

3.5. Qualitative Feedback on the Benefits and Disadvantages of Tai-Chi. Participants generally enjoyed Tai-chi for the benefit it brought to their physical and mental health. Others found it to be a pleasurable activity although a few did not enjoy the level of persistence required by the slow yet energy-demanding Tai-chi movements. Other difficulties arose from the complexity of movements. Table 4 lists the themes and examples of the feedback.

4. Discussion and Conclusion

Tai-chi is often taken as a form of alternative therapy in the treatment for physical or mental ailments [17, 38]. In schizophrenia research, the possible benefits of this traditional form of mind-body exercise have not been receiving similar attention as other types of physical exercises. The benefits of physical activity to the rehabilitation of psychosis are well established although patients tend to be less physically active compared to those without psychosis [39]. Poor physical fitness, low skeletal-muscle mass, and obesity, all of which are associated with a lack of exercise, are all contributing factors to mortality among patients with schizophrenia [40].

The purpose of this study was to demonstrate that the detrimental manifestations of schizophrenia are amendable by lifestyle modification like regularly practicing Tai-chi. Results lent evidence that Tai-chi can help protect against deteriorations in movement coordination after 6 weeks of Tai-chi. With regular weekly practice, it also buffered against a decline in interpersonal functioning which was sustained even 6 weeks after the class. Reasons for the deteriorations in the waitlist group may reflect the instability of psychomotor or functioning states of residential psychiatric patients. The majority of participants required long-stay care, with unstable illness prognosis and functioning. Particularly since the collection of T2 and T3 data happened to fall during festivities, participants' daily functioning and activities may have been affected by family visits, or other activities held at the facility.

Previous exercise interventions for schizophrenia rehabilitation focused primarily on the alleviation of psychotic symptoms rather than psychomotor outcomes, despite being an important illness manifestation. The current pilot

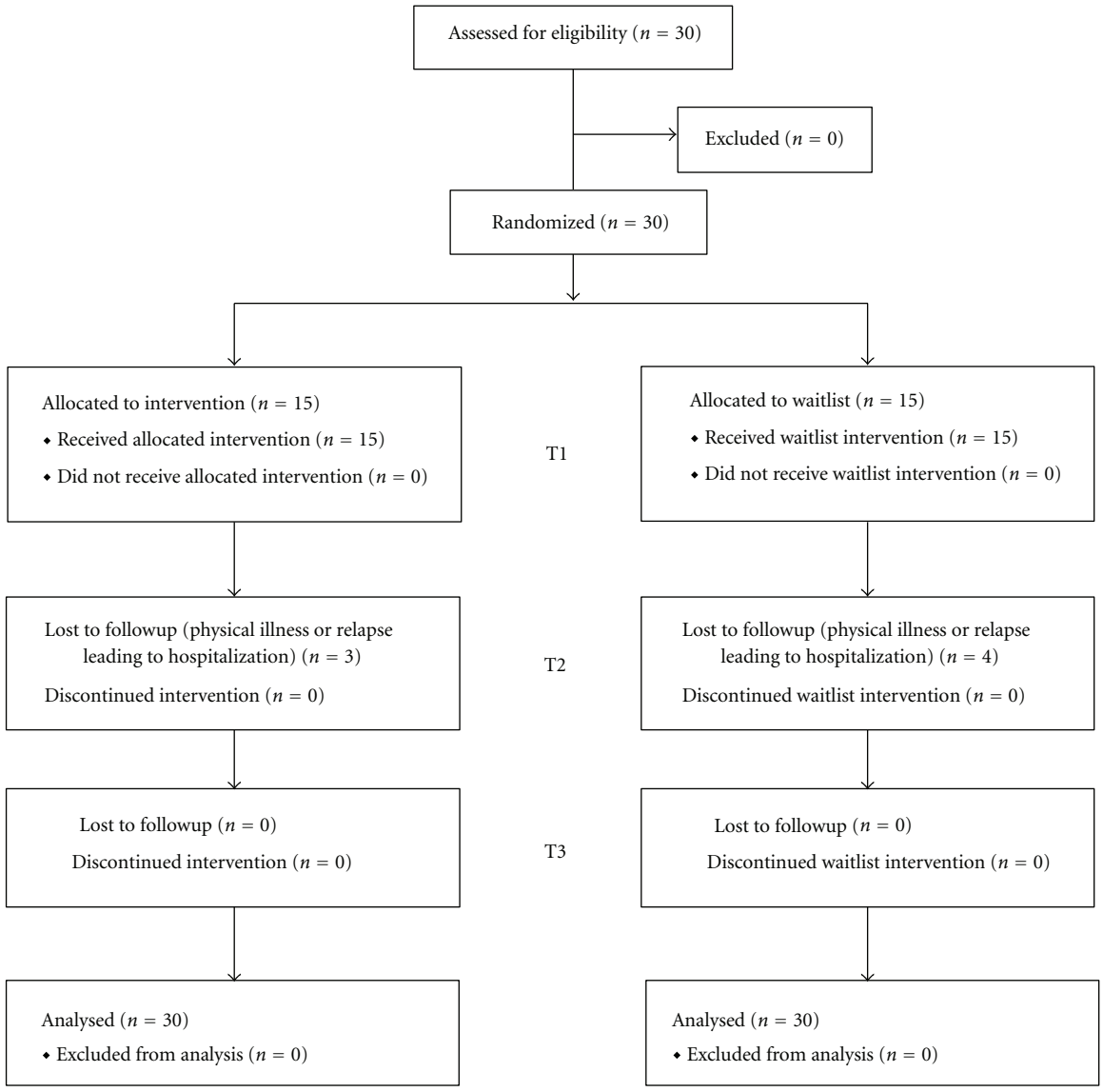

Figure 1: Participant flowchart.

trial showed how movement coordination can experience pronounced benefits after exercising. Tai-chi emphasizes movement rhythm, which may have helped prevent motor deteriorations as a result of schizophrenia or extra-pyramidal symptoms. This outcome concurs with research demonstrating improved motor responses and postural control among the elderly regularly practising Tai-chi [41]. For patients with schizophrenia, better psychomotor functioning is related to social, clinical, and functioning outcomes [42]. Motor functioning is a key feature of schizophrenia and can be tied in with a number of other psychological symptoms. Hallucination, for instance, was found to be related to the blood flow to the motor region of the brain [43] leading to growing interest in the way mental events control movements. This, among other evidence, demonstrates a sophisticated interaction between psychological and motor processes in patients. Mind-body exercises like Tai-chi not only restore muscular strength and coordination but further cultivate psychological focus and concentration [17]. Given the intricate associations between the mental and motor processes in schizophrenia, the benefits Tai-chi has on the psychological states of patients may possibly underlie one of the pathways to better motor functioning. While this pathway has yet to be attested in future research, the buffering effect Tai-chi demonstrated on motor deteriorations holds important clinical implications. In residential settings, movement coordination can possibly help sustain self-care abilities, the completion of daily tasks, while indirectly supporting participation in social activities. Among participants in the current study, the general level of movement coordination on all five tests was substantially impaired, falling within the 1st percentile of the population norm [44]. Their performance was also largely confounded by deficiencies in understanding instructions. Therefore, despite promising outcomes, a more simple coordination test may more reliably reflect movement coordination function in future research.

Table 2: Socio-demographical, clinical characteristics and assessment outcomes at baseline.

Variables	Tai-chi Mean (SD)	Waitlist Control Mean (SD)	P^*
Age	51.87 (10.85)	53.47 (8.63)	0.69
Gender			0.03*
Male	9	3	
Female	6	12	
Education level			0.47
No formal education	3	4	
Primary	3	7	
Lower secondary (Grades 7–9)	3	2	
Upper secondary (Grades 10–11)	4	2	
After secondary or above	1	0	
Missing	1	0	
Marital status			0.94
Single	10	9	
Married	1	2	
Divorced/Separated	3	3	
Widowed	1	1	
Employment			0.52
Full time employment	0	1	
Unemployed	4	9	
Retired	11	5	
Years of diagnosis	29.47 (14.86)	26.2 (10.09)	0.33
Length of stay at residencies (years)	12.87 (14.82)	10.73 (9.87)	0.45
Chlorpromazine equivalent (mg)	391.07 (472.25)	365.12 (221.92)	0.85
Assessment outcomes	Tai-chi	Waitlist Control	P^*
Movement Coordination (CMDT)			
Placing	82.17 (9.75)	98.29 (28.2)	0.12
Turning	76.73 (14.51)	101.04 (40.89)	0.10
Displacing	60.6 (10.13)	76.07 (26.61)	0.11
One-Hand Turning/Placing	102.37 (17)	124.82 (45.95)	0.17
Two-Hand Turning/Placing	65.53 (10.74)	89.96 (43)	0.16
Negative symptoms (SANS)			
Attention	4.27 (3.39)	5.6 (3.81)	0.21
Anhedonia-asociality	4.53 (4.29)	4.4 (4.6)	0.80
Avolition-apathy	1.67 (2.82)	2.27 (3.37)	0.79
Alogia	4.4 (4.97)	4.8 (5.17)	0.83
Affective flattening or blunting	8.2 (7.98)	8.67 (7.76)	0.68
Functioning disabilities (WHODAS II**)			
Cognition	12.2 (3.45)	11.33 (5.34)	0.31
Mobility	7.53 (2.39)	7.6 (2.87)	0.93
Self-care	3.4 (0.83)	3.2 (0.41)	0.61
Interpersonal interactions	7.47 (4.16)	5.27 (2.25)	0.08
Life activities	11 (3.61)	9.4 (1.76)	0.15
Community participation	17 (5.84)	14.73 (5.87)	0.38

Exercise-related benefits to interpersonal functioning are particularly relevant to group exercises like Tai-chi. Despite focusing on the inner self [17], traditional Tai-chi practice often takes place in a group, under a belief that stronger *qi* (a positive healing force) can be better cultivated in a group than by a single person alone. Therefore, the Tai-chi class allows for both verbal and nonverbal connections among participants. Another study on yoga intervention for patients with schizophrenia proposed the role of improved emotional recognition to enhancing social functioning [45]. Being socially integrated is especially important in residential settings, where many participants in the study complained of being emotionally affected by indifferent or disruptive relationships with fellow residents. Indeed, social functioning is

Table 3: Performances outcomes of the Tai-chi and the waitlist control group on the assessed variables.

Assessment outcomes	Tai-chi ($n = 15$)			Waitlist control ($n = 15$)			Between group interaction	
							PostGroup effect T1-T2	Maintenance effect T1–T3
	T1	T2	T3	T1	T2	T3	*P*	*P*
Movement Coordination (CMDT)								
Placing	82.17 (9.75)	85.42 (16.78)	81.5 (14.63)	98.29 (28.2)	114.13 (41.04)	111.27 (45.09)	0.17	0.24
Turning	76.73 (14.51)	81.71 (20.6)	76 (17.4)	101.04 (40.89)	122.92 (50.61)*	115.88 (50.22)	0.11	0.15
Displacing	60.6 (10.13)	59.21 (12.13)	58.83 (9.78)	76.07 (26.6)	81.25 (26.57)*	84.23 (38.13)	0.02*	0.50
1-Hand Turning/Placing	102.37 (17)	105 (20.45)	101.53 (15.61)	124.82 (45.95)	145.33 (62.87)**	147.92 (74.8)	0.07	0.15
2-Hand Turning/Placing	65.53 (10.74)	66.25 (17.49)	67.07 (14.25)	89.96 (43)	101.09 (44.5)	107.31 (68.32)	0.17	0.26
Negative symptoms (SANS)								
Attention	4.21 (3.51)	2.67 (7.27)	3.33 (3.33)	5.6 (3.81)	3.55 (2.2)	5.85 (4.28)	0.06	0.49
Anhedonia-asociality	4.53 (4.29)	3.58 (3.63)	3.13 (2.45)	4.4 (4.6)	6 (4.07)	3.4 (3.09)	0.24	0.63
Avolition-apathy	1.79 (2.89)	1.58 (2.02)	1.79 (2.36)	2.27 (3.37)	3.27 (3.35)	2.14 (3.28)	0.62	0.84
Alogia	4.4 (4.97)	2.08 (4.12)	3.27 (5.46)	4.8 (5.17)	6.91 (4.81)	6.8 (7.29)	0.06	0.15
Affective flattening/blunting	8.2 (7.98)	3.33 (6.21)	6.4 (7.34)	8.67 (7.76)	7.82 (6.75)	6.47 (8.27)	0.56	0.59
Functioning disabilities (WHODAS II***)								
Cognition	12.2 (3.45)	12.27 (4.86)	11.13 (4.85)	11.33 (5.34)	9.87 (2.9)	11.4 (5.46)	0.93	0.44
Mobility	7.53 (2.39)	7.47 (3.42)	8.73 (4.17)	7.6 (2.87)	6.6 (2.06)	7.73 (2.63)	0.75	0.67
Self-care	3.4 (0.83)	3.07 (0.26)	3.47 (1.06)	3.2 (0.41)	3.27 (1.03)	3.73 (1.33)	0.41	0.33
Interpersonal interactions	7.47 (4.16)	7.13 (2.59)	6.13 (2.07)	5.27 (2.25)	7 (2.39)*	7.2 (3.1)*	0.07	0.01**
Life activities	11 (3.61)	10.27 (4.01)	9.47 (3.44)*	9.4 (1.76)	10.53 (4.36)	8.8 (1.82)	0.21	0.64
Community participation	17 (5.84)	12.87 (4.12)**	14.27 (6.27)	14.73 (5.87)	12.4 (4.03)	13.53 (6.33)	0.42	0.33

T1: baseline; T2: after-intervention; T3: 6-week maintenance; *$P \leq .05$; ** $P \leq .01$. *** Slightly modified.

Table 4: Themes and selected quotes on the subjective advantages and disadvantages of Tai-chi.

Advantages of Tai-chi	Disadvantages of Tai-chi
(1) Improving physical well-being, flexibility and movement regulation	(1) Tiredness
Tai-Chi was good for my bones and ligaments	Classes were long and felt out of energy
Tai-Chi made me more flexible	(2) Bodily discomfort
I was able to regulate the rhythm	My arms and legs hurt and I felt dizzy
It improved my physical ability	(3) Difficulty of the Tai-chi movements
It made me healthier	Movements were hard to remember and follow
(2) Improving cognitive and psychological health	(4) Difficulty in practicing independently
It made me happier	I did not know how to practice by myself
It helped me relax	(5) Tai-chi being slow and mundane
I could think more openly	It was boring
I felt more alert	
(3) Possibility of becoming a leisure activity	
Tai-Chi was attractive	
It gave me something to do	
(4) Others	
It was the correct thing to do	
Tai-Chi was a form of exercise	

a much neglected aspect of adjunctive treatment outcomes that cannot be captured by psychopathological assessments alone [46]. Yet, it bears significant clinical relevance where interpersonal interactions and community participation are predictive of clinical outcomes in a high risk psychosis group [47].

Participant feedback provided anecdotal suggestions for the possible mechanisms of the benefits of Tai-chi. Similar to yoga, Tai-chi distinguishes itself from other forms of physical exercises. Recognizing the mind-body nature of this activity, some participants expressed appreciation for both physical and mental benefits. They experienced improvements in health, flexibility, assured of the benefits for bones and ligaments. On the cognitive and psychological level, some participants were happier, more relaxed, alert, thinking more openly, and feeling more regulated. A hallmark disability of schizophrenia is poor learning and memory, believed to arise from hippocampal atrophy. With a high cognitive component involving the memorization of movement sequence, it can possibly help instigate hippocampal neurogenesis, hence, leading to cognitive improvements [48]. Future studies could also expand understanding on the benefits of Tai-chi towards other functional arenas.

From this preliminary study, Tai-chi supplementing regular antipsychotic and rehabilitation care has a protective effect for institutionalized patients. It is also a sustainable form of treatment that may offer a sense of mastery towards illness control. A persistent obstacle is participants' low motivation to continue practising independently. Tai-chi calls for mental endurance and patience, which proved challenging for some who found it mundane, or experience difficulty remembering the movements. Consequently, trainer-led weekly practice sessions could be helpful. Outside residential facilities however, practice sessions may become less feasible in the community, where preintervention psychoeducation on the health benefits of exercise and enhancing self-efficacy may improve participation rates [49]. In addition, this study was conducted with participants with constrained lifestyles where diet, sleep, medication, exercise levels, smoking, amongst others were carefully controlled. Under such favourable conditions, the effectiveness of Tai-chi is maximal, as it often takes collaborative efforts in lifestyle changes to bring about improvements to illness symptoms. Consequently, the effectiveness of Tai-chi for community patients with a less healthy lifestyle has yet to be explored.

Despite numerous studies demonstrating the effects of exercising and Tai-chi, this is one of the few randomized controlled trials on Tai-chi for patients with schizophrenia. However, this remains a small-sampled pilot study, which is confounded by the lack of a group exercise control condition to account for the possible effects of exercise or peer gathering. Another limitation lies in the assessment of functioning disability, WHODAS-II which was translated to Chinese but has yet to be validated in the population. Two items were also removed from the scale for their irrelevancy to the context but should also be assessed in a larger study with both residential and community patients. Notwithstanding such limitations, Tai-chi proved promising in areas where psychotropic medication currently has limited effectiveness. As the rehabilitation of mental illness gradually moves away from the medical model, Tai-chi can be promoted as an adjunct to improving patients' general functioning.

Conflict of Interests

The authors declare no conflict of interests.

Acknowledgments

This project is funded by Hong Kong Sheng Kung Hui Welfare Council and The University of Hong Kong Small Project Funding (201007176145).

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 595710, 9 pages
doi:10.1155/2012/595710

Research Article

Getting Started with Taiji: Investigating Students Expectations and Teachers Appraisals of Taiji Beginners Courses

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Received 9 August 2012; Accepted 10 October 2012

Academic Editor: Hans-Christian Deter

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In recent years, Taiji has been frequently investigated and considered as a stress management intervention. Although health care providers' appraisals and consumers' expectations are regarded as essential for treatment outcome, little attention has been drawn to this issue in Taiji research. In our study we have conducted two surveys to explore beginners' ($n = 74$) expectations and teachers' ($n = 136$) appraisals of their Taiji courses in general as well as more particularly related to stress management. Qualitative data analysis revealed that beginners mainly expected to learn a new method that is applicable in their daily life to foster peace of mind and to enhance their stress management. Congruently moderate-to-high improvements in stress management have also been found in quantitative analysis, whereby a lower educational level predicted higher expectations ($P = 0.016$). Taiji-teachers stated body- and mind-related benefits most frequently and appraised moderate-to-high improvements in stress management. Higher appraisals were predicted by a shorter teaching experience ($P = 0.024$). Our results inform about beginners' expectations and teachers' appraisals related to a Taiji-beginners course and highlight the role of educational background and teaching experience in shaping stress-management-related beginners' expectations and teachers' appraisals.

1. Introduction

In the recent past, the interest in mind-body practices for health promotion and stress management has considerably increased in the general and clinical population as well as in the scientific community [1–5]. In particular, Taiji (or T'ai Chi, T'ai Chi Chuan, Taijiquan), a mind-body practice originating from China, became more popular in western countries in the last decades [6–8]. Taiji is defined by Wayne and Kaptchuk [6] as "an exercise based on slow intentional movements, often coordinated with breathing and imagery, which aims to strengthen and relax the physical body- and mind, enhance the natural flow of what the Chinese call *qi* (. . ., life energy), and improve health, personal development, and self-defense" (page 96). In fact, numerous clinical trials and systematic reviews examined the effectiveness of Taiji for various health conditions, underlining its preventive and therapeutic value, for example, for fall prevention [9–12], for treatment of chronic diseases [9, 13–16], and for improvement of mental health [9, 10, 17], where a particularly growing body of evidence is supporting the beneficial effects of Taiji practice on stress management [17–22]. However, hitherto only a few studies have been published explicitly investigating the underlying modes of action of Taiji [6, 23, 24]. Taiji is regarded as a complex intervention, comprising multiple components of which each may have independent and synergistic therapeutic value. Two of these components are students' expectations and teachers' attitudes [6].

As shown in previous research, treatment expectations of health care consumers may influence treatment outcome; in

particular higher treatment expectations have been repeatedly found to be associated with better treatment results [25–29]. The impact of health care practitioners' expectations on treatment results has also been documented [30–32] as well as the crucial importance of the match of treatment-related appraisals and expectations for an outcome enhancing working alliance [33–36].

Even though the above-mentioned findings underline the relevance of expectancies and appraisals on treatment results, to date studies exploring this issue in the field of Taiji and other mind-body practices are scarce. We have found an early Taiji study, where the enhancement of mood after Taiji practice has been partially explained by a higher expectation of a positive outcome (i.e., mood enhancement) in the Taiji group [37]. Although the need for further research into the role of participants' motivation in stress management practices such as Taiji has been highlighted [37], only one qualitative study assessed treatment-related expectations of Qigong beginners [38]. The findings of this study suggest that Qigong beginners with no further specified health status mainly expect improvement of their health condition and relaxation as well as professionalism, provision of information, and empathy from the teachers [38]. To the best of our knowledge, beginners' expectations and teachers' appraisals regarding the benefits of their Taiji courses have not yet been investigated.

Based on the relevance of treatment-related expectations and appraisals for treatment outcome, an increased awareness and knowledge about beginners' expectations and teachers' appraisals of their Taiji-beginners courses may have an impact on treatment outcomes in Taiji interventions. Therefore, the aim of our present study was to explore beginners' expectations and teachers' appraisals of their Taiji-beginners courses.

2. Methods

2.1. Study Design. We have conducted two surveys, one among Taiji-beginners in the area of Bern and one with Taiji teachers in the German speaking area of Switzerland including the Bern area. The survey of Taiji-beginners was nested within a trial examining psychobiological effects of Taiji on psychosocial stress reactivity [22] and was formally approved by the ethics committee of the Canton of Bern, Switzerland. For the survey of the Taiji teachers, no approval of the ethics committee was required. However, participants' information about the study and the voluntary nature of survey participation, and data protection were handled alike.

2.2. Selection of Subjects. In the first survey, healthy Taiji-beginners were recruited through announcements on pin boards and on the websites of the University of Bern and the University Hospital in Bern. Eligible participants had to be between 18 and 50 years old and fluent in German. Exclusion criteria are reported elsewhere in detail [22]. All participants who completed baseline examination were included in this study.

For the second survey, we identified electronically registered Taiji teachers in the German-speaking part of Switzerland by conducting an Internet search in November 2010 using the Google search engine. All of them were invited to participate in an online survey by e-mail. Participants had to be fluent in German and actively engaged as Taiji teachers.

2.3. Data Collection. Both study groups participated in an online survey. After assessing sociodemographic data (for all participants: gender, age, and occupation status; for Taiji-beginners only: education level; for Taiji teachers only: years of Taiji practice experience and years of Taiji-teaching experience) the first question asked to Taiji-beginners aimed to assess their general expectations and was "What are your expectations towards the upcoming Taiji course (= two lessons per week during 3 months)?" Comparably, the Taiji teachers were asked to answer the open question "Which benefits can a newbie expect from a Taiji-beginners course (= two lessons per week during 3 months)?" also by writing down their narrative responses.

To assess beginners' expectations and teachers' appraisals related to changes in stress management in response to regular Taiji practice, all study participants were additionally asked to rate 12 statements expressing Taiji-induced changes in stress coping (6 items) and resource activation (6 items), by indicating the degree of their agreement on a 6-point Likert scale ranging from 1 (strongly disagree) to 6 (strongly agree). To avoid priming effects, these items were presented on a new screen page. The full self-developed questionnaire is shown in the Appendix. We defined the sum of all rating scores as an index representing expected or appraised changes in overall stress management induced by regular Taiji practice. This stress management index with a theoretical score range from 12 to 72 has a high internal consistency in Taiji-beginners (Cronbach's $\alpha = 0.89$), as well as in Taiji teachers (Cronbach's $\alpha = 0.94$). Construct validity was estimated by pooling data of both study groups and calculating a principal component factor analysis across all 12 items. An analysis of the eigenvalues using scree test [39] resulted in a one general factor solution (eigenvalue = 6.5) with 54.4% explanation of variance. The item loadings on the general factor ranged from 0.45 to 0.83.

2.4. Data Analysis. Data analysis was conducted by using SPSS (version 18) statistical software package for Macintosh (IBM SPSS Statistics. Somers, NY, USA). Sociodemographic characteristics of Taiji-beginners and Taiji teachers were analyzed by using descriptive statistics. Unless indicated, all results are presented as mean ± standard deviation (SD).

Narrative questionnaire data were systematically prepared and analyzed by using a qualitative and quantitative approach [40]. In the qualitative approach, each analytical step has been conducted independently by two authors (MN and CB). After each step, results were compared and differences were discussed until consensus was found. In a first step, each narrative response was screened to detect and mark all analytical units (e.g., beginners' expectations, resp., teachers' perceived benefits). In a second

step, those analytical units lacking in terminological clarity were explicitly stated. Afterwards, all analytical units were reduced to short paraphrases, comprehensible independent from its originally embedded context. In a next step, we conducted a content analysis of about 50% of all analytical units and inductively generated thematic categories. The suitability of these categories was tested by classifying the remaining 50% of all analytical units. After amending the initially defined categories, we reclassified all analytical units. Finally, we thematically captured the final categories into main categories. Both the main and the subcategories were quantitatively described by indicating the frequency of mentions in absolute and percentage values.

In explorative data analysis, we compared beginners' general expectations with teachers' general appraisals related to Taiji-beginners courses by examining group differences of frequency values in each main category using χ^2 tests.

In the quantitative approach, we conducted explorative comparisons of stress-management-related to beginners' expectations and teachers' appraisals using a t-test for independent samples. Prior to t-test calculation, normal distribution of data and homogeneity of variance were verified by the Kolmogorov-Smirnov test and the Levene test. All analyses were two tailed, with the level of significance set at $P \leq 0.05$ and the level of borderline significance set at $P \leq 0.10$.

For Taiji-beginners, we calculated a hierarchical linear regression analysis to examine the predictive value of the independent variables "age," "gender," and "education level" on the expected changes in overall stress-management-related to regular Taiji practice (dependent variable). Similarly, we computed a hierarchical linear regression analysis in the group of Taiji teachers to investigate the potential role of the variables "age," "gender," and "teaching experience" as independent predictors of their appraised changes in Taiji-beginners' overall stress management due to regular Taiji practice (dependent variable).

3. Results

3.1. Group Characteristics. Of the 112 initially registered applicants for a Taiji-beginners course, 74 subjects completed baseline examination and met the inclusion but none of the exclusion criteria. There was no missing data in this group.

Of the 355 invited Taiji teachers, 24 had no valid e-mail address and could not have been reached otherwise, 19 were offering Qigong but no Taiji classes, 10 were not teaching anymore, and 10 were registered twice. Of the remaining 292 potentially eligible Taiji teachers, 136 (47%) completed the survey. Stress-management-related appraisals were missing from three Taiji teachers. An overview of sociodemographic characteristics of both study groups is presented in Table 1.

3.2. Beginners' Expectations towards Their Taiji Course

3.2.1. Qualitative Analyses. Analyzing Taiji-beginners' answers on the first question assessing course expectations in general, a total of 299 expectations (mean 4.04 ± 1.84) were stated. As shown in Figure 1, beginners mentioned daily-life-related expectations (comprising 20% of all expectations mentioned) approximately as frequently as knowledge related (19%), mind-related (17%), and mind-body-related expectations (17%), while body-related (15%) and process and context-related expectations (11%) were mentioned less frequently.

With respect to frequencies of expectations as represented in the subcategories, "get to know Taiji in general" was mentioned by 57% of all Taiji-beginners followed by "improvement of stress management" (41%) and "increase of internal balance and peace of mind" (32%). 27% of all beginners also expected "transferability of course content into daily life" and an "increase of body awareness". The expectation "increase of relaxation" was mentioned by 26% of the course applicants. Complete results are shown in Table 2.

3.2.2. Quantitative Analyses. From regular Taiji practice (i.e., one hour twice a week during three months) beginners expected a moderate-to-high improvement of their stress management (mean 53.50 ± 9.56; range = 12 to 72). Regression analysis revealed that a lower education level significantly predicted higher improvements in the successful management of stress ($\beta = -0.29$; $P = 0.016$), whereas age and gender did not (see Table 3). The whole model explained 9.1% of total variance in beginners expected stress-management-related changes ($R^2 = 0.091$; $R^2\text{corr} = 0.052$; $F = 2.32$, df = 3/73, $P = 0.083$) with 8.0% explained by "educational level" ($P = 0.016$).

3.3. Teachers' Appraisals of Their Taiji Courses

3.3.1. Qualitative Analyses. A total of 816 general appraisals (mean = 6.00 ± 2.76) were stated by the Taiji teachers in their answers to the initial question assessing potential benefits a Taiji-beginners course may offer to newbies. As shown in Figure 1, 76% of all appraisals belonged to the main categories of body-related (43%) and mind-related appraisals (33%), while the less frequently mentioned appraisals were captured by the remaining four main categories mind-body-related (17%), daily-life-related (4%), knowledge-related (2%), and process- and context-related appraisals (1%).

Analyzing frequencies of appraisals in the subcategories, results revealed that 60% of all Taiji teachers mentioned an "increase of internal balance and peace of mind" as a benefit Taiji-beginners may expect from regular Taiji practice. Other frequently mentioned benefits were "improvement of body awareness" (46%) and "improvement of physical functioning" (44%) such as breathing, circulation, blood pressure, immune system, digestion and sleep, "improvement of balance" (38%), "improvement of motor coordination" (37%), "increase of power of concentration" (32%), and "increase of flexibility" (32%). For complete results see Table 2.

3.3.2. Quantitative Analyses. Taiji teachers appraised a moderate-to-high improvement of stress management in beginners as a result of regular Taiji practice (mean 54.36 ±

Table 1: Socio-demographic data of study participants.

	Beginners ($n = 74$)	Teachers ($n = 136$)
Age in years (mean ± SD; range)	35.35 ± 7.49; 22–50	50.01 ± 8.46; 29–71
Gender		
Male (%)	30	49
Female (%)	70	51
Education level		
With high school degree (i.e., Swiss Matura) (%)	77	—
Without high school degree (%)	23	—
Occupation status		
Student (%)	11	0
Full- or part-time job (%)	89	100
Taiji practice in years (mean ± SD; range)	0	18.60 ± 8.26; 3–46
Taiji teaching practice in years (mean ± SD; range)	0	11.56 ± 7.75; 1–37

SD: standard deviation.

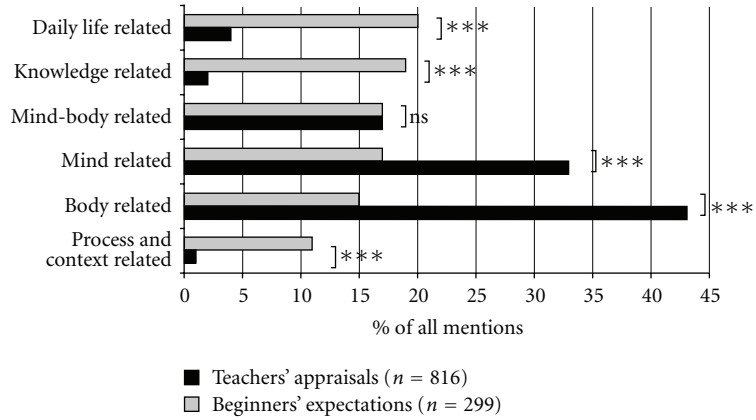

Figure 1: Comparison of aggregated beginners' expectations and teachers' appraisals; ns = not significant; *** = $P < 0.001$.

9.67; range = 12 to 72). As revealed in regression analysis, appraisal of a higher improvement of successful stress management in beginners was significantly predicted by lower teaching experience ($\beta = -0.22$; $P = 0.024$; see Table 3). The overall explanation of variance by our model is small ($R^2 = 0.075$; R^2corr = 0.053; F = 3.46, df = 3/13, $P = 0.018$) with "teaching experience" alone explaining 3.7% ($P = 0.024$).

3.4. Explorative Comparison of Beginners' Expectations with Teachers' Appraisals. The comparison of the main categories of beginners' expectations and teachers' appraisals is depicted in Figure 1. In contrast to the Taiji teachers, beginners generally stated significantly fewer expectations ($t = 6.14$; df = 200, $P < 0.001$). They addressed significantly more frequently daily-life-related ($\chi^2 = 73.48$; $P < 0.001$) and knowledge-related expectations ($\chi^2 = 104.61$; $P < 0.001$) toward their upcoming Taiji course. Taiji teachers in turn were more frequently emphasizing body-related ($\chi^2 = 74.72$; $P < 0.001$) and mind-related benefits ($\chi^2 = 27.06$; $P < 0.001$) a Taiji-beginners course may offer. No group differences were observed for mind-body-related statements ($P = 1.00$). Process- and context-related statements were the least mentioned ones in both groups, yet significantly more often mentioned by Taiji-beginners ($\chi^2 = 62.48$; $P < 0.001$). Both groups did not differ regarding their ratings related to expected, respectively, appraised Taiji-induced changes in overall stress management ($P = 0.54$).

4. Discussion

Our study is the first to examine beginners' expectations and teachers' appraisals towards Taiji-beginners courses. In the following, we will summarize, discuss, and compare our findings of our two surveys.

While both beginners and teachers expressed comparable mind-body-related expectations and appraisals, we found significant differences in daily-life-, knowledge-, mind- and body-related statements. Taiji-beginners expected to learn a new approach that is particularly helpful to foster peace of mind and to improve their stress management. They explicitly emphasized the transferability of course contents into their daily life. In contrast to Taiji-beginners, only a few teachers mentioned knowledge-related and daily-life-related benefits, but many of them stated mind- and body-related benefits of Taiji practice. It might be that Taiji teachers are

Table 2: Frequency of mentioned beginners' expectations and teachers' appraisals of the benefits of a Taiji-beginners course.

Mentioned expectations/appraisals	Beginners ($n = 74$) results in %[1]	Teachers ($n = 136$) results in %[1]
Daily-life-related expectations/appraisals		
Improvement of stress management	41	13
Transferability of course content into daily life	27	9
Counterbalance to daily work	14	3
Knowledge-related expectations/appraisals		
Get to know Taiji in general	57	2
Learning the motion sequences	15	4
Get to know the philosophical background	5	2
Improvement of self-defense	1	1
Mind-body-related expectations/appraisals		
Increase of body awareness	27	46
Increase of relaxation	26	29
Holistic health promotion	16	19
Perception of the flow of Qi/energy	1	8
Mind-related expectations/appraisals		
Increase of internal balance and peace of mind	32	60
Increase of power of concentration	14	32
Expansion of consciousness	5	6
Fostering of self-compassion	5	7
Fostering of equanimity	4	16
Increase of contentedness	3	16
Fostering of mindfulness	3	5
Increase of mental flexibility/openness	1	11
Increase of self-efficacy	1	5
Increase of patience and tenacity	1	1
Increase of self-esteem	0	10
Fostering of compassion and tolerance towards others	0	8
Increase of mental alertness	0	18
Improvement of memory	0	2
Body-related expectations/appraisals		
Be physically active	16	3
Increase of physical well-being	14	16
Strengthening of the body	8	21
Improvement of motor coordination	7	37
Increase of flexibility	5	32
Improvement of balance	4	38
Improvement of body alignment/posture	3	21
Improvement of physical functioning	3	44
Alleviation of physical ailments	1	23
Increase of postural stability	0	16
Increase of looseness	0	4
Reduction of risk of falls	0	1
Process- and context-related expectations/appraisals		
Enjoyment of practicing Taiji	12	5
Meeting new people	9	2
Professional instruction	9	0
Experience of learning progress	7	1
Pleasant course ambience	5	1

[1] % values refer to the percentage of subjects in each study group.

Table 3: Hierarchical regression analyses for (a) Taiji-beginners' expectations related to stress management and (b) for Taiji-teachers' appraisals related to stress management.

Variables entered	Standardized β-coefficient	t	P value	R^2 change
(a) Stress management ($n = 74$)				
Age	−0.16	−1.39	0.17	0.009
Gender	−0.08	−0.68	0.50	0.001
Education level*	−0.29	−2.48	0.016	0.080
(b) Stress management ($n = 133$)				
Age°	0.17	1.83	0.07	0.010
Gender°	0.14	1.68	0.10	0.027
Teaching experience*	−0.22	−2.28	0.024	0.037

°$P \leq 0.10$; *$P \leq 0.05$.

mainly aiming to transmit implicit procedural rather than explicit declarative knowledge about Taiji to their students. As the retention of procedural knowledge is thought to be longer lasting [41], teachers might have implicitly assumed that the skills their students acquire during their Taiji training would have an impact on their daily life. On the other hand it should be kept in mind that the beginners under study took part in a research project that examined whether Taiji training-related to psychosocial stress reactivity [22]. This participation might have contributed to a frequent mentioning of improvement of stress management among beginners' daily-life-related expectations. However, since stress-management-related benefits of Taiji practice are commonly described in basic literature for Taiji-beginners [7, 42, 43], these expectations might also occur in subjects attending Taiji-beginners classes in naturalistic settings. A possible reason explaining why beginners did not mention body- and mind-related expectations as frequently as teachers did might be the lack of knowledge about these potential effects of Taiji practice. This reasoning is in line with the high frequency of knowledge related expectations in Taiji-beginners. Also to be taken into account is the young to middle age and the good health status of the beginners under study. While older people with an impaired physical condition are likely to expect more body-related benefits when engaging into physical activity programs [44] this might not have been the case for our study group.

Only a few beginners and even fewer teachers mentioned process- and context-related expectations and appraisals. This finding suggests that the vast majority of our study participants are not aware of the potential relevance of process- and context-related factors for treatment outcome [45–48]. It may be that Taiji teachers take the agreeableness and the appropriateness of their teaching methods employed in their courses for granted and therefore rarely mention context and process related aspects of their work. For Taiji-beginners, it is very unlikely that they are already familiar with the special role of a Taiji-teacher in terms of being not only teacher but also motivator, coach and therapist [6] as they never experienced a Taiji-lesson before.

Congruence of both study groups was observed in terms of moderate to high expected and appraised improvements in stress management in response to regular Taiji practice. Our quantitative data shows that a lower educational level predicted higher stress-management-related expectations in Taiji-beginners. This might be due to the fact that people with a less favorable educational background are affected more strongly by the presence of various stressors and absence of multiple resources [49] and therefore are more likely to express higher stress-management-related expectations. Personal resource factors such as mindfulness and self-compassion are regarded as stress protective trait characteristics [50, 51]. Therefore, it may be speculated, that subjects with low scores in these two variables have a higher need for improvements in stress management and that this need influences stress-management-related expectations. Notably, in this study we have also assessed self-reported mindfulness and self-compassion scores in all study participants at baseline examination [52]. Indeed, our explorative analysis revealed that there are significant negative correlations of the sum score of stress-management-related expectations with self-reported self-compassion total score ($r = -0.27$; $P = 0.019$), self-compassion subscales "isolation" ($r = 0.34$; $P = 0.003$), and "overidentification" ($r = 0.30$; $P = 0.011$) but not with mindfulness ($r = -0.17$; $P = 0.15$). Hence, our data partially support a potential association between lower levels of personal resource factors and a higher level of stress-management-related expectations. For the Taiji teachers interestingly, a shorter teaching experience predicted more optimistic teachers' appraisals regarding improvement in stress management. As more experienced teachers are believed to have larger teaching experience with advanced Taiji students, they therefore might perceive beneficial effects in long-term Taiji-practitioners as more pronounced than in beginners. Hence, our finding might be explained by a broader frame of reference employed by the more experienced Taiji teachers.

Our study results provide information with practical relevance. Considering the self-confirming nature of expected treatment responses [25–28], our data suggest that Taiji-beginners are likely to foster mental well-being and enhance stress management by implementing their acquired Taiji-related knowledge and skills in their everyday lives. In fact, we have observed decreased psychobiological reactivity to psychosocial stress [22] and enhanced levels of mindfulness and self-compassion [52] in subjects in

the Taiji group compared to subjects in the waiting-list control group. However, as explorative analyses revealed, these effects have not been found to be directly modulated by stress-management related expectancies (data not shown). Potential synergistic effects of beginners' expectations with other treatment components such as teacher's appraisals on treatment outcomes should be subject of future research. Since beginners' expectations and teachers' appraisals differ in several points, we recommend Taiji teachers to proactively ask their new students about their course expectations and to inform them about potential benefits of regular Taiji practice early in the course. This can prevent students from disappointment due to clinging to inadequate expectancies and helps them to modify their expectations towards greater congruence with teachers' appraisals of potential benefits a Taiji beginner course may offer. Also teachers might adapt their courses to respond to their students' needs more effectively. Such congruence in turn would be likely to enhance the working alliance and to increase beginners' course satisfaction and course adherence. Despite this reasoning being highly plausible, our data do not allow to draw any conclusion about the impact of the observed incongruence between beginners' expectations and teachers' appraisals on the outcomes of the Taiji courses or the beginners' and/or teachers' course satisfaction. Still our findings may provide information of practical relevance: Since Taiji is not commonly practiced among health care professionals [53], our data collected from 136 Taiji teachers provides valuable insights into potential benefits of Taiji-beginners courses that might be helpful for health care professionals for their own as well as for their patients' information.

The following limitations need to be addressed. First, Taiji-beginners were not students of the investigated teachers; thus we were not able to assess the degree of working alliance between both study groups. For the same reason a potential negative influence of the mismatch between beginners' expectations and teachers' appraisals on course-related outcome values could not have been investigated. Secondly, the results of Taiji-beginners' expectations are restricted to healthy young to middle-aged and predominantly well-educated participants. People with functional limitations should be included in future studies, as this population is regarded to represent a large proportion of all Taiji practitioners [54]. Third, because our survey of Taiji-beginners was nested within a trial examining effects of Taiji on psychobiological stress reactivity, this circumstance might have influenced stress-management-related expectations of our Taiji novices. Therefore, we recommend for future studies in this field to investigate Taiji-beginners and their corresponding teachers under naturalistic conditions.

In addition to the above-mentioned practical implications of our findings, the main strengths of this study are the consideration and comparison of both beginners' expectations as well as teachers' appraisals, the combination of qualitative and quantitative data assessment, which allows us to provide an overview of general as well as more specifically stress-management-related expectations and appraisals. Moreover, a relatively large population of active Taiji teachers has participated in our survey.

5. Conclusion

The results of our study increase the awareness of and knowledge about the nature of expectancies and appraisals in Taiji-beginners practice. We have found that educational background, the level of self-compassion, and teaching experience are involved in shaping stress-management-related expectations and appraisals. The impact of students' expectations, teachers' appraisals, and the interaction of both on treatment outcomes of Taiji interventions remains to be further investigated.

Appendix

Questionnaire Assessing Expected/Perceived Changes in Stress Management Attributed to Taiji Practice

Please indicate to which degree the below mentioned statements match your personal opinion: 1 = strongly disagree; 2 = disagree; 3 = rather disagree; 4 = rather agree; 5 = agree; 6 = strongly agree.

(i) Items answered by Taiji-beginners: From regular Taiji practice, *I do expect that I can...

(ii) Items answered by Taiji teachers: A beginner who is regularly practicing Taiji* can expect that he/she can...

(1) deal with stressful situations in a more relaxed manner;
(2) be more self-aware in difficult situations;
(3) increase my, resp., his/her feeling of physical fitness;
(4) better perceive the needs of my, resp., his/her body;
(5) generally feel more calm and balanced;
(6) be more mindful in daily life;
(7) feel less troubled by unexpected inconveniences;
(8) rely more on my, resp., his/her inner strengths when facing unexpected inconveniences;
(9) maintain calmness in challenging situations;
(10) recover more rapidly after a demanding task;
(11) increase my, resp., his/her power of concentration;
(12) socialize more with others.

*Regular class attendance twice a week during three months including independent Taiji practice at home.

Acknowledgments

The authors acknowledge the financial support of Stiftung für Komplementärmedizin, Gottfried und Julia Bangerter-Rhyner Stiftung and Parrotia Stiftung (to M. Nedeljkovic and B. Ausfeld-Hafter), and of the Swiss National Foundation

Grant to PP00P1_128565/1 (to P. H. Wirtz). The funding sources had no role in study design, in the collection, analysis and interpretation of data, in the writing of the paper, and in the decision to submit the paper for publication. Further, the authors would like to thank Ms. Isabelle Pfaff for her skillful assistance in conducting the online survey and Mr. Dominikus Vogl for his helpful advice in statistical analyses.

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Hindawi Publishing Corporation
Evidence-Based Complementary and Alternative Medicine
Volume 2012, Article ID 151737, 8 pages
doi:10.1155/2012/151737

Research Article

Effects of Auricular Acupressure on Body Weight Parameters in Patients with Chronic Schizophrenia

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Received 21 April 2012; Revised 6 July 2012; Accepted 2 August 2012

Academic Editor: Jörg Melzer

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Auricular acupressure is widely used in complementary and alternative medicine to reduce body weight, but little is known about the effects of auricular acupressure on body weight parameters in patients with chronic schizophrenia. The purpose of this study was to evaluate the effects of auricular acupressure on body weight parameters in patients with chronic schizophrenia. Eighty-six inpatients with schizophrenia were recruited from chronic wards in a psychiatric center. The participants were randomly divided into experimental (acupressure at 4 acupuncture sites: hunger, stomach, shenmen and endocrine) and control groups, and body weight parameters were determined weekly for 8 weeks. There was no significant difference between the experimental and control groups in mean body weight, waist circumference, or body fat percentage at the pretest or during the entire 8-week study period. Therefore, auricular acupressure did not cause body weight reduction in patients with chronic schizophrenia.

1. Introduction

Schizophrenia is a severe mental illness with a chronic course. The diagnosis of schizophrenia, excluding schizoaffective or mood disorder, substance use or general medical condition, and pervasive developmental disorder, is defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) as the presentation of positive and negative symptoms for ≥1 month (or less if successfully treated) and deterioration of interpersonal and occupational relations for ≥6 months [1]. The positive symptoms include delusions, hallucinations, disorganized speech, and disorganized or catatonic behavior, and the negative symptoms include affective flattening, alogia, social withdrawal, and the lack of spontaneity.

Patients with schizophrenia have an increased prevalence of obesity and unfavorable body composition compared with the general population [2–4]. The prevalence of obesity among patients with schizophrenia is increasing each year [5–9].

Obesity is a major risk factor for type 2 diabetes, metabolic syndrome, and cardiovascular disease [10–16]. Obesity also has become a major concern in the treatment of mental disorders because it may adversely affect treatment adherence and relapse rates [17, 18].

Furthermore, obesity is associated with reduced quality of life [19], social stigma [20], and greater morbidity and mortality [21]. The United States National Institute of Mental Health convened a meeting in October 2005 and concluded that obesity among individuals with mental disorders has not received adequate research attention [22].

Auricular acupressure is a simple, self-manipulated treatment method that applies *vaccaria* seeds or steel beads to the ear to stimulate auricular acupoints. It is widely used in complementary and alternative medicine to reduce body weight, but little is known about its effect on weight reduction. Previous animal studies suggest that stimulation of the auricular regions is associated with the ventromedial hypothalamus, which affects the satiety center and leads to weight loss [23]. Needle point stimulation on auricular

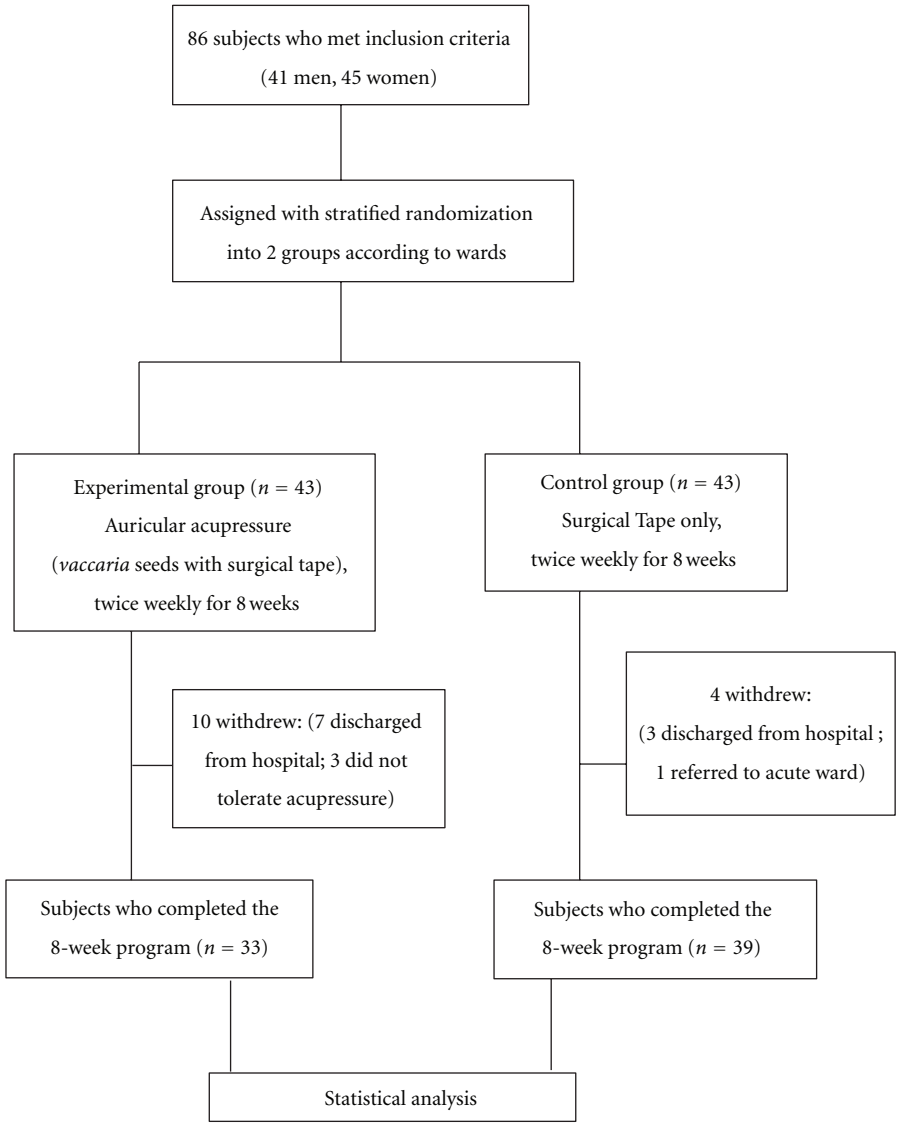

Figure 1: Study flowchart.

acupoints may increase the secretion of ghrelin, which is a peptide hormone that induces satiation and is inversely related to caloric intake [24]. The purpose of this controlled, single-blind study with stratified random sampling was to explore the effects of auricular acupressure on body weight parameters, including body weight, waist circumference, and body fat percentage, in patients with chronic schizophrenia.

2. Methods

The study protocol was approved by the ethics committee of the Tsao-Tun Psychiatric Center Institutional Review Board (TTPC IRB99002) in February 2010, and carried out in compliance with the Declaration of Helsinki. Volunteers were recruited through posters placed in chronic psychiatric wards, all of them were hospitalized Chinese schizophrenia patients. Protocol contents were thoroughly explained to each patient by the investigator. Patients were told that they could withdraw from the study anytime if they were not willing to continue. After patients and their families agreed and signed the informed consent forms, the patients were given the "precautions for auricular acupressure for weight reduction" and related health education pamphlets.

There were 86 patients (41 men [48%] and 45 women [52%]) who were recruited and assigned by stratified randomization according to the wards. Each patient was assigned a sequence number according to the medical record number, and then random numbers were obtained from a random number table to divide the patients into 2 groups (43 patients in each group): (1) experimental auricular acupressure group and (2) control group (Figure 1).

During the study period, patients maintained their normal daily lives and were not required to manage diet and exercise themselves to control weight.

Inclusion criteria were meeting the DSM-IV criteria for schizophrenia, staying in a chronic psychiatric ward for >2

Table 1: Standards for reporting interventions in clinical trials of acupuncture (STRICTA 2010).

Acupoint rationale	(1) According to meridian theory of traditional Chinese medicine (2) Ear acupoints (hunger, stomach, shenmen, and endocrine)
Acupressure detail	(1) 4 *vaccaria* seeds with Surgical Tape. (2) Bilateral (each ear acupoints for 3 and 4 consecutive days alternately) (3) Pressure feeling (4) Burning sensation of the ear (5) Manual acupressure (6) 4 minutes each time (1 min for each acupuncture point) (7) Crude *vaccaria* seeds, diameter of *vaccaria* seed = 2 mm
Treatment regimen	(1) 16 sessions (twice per week) (2) Duration, 8 weeks duration
Cointerventions	(1) None of herbs, moxibustion, cupping, massage, exercise, dietary advice, or lifestyle modification
Practitioner background	Licensed Chinese medical doctor, who has had 540 hours of acupuncture training
Control intervention	(1) Same ear acupoints (2) Surgical Tape (3) No acupressure

months, and meeting the following criteria: (1) age between 20 and 60 years; (2) body mass index (BMI) $\geqq 24\,kg/m^2$; (3) current stable mental status and able to communicate with researchers by written or verbal communication.

Exclusion criteria were (1) a person was determined by a court to be incapable of consistently making decisions about his person and his property or some part of either; (2) endocrine disorders: such as abnormal function of thyroid, pituitary, and sex glands; (3) heart diseases: such as arrhythmia, myocardial infarction, heart failure, or installed pacemaker; (4) immune and allergic diseases: such as systemic lupus erythematosus and asthma; (5) liver or kidney dysfunction: GOT or GPT > 80 IU/L, Cr > 2.5 mg/dL; (6) pregnant or lactating women; (7) <6 months postpartum; (8) physical dysfunction because of stroke; (9) involvement in any weight control program within the previous 3 months; (10) determined by the attending psychiatrist to be unsuitable for participation, because of flare ups of psychosis or risk of violence or self-harm.

2.1. Experimental Design. The participants were randomly divided into a treatment and a control group, that measurements would take place weekly and that pre- and posttreatment data would be compared.

To improve data objectivity, auricular acupressure was performed and main outcome measures were determined by different persons. There were 6 staff members who were responsible for collecting effect indicators. To increase reliability of data collection, the interrater agreement on waist circumference was assessed from March 8 to 12, 2010; after 6 raters measured 20 patients for waist circumference, the interrater reliability of the results were computed by Pearson correlation analysis. Through communication and training, the interrater reliability reached 0.95 to 1.0 among the 6 raters.

The weight control program was conducted over 9 weeks (including one pretest and 8 subsequent tests, at 1-week intervals); the follow-up time between the 2 groups was conducted as follows for the effect indicators: (1) body weight and waist circumference were measured weekly 9 times in a time series, including once at 1 week before the intervention and weekly through the first to the eighth weeks after the intervention; (2) body fat percentage was measured only 1 week before the intervention and at 8 weeks after the intervention. The study flowchart is shown in Figure 1.

2.2. Auricular Acupressure Group. Auricular acupressure was performed by a licensed acupuncturist, who had 540 hours of acupuncture training before participating in the trial. The checklist of consolidated standards of reporting trials (CONSORT) was complete [25]. The complete details of the intervention are presented in Table 1 in conformance to standards for reporting intervention in clinical trials of acupuncture (STRICTA 2010) [26]. Auricular acupressure was given twice weekly for 8 weeks; auricular acupressure was administered to each ear and left in place for 3 and 4 consecutive days alternately. *Vaccaria* seeds with Surgical Tape (3M, Taiwan) were applied at 4 acupuncture points, including the hunger, stomach, shenmen, and endocrine points on the ear. Acupuncture points were selected based on previous studies and clinical experience. Patients were instructed to press on the *Vaccaria segetalis* plaster at each acupuncture point before consuming each of 3 meals every day (4 minutes total, 1 minute for each acupuncture point until the ear had a burning sensation). Compliance with self-pressure at the acupuncture points was monitored with 2 methods: (1) nursing staff of the chronic psychiatric wards reminded and monitored patients while they pressed the acupuncture points at morning, noon, and evening meals and (2) researchers provided a form on which each patient recorded the time of self-application of acupressure.

2.3. Control Group. In the control group, Surgical Tape was applied twice weekly, for 3 and 4 consecutive days, for 8 weeks. Selected acupuncture points were the same as those for the AA group, but only Surgical Tape was applied and no points were pressed. The contact moment was just comparable to that in the AA group. The same acupuncturist applied the Surgical Tape in the control group.

2.4. Body Composition Measurement. Inpatients received controlled meals from the central kitchen in the hospital. Body weight and waist circumstance were measured 2 hours after dinner. A night snack and drink were served 2.5 hours after dinner. All patients had weight parameters measured before having the night snack and drink.

Table 2: Comparison of control variables and dependent categorical variables between the two groups.

Variable	Group		χ^2 value	P value
	AA group	Control group		
Sex				
Men	15 (46)	18 (46)	0.000	1.000
Women	18 (54)	21 (54)		
Join sheltered workshop				
Yes	10 (30)	11 (28)	0.000	1.000
No	23 (70)	28 (72)		
Second generation antipsychotics				
No	9 (27)	6 (15)	0.896	0.344
Yes	24 (73)	33 (85)		

AA group: experimental group, auricular acupressure with *vaccaria* seeds and Surgical Tape; control group: Surgical Tape only.

Table 3: Comparison of control variables and dependent continuous variables between the two groups.

	Number	Mean	Standard deviation	95% confidence interval for the mean		F value	P value
				L	U		
Body height (cm)							
AA group	33	160.6	1.5	157.6	163.6	0.111	0.740
Control group	39	161.2	1.1	158.9	163.5		
Age (y)							
AA group	33	46.8	1.6	43.6	50.0	0.729	0.396
Control group	39	48.6	1.4	45.7	51.4		
Disease duration (y)							
AA group	33	15.9	0.9	14.0	17.7	1.584	0.212
Control group	39	14.2	0.9	12.4	16.1		
Onset age (y)							
AA group	33	30.9	1.3	28.2	33.6	2.287	0.135
Control group	39	34.4	1.8	30.8	37.9		
Length of hospitalization (y)							
AA group	33	5.6	0.6	4.4	6.8	0.768	0.384
Control group	39	4.9	0.6	3.6	6.1		

AA group: experimental group, auricular acupressure with *vaccaria* seeds and Surgical Tape; control group: Surgical Tape only.

For the measurement, patients were asked to wear only underwear. The scale precision was calculated as ±0.1 kg. The BMI was calculated by dividing weight in kilograms by the square of height in meters. The measuring tape was placed around the waist at the level of the umbilicus. The tape was held horizontally and close to the skin without disturbing breathing. At the end of expiration, the waist circumference was measured with a precision of ±0.1 cm.

Body fat percentage was measured 2 hours after meals with a body fat analyzer, based on bioelectrical impedance analysis (Type Tanita-519, Japan). Patients were asked to urinate before measurement.

2.5. Statistical Analysis. Data were entered in an Excel worksheet and were analyzed with SPSS Statistical Software (version 14.0) (SPSS, Chicago, IL, USA), for descriptive statistics (percentage, mean, standard error, and 95% confidence interval) and analytical statistics (chi-square test, ANOVA, and generalized estimation equation; GEE) [27].

3. Results

All 33 experimental patients and 39 control patients completed the auricular acupressure or control treatment for each week. There were 39 women (54.1%) and 33 men (45.9%); 51 (70.8%) patients did not join any sheltered workshops in the hospital. In 72 patients, there were 57 patients (79.2%) taking second generation antipsychotics (SGA), 20 patients (27.8%) taking Clozapine in dosage between 225 and 600 mg daily, 18 patients (25%) taking Risperidone in dosage between 4 and 8 mg daily, 8 patients (11.1%) taking Olanzapine in dosage between 5 mg and 20 mg daily, 6 patients (8.3%) taking Zotepine in dosage between 100 mg and 300 mg daily, 4 patients (5.5%) taking Amisulpride in dosage between 400 mg and 1200 mg, and 1 patient (1.4%) taking 10 mg Aripiprazole daily; there were 15 patients (20.8%) taking first generation antipsychotics (FGA), 8 patients (11.1%) taking Haloperidol in dosage between 10 mg and 20 mg daily, 5 patients (6.9%) taking sulpiride in dosage between 600 mg and 1200 mg daily, 2

Table 4: Changes in mean waist circumference, body weight, and body fat percentage.

Time	AA group ($n = 33$)			Control group ($n = 39$)		
	i1	i2	i3	i1	i2	i3
Week 0						
Mean	95.9	71.4	32.9	95.9	71.7	34.1
sd	7.6	8.6	8.7	6.5	6.8	7.4
Week 1						
Mean	96.9	71.2		98	72.2	
sd	7.8	8.5		7	7.4	
Week 2						
Mean	95.8	71.4		95.7	71.7	
sd	8.3	8.9		6.6	7.3	
Week 3						
Mean	96.7	71.1		96.6	71.6	
sd	7.8	8.8		6.4	7.1	
Week 4						
Mean	96.1	71.3		96.4	72	
sd	8	8.7		6.7	6.9	
Week 5						
Mean	95.5	71.2		96.2	71.7	
sd	8.1	8.9		6.8	7	
Week 6						
Mean	95.1	70.8		95.8	71.6	
sd	8.4	8.7		6.7	6.8	
Week 7						
Mean	96.3	71.2		96.9	71.5	
sd	7.5	8.7		6.4	6.8	
Week 8						
Mean	94.8	70.7	33.2	95.2	71.2	33.1
sd	8.1	8.6	8.9	6.6	6.5	7.1

AA group: experimental group, auricular acupressure with *vaccaria* seeds and Surgical Tape; Control group: Surgical Tape only; i1: waist circumference; i2: body weight; i3: body fat percentage.

patients (2.8%) taking 30 mg Trifluoperazine daily. There were 8 patients (11.1%) taking mood stabilizer with SGA or FGA (Lithium: 2, Valproic acid: 4, Lamotrigine: 2), 3 patients (4.2%) taking SGA with selective serotonin reuptake inhibitor (SSRI), 3 patients (4.2%) taking 2 types of SGA, and 4 subjects (5.5%) taking SGA with FGA. The mean body height was 160.6 ± 1.5 cm in the AA group, 161.2 ± 1.1 cm in the control group; mean age was 46.8 ± 1.6 years in the AA group, 48.6 ± 1.4 years in the control group; mean disease duration of schizophrenia was 15.9 ± 0.9 years in the AA group, 14.2±0.9 years in the control group; mean onset age of schizophrenia was 30.9 ± 1.3 years in the AA group, 34.4 ± 1.8 years in the control group; mean length of hospitalization was 5.6 ± 0.6 years in the AA group, 4.9 ± 0.6 years in the control group.

There was no difference in sex, joining a sheltered workshop (occupational training), or use of second generation antipsychotics between the AA group and control group (Table 2). There was no difference between the AA group and control groups in mean body height, age, disease duration, age at onset of schizophrenia, or length of hospitalization (Table 3).

In waist circumference and body weight, there was no significant difference between the 2 groups at pretest (week 0), and no significant difference from week 1 to 8 compared with week 0 in the control group, and no significant difference between the slopes of AA group and control group from week 1 to week 8 (Tables 4 and 5). No significant differences were shown in body fat percentage between the two groups at pretest; no significant differences were found between pre- and posttest body fat percentage in the control group.

During the study, 10 experimental patients withdrew from the study; 7 patients refused to continue and 3 patients could not perform the auricular acupressure or reliably record a treatment form. 4 control patients withdrew from the study; 3 patients refused to continue and 1 patient was referred to an acute ward because of relapse of psychosis.

3 experimental patients and 1 control patient experienced skin itch after applying plasters on the ear for 2–4 days. The symptom improved and disappeared completely after sticking the plaster on the contralateral ear. And no one withdrew the study because of skin itch.

4. Discussion

The present study showed that auricular acupressure did not reduce body weight parameters significantly in patients with chronic schizophrenia. All participants were inpatients, and factors relating to diet, and activity level were better controlled than in outpatient studies. It had been suggested that auricular acupressure may stimulate the sympathetic nervous system, and cause a temporary increase in basal metabolic rate and decrease in appetite that would resolve after the second week [28]. The failure of auricular acupressure to decrease body weight may be a result of the effects of antipsychotic medication. These drugs were required for treatment, and 80% patients treated with antipsychotic medication experience medication-induced weight gain [29]. Second-generation antipsychotics have fewer extrapyramidal adverse reactions than first-generation antipsychotics, but they increase body weight and risk of comorbidities such as hypertension, coronary heart disease, diabetes, and stroke [30, 31].

For example, weight gains for patients treated with Clozapine, Olanzapine, and Risperidone were 4.5, 4.2, and 2.1 kg, respectively, over 10 weeks of treatment [32]. Additional studies showed that the use of Aripiprazole for 1 year caused a mean weight gain of approximately 1 kg [33].

The American Diabetes Association reported that Clozapine and Olanzapine were associated with the greatest potential for weight gain, with evidence of increased risk of diabetes and dyslipidemia. Risperidone was associated with

Table 5: Comparison of intervention effects between the two groups.

Variables	Regression coefficient	standard error	t value	P value
Waist circumference (cm)				
Control group at week 0	95.91			
Week 0 (AA group/control group)	−0.04	1.72	−0.03	0.979
Control group (week 1/week 0)	2.09	1.67	1.25	0.211
Control group (week 2/week 0)	−0.20	1.64	−0.12	0.905
Control group (week 3/week 0)	0.69	1.64	0.42	0.676
Control group (week 4/week 0)	0.52	1.64	0.31	0.754
Control group (week 5/week 0)	0.29	1.64	0.18	0.859
Control group (week 6/week 0)	−0.09	1.64	−0.06	0.954
Control group (week 7/week 0)	0.98	1.64	0.60	0.552
Control group (week 8/week 0)	−0.72	1.64	−0.43	0.664
Difference of slopes from week 0 to week 1 between 2 groups	−1.05	2.47	−0.42	0.671
Difference of slopes from week 0 to week 2 between 2 groups	0.10	2.43	0.04	0.968
Difference of slopes from week 0 to week 3 between 2 groups	0.18	2.43	0.07	0.942
Difference of slopes from week 0 to week 4 between 2 groups	−0.30	2.43	−0.12	0.902
Difference of slopes from week 0 to week 5 between 2 groups	−0.63	2.43	−0.26	0.796
Difference of slopes from week 0 to week 6 between 2 groups	−0.70	2.43	−0.29	0.773
Difference of slopes from week 0 to week 7 between 2 groups	−0.49	2.43	−0.20	0.840
Difference of slopes from week 0 to week 8 between 2 groups	−0.36	2.43	−0.15	0.882
Body weight				
Control group at week 0	71.68	1.25	57.31	
Week 0 (AA group/control group)	−0.27	1.85	−0.14	0.885
Control group (week 1/week 0)	0.54	1.79	0.30	0.761
Control group (week 2/week 0)	0.06	1.77	0.03	0.972
Control group (week 3/week 0)	−0.06	1.77	−0.03	0.972
Control group (week 4/week 0)	0.28	1.77	0.16	0.876
Control group (week 5/week 0)	0.06	1.77	0.03	0.972
Control group (week 6/week 0)	−0.12	1.77	−0.07	0.945
Control group (week 7/week 0)	−0.20	1.77	−0.11	0.910
Control group (week 8/week 0)	−0.47	1.77	−0.27	0.790
Difference of slopes from week 0 to week 1 between 2 groups	−0.80	2.65	−0.30	0.763
Difference of slopes from week 0 to week 2 between 2 groups	−0.10	2.61	−0.04	0.969
Difference of slopes from week 0 to week 3 between 2 groups	−0.28	2.61	−0.11	0.915
Difference of slopes from week 0 to week 4 between 2 groups	−0.38	2.61	−0.14	0.885
Difference of slopes from week 0 to week 5 between 2 groups	−0.28	2.61	−0.11	0.915
Difference of slopes from week 0 to week 6 between 2 groups	−0.46	2.61	−0.18	0.861
Difference of slopes from week 0 to week 7 between 2 groups	−0.05	2.61	−0.02	0.983
Difference of slopes from week 0 to week 8 between 2 groups	−0.23	2.61	−0.09	0.929
Body fat percentage				
Control group at week 0	34.15	1.28	26.66	
Week 0 (AA group/control group)	−1.24	1.89	−0.66	0.512
Control group (week 8/week 0)	−1.01	1.81	−0.56	0.577
Difference of slopes from week 0 to week 8 between 2 groups	1.26	2.68	0.47	0.638

AA group: experimental group, auricular acupressure with *vaccaria* seeds and Surgical Tape; control group: Surgical Tape only.

a less potential for weight gain, with discrepant results concerning the risk of diabetes and dyslipidemia. Aripiprazole was associated with minimal weight gain, with no evidence of risk for diabetes and dyslipidemia [34]. A review of Zotepine studies reported a mean body weight gain of 3.6 kg and that 28% of Zotepine-treated patients experienced body weight gain [35]. There were limited published data examining the possible association between Zotepine therapy and the development of diabetes, hyperglycemia, and dyslipidemia. A pooled analysis of data reported an estimated mean

weight gain of 0.8 kg with Amisulpride after 10 week of treatment [35], this limited weight gain potential predicts that Amisulpride may be associated with a low risk of adverse metabolic events. The mechanisms may be related to several neurotransmitters, including serotonin, histamine, and dopamine and the adrenergic and muscarinic systems [36, 37].

In addition to medical treatment, all patients received supportive psychotherapy, family therapy, and a series of curriculums on psychiatric rehabilitation, including social skills training, self-care training, and psychoeducation on drug compliance.

Referring to dropouts and withdrawals it has to be mentioned that the Chinese Dragon Boat Festival conflicted with the study schedule, 7 patients in the AA group and 3 patients in the control group were discharged for family gathering. 3 patients in the AA group could not perform the auricular acupressure or record the form by themselves reliably, possibly due to cognitive function decline caused by the mental illness.

There was one patient in the control group who withdrew from the study due to flare up of psychosis (Figure 1), and was transferred from chronic psychiatric ward to acute psychiatric ward which was not related to the use of Surgical Tape. It happens frequently in the chronic psychiatric ward and previous studies have revealed that significant predictors for the relapse of schizophrenia are the number of previous hospitalizations and the number of different antipsychotics previously used [38].

The ear skin itch was related to the use of the Surgical Tape, for it happened in both AA group and control group. According to the classification of WHO's Adverse Reaction Terminology (WHO-ART) [39], the adverse reaction was classified as time-related type. The symptom improved and disappeared after sticking the Surgical Tape on the contralateral ear. We chose the Surgical Tape due to its high viscosity, preventing the tape from sliding off the ear. It is suggested that future studies should consider both the viscosity and antianaphylaxis before performing auricular acupressure.

The traditional Chinese medicine syndrome, a profile of symptoms and signs, is important for understanding human homeostasis and guiding the application of Chinese herbs and acupuncture [40]. Damp stasis syndrome (excess) and Qi deficiency syndrome (deficiency), are common syndromes in obese patients. The excess syndrome includes accumulation or stagnation of metabolic waste, body fluids, and blood, and the deficiency syndrome includes weakness and the deficiency of nutrients [40]. Depending on the symptoms and signs, different patients may be given different traditional Chinese medicine treatments, even when they have the same clinical diagnosis. Future studies may include auricular acupressure according to the differentiation of traditional Chinese medicine syndrome and the needs of each patient.

In the present study, we adopted random assignment by wards primarily to control the 2 confounding factors, diet and exercise, which could greatly affect body weight. The diets in each ward were similar, and it was assumed that similar diet and exercise frequency or intensity were a feature of all the wards. Other confounding factors such as sex, age, and medications were controlled.

Limitations of the present study included the small sample size, which enabled only 2 study arms, and a sham group was not included. Furthermore, the antipsychotic medication were classified only as typical (first generation) and atypical (second generation) drug therapies. The single-blind study design could not be extended to a double-blind design because the AA group patients could easily become aware that the seeds of *Vaccaria segetalis* were contained in the plaster when they performed acupressure. Furthermore, the baseline BMI in the first intervention episode could not be obtained retrospectively.

5. Conclusion

Auricular acupressure had no demonstrated efficacy in controlling body weight and waist circumference in patients with chronic schizophrenia. Applying the principles of traditional Chinese medicine, future studies may evaluate auricular acupressure according to the differentiation of traditional Chinese medicine syndrome and each subject's individual needs.

Acknowledgment

This study is supported in part by the Taiwan Department of Health Clinical Trial and Research Center of Excellence Grant no. (DOH101-TD-B-111-004).

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