Homeopathic Treatments in Psychiatry: A Systematic Review of Randomized Placebo-Controlled Studies

Jonathan R. T. Davidson, MD; Cindy Crawford, BA; John A. Ives, PhD; and Wayne B. Jonas, MD

Objective: To systematically review placebo-controlled randomized trials of homeopathy for psychiatric conditions.

Data Sources: Eligible studies were identified using the following databases from database inception to April 2010: PubMed, CINAHL, PsycINFO, Hom-Inform, Cochrane CENTRAL, National Center for Complementary and Alternative Medicine grantee publications database, and ClinicalTrials.gov. Gray literature was also searched using Google, Google Scholar, the European Committee for Homeopathy, inquiries with homeopathic experts and manufacturers, and the bibliographic lists of included published studies and reviews. Search terms were as follows: (*homeopath* or homoeopath**) and (*placebo or sham*) and (*anxiety or panic or phobia or post-traumatic stress or PTSD or obsessive-compulsive disorder or fear or depress* or dysthym* or attention deficit hyperactivity or premenstrual syndrome or premenstrual disorder or premenstrual dysphoric disorder or traumatic brain injury or fibromyalgia or chronic fatigue syndrome or myalgic encephalitis or insomnia or sleep disturbance*). Searches included only English-language literature that reported randomized controlled trials in humans.

Study Selection: Trials were included if they met 7 criteria and were assessed for possible bias using the Scottish Intercollegiate Guidelines Network (SIGN) 50 guidelines. Overall assessments were made using the Grading of Recommendations Assessment, Development and Evaluation procedure. Identified studies were grouped into anxiety or stress, sleep or circadian rhythm complaints, premenstrual problems, attention-deficit/hyperactivity disorder, mild traumatic brain injury, and functional somatic syndromes.

Results: Twenty-five eligible studies were identified from an initial pool of 1,431. Study quality according to SIGN 50 criteria varied, with 6 assessed as good, 9 as fair, and 10 as poor. Outcome was unrelated to SIGN quality. Effect size could be calculated in 16 studies, and number needed to treat, in 10 studies. Efficacy was found for the functional somatic syndromes group (fibromyalgia and chronic fatigue syndrome), but not for anxiety or stress. For other disorders, homeopathy produced mixed effects. No placebo-controlled studies of depression were identified. Meaningful safety data were lacking in the reports, but the superficial findings suggested good tolerability of homeopathy. A funnel plot in 13 studies did not support publication bias ($\chi^2_1 = 1.923$, $P = .166$).

Conclusions: The database on studies of homeopathy and placebo in psychiatry is very limited, but results do not preclude the possibility of some benefit.

J Clin Psychiatry 2011;72(6):795–805

Submitted: *September 15, 2010; accepted December 15, 2010 (doi:10.4088/JCP.10r06580).*

Corresponding author: *Jonathan R. T. Davidson, MD, 3068 Baywood Dr, Seabrook Island, SC 29455 (jonathan.davidson@duke.edu).*

Use of complementary and alternative medicine (CAM) to treat psychiatric problems is widespread, and the need has been identified for more high-quality controlled trials. A task force of the American Psychiatric Association concluded that several CAM treatments, including omega-3 fatty acids, St John's wort, folate, acupuncture, and others, show promise for depression, but that more rigorous and larger studies were needed.[1] A meta-analysis by Freeman et al[2] reported comparable efficacy but greater safety for a number of herbal and dietary supplements than for standard antidepressants. Among the many forms of CAM, homeopathy is one of the most widely used on a global basis.[3] Meta-analyses and systematic reviews have drawn mixed conclusions as to whether homeopathy is more effective than placebo in general medicine.[4–10] In assessing these studies, Lewith[7] has pointed out that where reports are few and based on small samples, results of systematic reviews depend on which studies are included and which are excluded. Thus, any fair assessment needs to be systematic and comprehensive and use established quality and scoring approaches on all studies. No comprehensive review of research on homeopathy for psychiatric conditions has been conducted. Our aim in this article was to undertake such a systematic review.

Although widely used in many parts of the world, homeopathy remains controversial within the Western medical paradigm. This is due principally to discordance between the principles of homeopathy and those of accepted biomedical theory. The system of homeopathy rests on 2 fundamental principles: (1) similarity, whereby the indicated remedy for particular symptoms is that which elicits similar symptoms when given to a healthy person, and (2) the power of the minimum dose, whereby a substance that is repeatedly diluted and agitated ("succussed") is believed to preserve its effect even into "ultramolecular" solutions.[4]

In all major reviews of homeopathy, there is an absence of comprehensive reviews of studies relevant to psychiatry, even though there are some encouraging findings. For example, in one review homeopathy was superior to placebo on at least 1 clinically meaningful measure in 6 of 7 trials of fibromyalgia, anxiety, agitation, traumatic brain injury (TBI), and premenstrual syndrome (PMS).[9] On the other hand, a Cochrane review of attention-deficit/hyperactivity disorder (ADHD) showed no overall benefit for homeopathy over placebo in 3 randomized clinical trials.[11] Two systematic reviews in depression[12] and anxiety[13] found insufficient good quality data to judge the efficacy of homeopathy for these conditions. A Cochrane review of homeopathy for dementia found no placebo-controlled studies of adequate quality.[14] Evidence in support of homeopathy for fibromyalgia is more encouraging,

Clinical Points

- Randomized placebo-controlled studies suggest that homeopathy is without benefit for anxiety, that it may be useful for functional somatic syndromes, and that for other conditions such as ADHD, premenstrual and sleep-related problems, its benefit is undetermined. For other common psychiatric conditions such as depression, posttraumatic stress disorder, and dementia, there are no informative data.
- Although homeopathic medicines are well tolerated and believed to carry few side effects, there has to date been no adequate demonstration of their safety.
- It is unknown whether a single individually chosen medicine is more effective than a fixed-dose combination formula.

however.[15,16] A review of homeopathy for insomnia called for more research.[17] Because patients with psychiatric problems are well represented in homeopathic practice,[18,19] it is important to examine whether homeopathy is beneficial in the more commonly seen psychiatric conditions, defined here as anxiety, depression, sleep problems, ADHD, PMS, mild TBI, and somatic spectrum disorders.

Our objective was to conduct a comprehensive, systematic literature review of placebo-controlled, randomized clinical trials of homeopathy for psychiatric conditions, to assess the quality and risk of bias in each study's design and execution, to report on outcome when possible by means of effect size (ES) or number needed to treat (NNT) statistics, to review safety, and to grade the overall evidence for each condition according to internationally standardized methods. Because of the heterogeneity of studies in each psychiatric category, we did not undertake meta-analysis of the data but did check for likelihood of publication bias in a subset of the data.

METHOD

Data Sources and Search Strategy

A systematic search was conducted for literature that described homeopathic treatment of the following 7 groups of psychiatric conditions: depression, anxiety, sleep and circadian rhythm problems, ADHD, PMS, mild TBI, and functional somatic syndromes (FSS), specifically fibromyalgia and chronic fatigue syndrome. The following databases were examined for studies reported from database inception to April 2010: PubMed, CINAHL, PsycINFO, Hom-Inform, Cochrane CENTRAL, National Center for Complementary and Alternative Medicine grantee publications database, and ClinicalTrials.gov. Gray literature was also searched using Google, Google Scholar, the European Committee for Homeopathy, inquiries with homeopathic experts and manufacturers, and the bibliographic lists of included studies and published reviews. Search terms used were as follows: (*homeopath* or homoeopath**) and (*placebo or sham*) and (*anxiety or panic or phobia or post-traumatic stress or PTSD or obsessive-compulsive disorder or fear or depress* or dysthym* or attention deficit hyperactivity or premenstrual syndrome or premenstrual disorder or premenstrual dysphoric disorder or traumatic brain injury or fibromyalgia or chronic fatigue syndrome or myalgic encephalitis or insomnia or sleep disturbance*). The following limits were placed on searches: only literature presented in the English language that reported randomized controlled trials (RCTs) in human subjects. All searches were performed across titles/abstracts where possible. Where some of these restrictions were not possible, we screened the titles and abstracts manually.

Inclusion and Exclusion Criteria

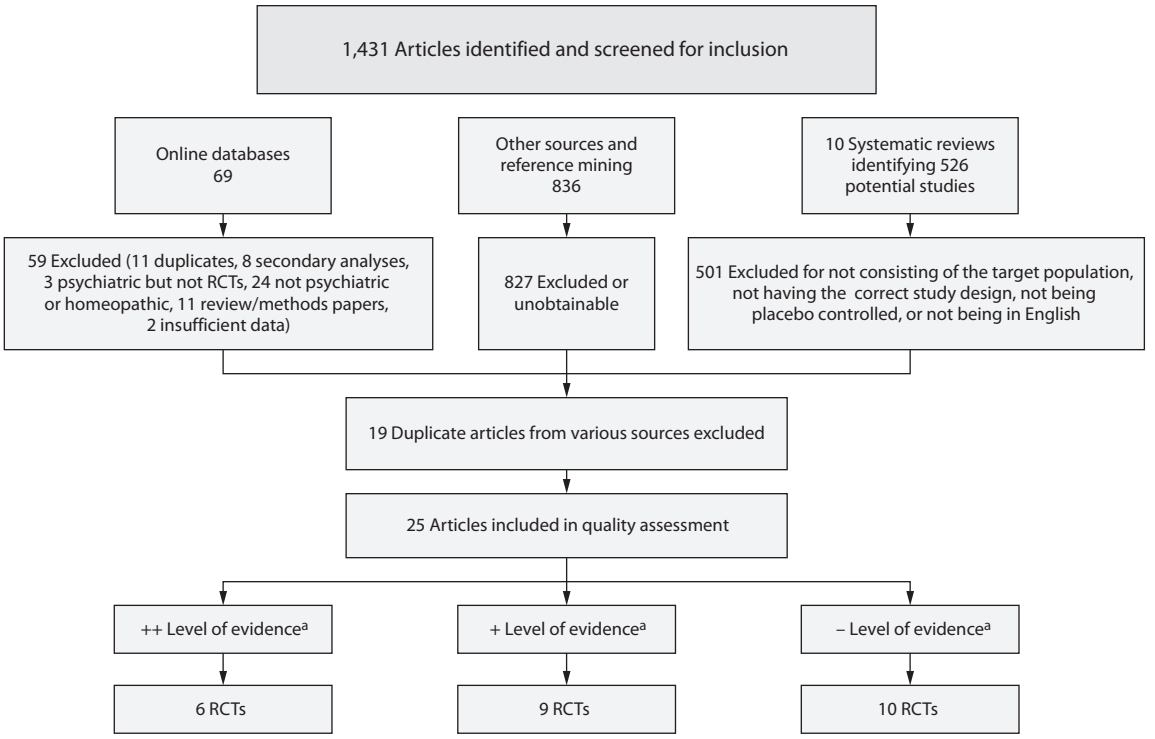
Four investigators (C.C., J.A.I., W.B.J., and J.R.T.D.) independently screened titles and abstracts for relevance based on the inclusion criteria for this systematic review. Any disagreements about including a study were resolved through discussion and consensus. Articles were included in this systematic review if they met the following criteria: (1) randomized controlled trial (RCT) design was used; (2) a placebo control was used; (3) between-treatment comparisons were made of homeopathic treatment versus placebo; (4) treatment was given in a double-blind fashion; (5) the report assessed a psychiatric condition as specified in the keyword list above; (6) the report was presented in English; and (7) the study involved treatment-seeking human subjects; that is, we did not review any animal model studies, studies in healthy volunteers, or studies in patient groups in which the focus was on mechanism of action or prediction of treatment effect.

Quality Rating of Individual Studies

Methodological quality of the included studies was assessed independently by the 4 reviewers for the individual studies and then by 2 reviewers (W.B.J. and J.R.T.D.) on the quality of the overall literature pool with regard to the minimization of bias. The individual studies were all RCTs and were evaluated for study quality and bias using the Scottish Intercollegiate Guidelines Network (SIGN) 50 checklist for RCTs.[20] SIGN is an internationally developed and accepted assessment approach widely used for both conventional and complementary medicine research. Once the quality assessment of the individual studies was completed, 2 reviewers conducted a quality assessment of the overall literature pool for each condition using the Grading of Recommendations Assessment, Development and Evaluation (GRADE), looking at the (1) confidence in the estimate of the ES, (2) magnitude of the effect, (3) safety grade, and (4) strength of the recommendation.[21] GRADE is also an internationally accepted approach for quality assessment of literature sets.

All reviewers were trained in the quality assessment of individual studies (SIGN) and the quality assessment of overall literature pool (GRADE) by 1 of the authors (C.C.), and each article was assessed by 2 reviewers. For any discrepancies, discussion occurred between reviewers in order to

Figure 1. Study Flowchart



[a]Level of evidence with respect to minimizing bias was rated as "good" (++), "fair" (+), or "poor" (–) according to Scottish Intercollegiate Guidelines Network (SIGN) quality analysis.
Abbreviation: RCT = randomized controlled trial.

achieve consensus. Final judgment was reserved for the first author (J.R.T.D.).

Data Analysis

For every study that provided a mean score and SD, SE, *t,* or *F* statistic, we calculated the ES between treatments using the Hedges unbiased *g*,[22] which mathematically adjusts for small samples. The ES was recorded as positive if it favored homeopathy and negative if placebo was more effective. Consistent with the GRADE conventions, an ES that ranges from 0.20 to 0.49 is considered to be small, 0.50 to 0.79 is medium, and 0.8 or greater is large. For studies reporting rates of response, the NNT was calculated.[23] For a subset of 13 studies that gave sufficient information to derive ES and the 95% CIs, we calculated an estimate for possible publication bias by graphing the 1/var to *g* and running the nonparametric selection model applied to the 13 studies.[3] The outcome measures chosen for calculating ES were those identified in the respective publications as primary. When more than 1 primary measure was identified and results were conflicting, ES were calculated separately for the most and least favorable toward homeopathy. In studies in which primary outcomes uniformly failed to show a statistically significant difference, a single scale was chosen at random.

In some cases, as shown in the tables, a study appeared more than once, usually because it was published as a thesis at a university Web site, and elsewhere as a peer-reviewed publication. SIGN ratings were conducted on each communication and on the combination, assigning the higher ratings (if they differed) if one report gave more complete information than the other; the overall evaluation was based on information from both.

RESULTS

Study Selection and Quality

The search strategy led to the identification of 69 reports from online databases (Hom-Inform, n = 29; ClinicalTrials.gov, n = 1; MEDLINE [PubMed], n = 14; PsycINFO, n = 6; Cochrane CENTRAL, n = 19; CINAHL, n = 0), 836 from other sources (n = 834 from the following sources: European Committee for Homeopathy List of Dissertations and Theses in Homeopathy, n = 644; theses and dissertations from Durban University of Technology [Health Sciences], n = 66; and theses and dissertations from University of Johannesburg, n = 124; plus reference mining, n = 2), and 526 from 10 systematic reviews (Figure 1). As shown in Table 1, 25 studies fulfilled the specified criteria.[24–51] According to SIGN quality analysis, 6 studies were rated as "good" (++) with respect to minimizing bias, 9 as "fair" (+), and 10 as "poor" (–). These are shown individually in eAppendix 1.

Of the 25 studies, 6 were conducted in populations suffering from anxiety or stress; 5, in subjects with sleep or circadian rhythm disturbances; 4, in subjects with premenstrual problems; 3, in subjects with ADHD; 1, in subjects with mild TBI; and 6, in subjects with functional somatic syndromes.

Table 1. Placebo-Controlled, Randomized Clinical Trials of Homeopathy for Common Psychiatric Conditions: Quality of Individual Studies

Reference	Condition	Treatment	No. of Subjects Entered/ Completed	Trial Duration	Primary Outcomes (*P* value)	Rates of Response	Reviewer Comments	Authors' Main Conclusions	SIGN Score[a]
Bonne et al (2003)[24,b]	GAD	Individualized homeopathy	H = 22/20 P = 22/19	10 wk	HARS (NS)	H = 40% P = 42%	Larger sample unlikely to overturn the results	No difference between treatments; unlikely that this would have been different with a larger sample	+
Ngobese (2006)[25,c]	GAD	Individualized homeopathy	H = 14/11 CBT = 14/10 P = 13/10	4 wk	HARS (NS) BAI (NS) PPQ (NS)	Not given	A proven treatment for GAD, cognitive therapy, failed to work; study can be regarded as a "failed" study rather than a negative study for homeopathy. In other words, it is not informative Length of treatment may have been inadequate	No difference between treatments	+
Baker et al (2003)[26,d]	Test anxiety	*Argentum nitricum*	70 Enrolled total (2 placebo groups)/H = 21, P1 = 23, P2 = 18	4 d	RTA (NS)	Not given	Adequately powered. Results favored placebo (weak ES). Lack of stress-provoking test a limitation. No evidence that presence of the specific profile for the remedy made a difference to the outcome	No evidence that homeopathy was better than placebo	+
McCutcheon (1996)[27,c]	High trait anxiety	Combined 9-remedy product	H = 38/35 P = 39/37	15 d	STAI(T) (NS) STAI(S) (NS) Sleep ($P < .05$) Pulse (NS)	Not given	No benefit on state anxiety but significant improvement on sleep. Trait anxiety unlikely to change in short term with any treatment. Effect sizes based on sleep and state anxiety measures; pulse and trait anxiety considered as either not useful (pulse) or likely to change in the short term (trait anxiety)	Mixed results	+
Traub (2000)[28,c]	Test anxiety	Combined 3-remedy product	47 Total enrolled/H = 14, P = 18	5 d	Feelings of anxiety (NS) Thought interference (NS)	Not given	No effect on the total scores of the primary measures. Weak evidence for homeopathy on scale items	Some benefit for homeopathy	–
Vaithilingam (2005)[29,c]	Job-related burnout	Individualized homeopathy	Not given/H = 14, P = 16	8 wk	MBI subscales (NS)	Not given	Homeopathy worse than placebo on depersonalization scale of MBI	No benefit for homeopathy	–
Lipman et al (1999)[30,c]	Severe snoring	Combined 9-remedy product	101 Total enrolled/H = 44, P = 46	10 d	Snoring daily score ($P < .001$)	H = 80% P = 46%	Positive result for homeopathy	Homeopathy effective	+

(continued)

Table 1 (continued). Placebo-Controlled, Randomized Clinical Trials of Homeopathy for Common Psychiatric Conditions: Quality of Individual Studies

Reference	Condition	Treatment	No. of Subjects Entered/ Completed	Trial Duration	Primary Outcomes (*P* value)	Rates of Response	Reviewer Comments	Authors' Main Conclusions	SIGN Score[a]
Naudé et al (2010)[31,c]; David Naudé, M Tech (Hom), e-mail communication to JRTD, July 14, 2010; and Maharaj thesis (2005)[32] composite	Primary insomnia	Individualized homeopathy	H = 16/14 P = 17/16	4 wk	Sleep diary ($P < .05$)) SII ($P < .0001$) DBAS[e] (NS)	Not given	When the published and unpublished reports were assessed, SIGN was rated as + in both cases. ES provided for SII only; unavailable for other scales	Benefit for homeopathy	+
Kumar (2010)[33,c] and Andrew Criglington, B Comm, e-mail communications to JRTD, March 16, 2010, and August 9, 2010	Jet lag	Combined multiple remedy product	23 Entered/19 completed crossover	Crossover design 24 h each treatment	POMS-Fatigue ($P < .05$) POMS-Vigor (NS)	Not given	Inconsistently reported *P* values on POMS-Vigor. Ambiguous, but results warrant further study	Results favor homeopathy; suggests additional and more targeted questionnaires in future studies of jet lag	–
La Pine et al (2006)[34,c]	Shift lag in night shift workers	Combined 5-remedy product	34 Entered/28 completed crossover	Crossover 7 d for each treatment	CAVT (NS) IIQ (NS)	Not given	No benefit for homeopathy	Equal response to homeopathy and placebo	–
Kolia-Adam combined publication (2008)[35,c] and thesis (2010)[36] and Elizabeth Solomon, HD, ND, DO, e-mail communications to JRTD; April 12, 2010, and July 14, 2010	Insomnia less than 1 y in duration	*Coffea cruda* 200C	H = 15/15 P = 15/14	30 d	Hours of sleep (NS) Sleep satisfaction (NS) Change in sleep pattern (NS)	H = 33% P = 50%	Negative study SIGN rating remains the same for publication, thesis, and combined assessment	No benefit for homeopathy when compared against placebo	–
Chapman et al (1994)[37,c]	PMS	Individualized homeopathy	H = 5/5 P = 5/5	4 mo	Global (NS)	H = 40% P = 60%	Impossible to interpret. Over 200 screened and 36 entered study. Only 10 were randomized	No benefit. High placebo response and subjects received therapy for abuse-related trauma symptoms	+
Yakir et al (2001)[38,c]	PMS	Individualized homeopathy	H = 13/11 P = 10/8	3 mo (Only 1 dose of remedy was given)	MDQ (NS)	H = 90% P = 38%	Some secondary outcomes seem to be post hoc choices	Suggestive of greater benefit for homeopathy, but acknowledge limited sample size	+
Laister (2008)[39,c]	PMS	Individualized homeopathy	H = 18/13 P = 21/14	3 mo	MDQ (NS)	Not given		Homeopathic simillimum not effective in treating PMS	++
Kirtland (1994)[40,c]	PMS	*Folliculinum* 15C	34 or 35 Entered/H = 16, P = 15	6 mo	Each item on MDQ PAF $P < .05$ on 5/28 items	Not given		Suggests an effect for homeopathy	–

(continued)

Table 1 (continued). Placebo-Controlled, Randomized Clinical Trials of Homeopathy for Common Psychiatric Conditions: Quality of Individual Studies

Reference	Condition	Treatment	No. of Subjects Entered/ Completed	Trial Duration	Primary Outcomes (*P* value)	Rates of Response	Reviewer Comments	Authors' Main Conclusions	SIGN Score[a]
Jacobs et al (2005)[41,c]	ADHD	Individualized homeopathy	H = 22/22 P = 21/21	18 wk	Conners Global Index-Parent (NS)	Not given	P tended to be better than H, but not significantly so	No benefit, no trend	++
Frei et al (2005)[42,d]	ADHD	Individualized homeopathy	H = 31, P = 31/ all completed crossover	6 wk crossover each treatment	Conners Global Index-Parent ($P < .05$)	Not given	Positive result on primary outcome in adequately powered study	Trial suggests effectiveness of homeopathy, particularly in behavioral and cognitive functions	++
Strauss (2000)[43,c] and Cole (1998)[44]; composite	ADHD	Individualized homeopathy	Unknown/H = 10, P = 10	8 wk	CPSQ ($P < .05$) CCT (NS)	Not given	Weak effect at best. Subsequent review in Cochrane analysis failed to show significance on any measure	Overall hyperactivity improved more on homeopathy than placebo	–
Chapman et al (1999)[45,d]	Mild TBI	Individualized homeopathy	H = 33/27 P = 28/23	4 mo	Overall MANOVA for FA ($P < .05$)	H = 85%, P = 55% on SRS H = 74%, P = 74% on DAS	Mostly positive study. An intent-to-treat analysis showed significant effects for homeopathy on all scales	Significant improvement favoring homeopathy. Call for further studies	++
Fisher (1986)[46,c]	Fibromyalgia	*Rhus toxicodendron, Bryonia alba,* or *Arnica montana*	Unknown/H = 12, P = 12	3 mo	VAS pain (NS) VAS sleep (NS) No tender spots (NS) Analgesic use ("No effect")	Not given	Underpowered, but results in the expected direction. Missing information is a problem. Information on randomization method (Minitab) (Peter Fisher, FF Hom, FRCP, electronic communication, May 23, 2010)	Study supports feasibility of the method of targeted remedy choice in fibromyalgia. Analysis of predetermined outcomes gave significant differences on pain and sleep for indicated remedy	–
Fisher et al (1989)[47,c]	Fibromyalgia	*Rhus toxicodendron* 6C	Unknown/30 completed crossover	Crossover of 4 wk on each treatment	Pain (not given) Sleep (not given) Tender points ($P < .01$) Global (NS)	H = 37% P = 13% (Global outcome[5[p376]])	Lack of detail a cause for cautious interpretation of what seems to be a positive study	Positive results for homeopathy, especially on tender points	–
Awdry (1996)[48,c]	CFS	Individualized homeopathy	H = 32/30 P = 32/31	12 mo	Global response (not analyzed)	H = 43% P = 4%	Advantages seem evident on many measures, but statistical analysis not carried out. Some of the published numbers do not add up in subscales (fatigue, disability, and myalgia).	Guarded in stating advantages for homeopathy	+
Weatherley-Jones et al (2004)[49,d]	CFS	Individualized homeopathy	H = 53/43 P = 50/43	6 mo	5 MFI scales General fatigue ($P < .05$) Physical fatigue (NS) Mental fatigue (NS) Reduced activity (NS) Reduced motivation (NS)	H = 26% P = 9% (For clinically significant improvement on all primary outcomes)	Mixed results, but the most rigorous measure supports homeopathy	Weak but equivocal evidence favoring homeopathy	++

(continued)

Table 1 (continued). Placebo-Controlled, Randomized Clinical Trials of Homeopathy for Common Psychiatric Conditions: Quality of Individual Studies

Reference	Condition	Treatment	No. of Subjects Entered/ Completed	Trial Duration	Primary Outcomes (*P* value)	Rates of Response	Reviewer Comments	Authors' Main Conclusions	SIGN Score[a]
Bell et al (2004)[50,d]	Fibromyalgia	Individualized homeopathy	H = 30/26 P = 32/27	3 mo	Tender point pain on palpation ($P < .01$) Tender point count ($P < .05$) MAP ($P < .01$) MSP (NS) AF ($P < .05$)	H = 50%, P = 15% on 25% improvement in tender point pain on palpation	Overall positive trial. Author accepted significance at $P < .1$ to assess for trends. Three of 7 comparisons would no longer be statistically significant if the .05 criterion had been used Rates of response based on the tender point pain on palpation measure	Positive outcome on main measure used to power the study, and on many others	++
Saul (2005)[51,c]	CFS	Individualized homeopathy	37 Entered/H = 15, P = 15	3 mo	CFS-Q (NS) F-VAS (NS)	Not given	Negative trial	No benefit for homeopathy	–

[a]Level of evidence with respect to minimizing bias was rated as "good" (++), "fair" (+), or "poor" (–) according to Scottish Intercollegiate Guidelines Network (SIGN) quality analysis.
[b]Power calculation was done but sample was insufficient.
[c]No power calculation.
[d]Power calculation was done and adequate sample was achieved.
[e]Only presented in Maharaj thesis.[32]
Abbreviations: ADHD = attention-deficit/hyperactivity disorder, AF = Appraisal of Fibromyalgia, BAI = Beck Anxiety Inventory, CAVT = Computer Assisted Vigilance Test, CBT = cognitive-behavioral therapy, CCT = Children's Checking Test, CFS = chronic fatigue syndrome, CFS-Q = Chronic Fatigue Syndrome Questionnaire, CPSQ = Conners Parents Symptom Questionnaire, DAS = Daily Activities Scale, DBAS = Dysfunctional Beliefs About Sleep, ES = effect size, FA = Functional Assessment, F-VAS = Fatigue Visual Analog Scale, GAD = generalized anxiety disorder, H = homeopathy, HARS = Hamilton Anxiety Rating Scale, IIQ = Impact of Intervention Questionnaire, MANOVA = multivariate analysis of variance, MAP = McGill Affective Pain, MBI = Maslach Burnout Inventory, MDQ = Menstrual Distress Questionnaire, MFI = Multidimensional Fatigue Inventory, MSP = McGill Sensory Pain, NS = nonsignificant, P = placebo, PAF = Premenstrual Assessment Form, PMS = premenstrual syndrome, POMS = Profile of Mood States, PPQ = Patient Perception Questionnaire, RTA = Revised Test Anxiety Scale, SII = Severity of Insomnia Index, SRS = Symptoms of Traumatic Brain Injury, STAI(S) = State Trait Anxiety Inventory (State), STAI(T) = State Trait Anxiety Inventory (Trait), TBI = traumatic brain injury.

Relevant details of these studies are shown in Tables 1 and 2. No placebo-controlled studies of depression were identified.

Table 1 presents details of each study, and Table 2 presents the overall GRADE assessment. Taking a statistically significant *P* value as a crude indicator of possible efficacy, the following assessment for each condition was found:

- There is no support for the efficacy of homeopathy in anxiety- or stress-related conditions. In only 1 study,[27] on a sleep measure, did the difference reach significance.
- For sleep- and circadian rhythm–related problems, the evidence is mixed. Two studies[30,31] yielded predominantly positive results, and these were the studies that scored higher on GRADE evaluation (Table 2). Because each study addressed a different problem, however, we do not think the cumulative evidence for any one condition warrants either a positive or a negative overall recommendation for this group.
- For premenstrual problems, there was little evidence of efficacy, other than 1 suggestive study,[38] which was limited by a small sample size.
- Of 3 ADHD studies, 1 relapse prevention design was positive,[42] and 2 acute symptom reduction trials were negative,[41,43,44] although the report by Strauss[43] indicated statistical significance on 1 measure. Two[41,42] of the 3 ADHD studies scored strongly on SIGN evaluation.
- For mild TBI, the 1 available study[45] scored favorably on attempts to reduce bias and produced weakly positive results in favor of homeopathy.
- Of 6 FSS studies,[46–51] all except 1 yielded positive evidence that homeopathy was superior to placebo, and the negative study[51] was one of the smallest and methodologically the weakest. Fisher's first study[46] failed to show positive effect for homeopathy on the all-comers sample but was positive on 2 key predefined measures when prospective matching of remedy to clinical picture was taken into account. His second study[47] was positive on 1 measure, but impossible to interpret on 2 of the 4 primary outcomes.[52,53] Three positive FSS trials[46–48] were given low ratings according to the SIGN and GRADE assessments, but the 2 methodologically strongest studies[49,50] were positive for homeopathy. In one of these,[49] although several outcomes failed to show a difference, the most rigorous measure of clinically significant improvement in all primary scales was positive.

© Copyright 2011 Physicians Postgraduate Press, Inc.

Table 2. Placebo-Controlled, Randomized Clinical Trials (RCTs) of Homeopathy for Common Psychiatric Conditions: Quality of the Overall Literature Pool[a]

Psychiatric Condition	Response Rates on Placebo (range across studies)	Response Rates on Homeopathy (range across studies)	No. of Participants Completed (no. of studies)	Confidence in Estimate of Effect GRADE[b]	Magnitude of Estimate of Effect GRADE[b]	Safety GRADE[b]	GRADE Recommendation[b]
Anxiety or stress	42%, but reported in only 1 of the studies	40%, but reported in only 1 of the studies	269 (6)	B	No effect (−0.43, −0.07, 0.50)	No information provided	Weak recommendation against use
Sleep or circadian rhythm disturbances	46%, reported in only 1 of the studies	80%, reported in only 1 of the studies	243 (5)	C	Small (0.03, 0.24, 0.17–0.24, 0.78, 2.40)	+2 Based on 2 studies reported	No recommendation
Premenstrual syndrome	38%–60%, reported across 2 studies	40%–90%, reported across 2 studies	87 (4)	C	Small (−0.17, 0.94)	No information provided	No recommendation
Attention-deficit/ hyperactivity disorder	Not provided	Not provided	125 (3)	B	None to small (−0.12, 0.34, 0.17)	+2 Based on 2 studies reported	Weak recommendation against use
Mild traumatic brain injury	55%–74%	74%–85%	50 (1)	B	Small; 0.14 overall and 0.27–0.49 on subscales	+2 Based on 1 study reported	No recommendation
Fibromyalgia/ chronic fatigue syndrome	4%–15%	26%–50%	314 (6)	B	None or small, according to measure (−0.07, −0.07, and 0.31–0.40)	+2 Based on 2 studies reported	Weak recommendation for use

[a]See Table 1 for outcomes assessed.

[b]Four major domains comprise the core of the evidence-based evaluation methodology:

Confidence in the estimate of the effect. This algorithm follows the GRADE working group approach. There are 4 possible levels, A–D, as follows. (A) High: Further research is very unlikely to change our confidence in the estimate of effect; several high-quality RCTs with consistent results or in special cases: 1 large, high-quality multicenter RCT. (B) Moderate: Further research is likely to have an important impact or confidence in the estimate of effect and may change the estimate: 1 high-quality RCT or several RCTs with some limitations. (C) Low: Further research is very likely to have an important impact or confidence in the estimate of effect and is likely to change the estimate: 1 or more RCTs with severe limitations. (D) Very low: Any estimate of effect is very uncertain: expert opinion, no direct research evidence or 1 or more RCTs with very severe limitations.

Magnitude of the effect size. We categorize this data element into 4 levels (none, small, moderate, and large). We attempted to calculate effect size for the studies meeting inclusion criteria if an effect size was not provided. We report how many studies reported a small effect (0.2–0.5), moderate (0.5–0.8), and large (>0.8) effect. We also report the number of studies from which we were not able to calculate an effect size.

Safety GRADE. Formulating the safety grade is dependent on the frequency and severity of adverse effects and interactions. The criteria developed are as follows: +2 = appears safe with infrequent adverse events and interactions, +1 = appears relatively safe but with frequent but not serious adverse events and interactions, 0 = safety not well understood or conflicting, −1 = appears to have safety concerns that include infrequent but serious adverse events and/or interactions, and −2 = has serious safety concerns that include frequent and serious adverse events and/or interactions.

Strength of the recommendation. GRADE has defined the levels as follows: strong recommendation in favor, weak recommendation in favor, no recommendation, weak recommendation against, and strong recommendation against.

Abbreviation: GRADE = Grading of Recommendations Assessment, Development and Evaluation.

Effect Size and Number Needed to Treat

It was possible to calculate ESs in 16 of the 25 studies. Of the 12 studies in which a single outcome was used to determine ES, results favored homeopathy in 8 and placebo in 4 cases; The magnitude of effect in favor of homeopathy was large in 2, medium in 1, small in 2, and negligible in 3. ES in favor of placebo was small in 1 study and below 0.2 in 3 studies. For the 4 studies with multiple primary outcomes that yielded discrepant results, the most favorable ES for homeopathy was medium in 1 study and small in 3 studies. For those outcomes least favorable to homeopathy, the ES was small in 2 cases and negligible (ie, below 0.2) in 2 cases. Across the 13 studies in which it was possible to obtain confidence intervals for the ES, the upper and lower bounds of 95% confidence intervals crossed zero in all except 3 instances, thus indicating substantial imprecision in the estimates of treatment effect, which are shown in Table 3.

In 10 studies, it was possible to obtain response rates and derive the NNTs, which are given by category. NNT results were obtained for 4 of the 6 FSS studies,[47–50] which when pooled (N = 260) yield an NNT of 3.67.

The chance of obtaining a positive result favoring homeopathy was unrelated to study quality. Quality of the 25 studies was variable with respect to minimization of bias, but there was no suggestion that the more favorable outcomes for homeopathy were associated with lower quality or weaker methodology, in that a higher proportion (66%) of the 6 best-quality reports could be taken as supportive of homeopathy to varying degrees, while only 4 of 10 (40%) in the weakest group provided positive evidence. This lack of association between quality and outcome is possibly due to the low number of studies for which ES could be calculated (16), the rather crude nature of quality rating schemes in general, and the small sample sizes, which have a large impact on estimates of precision. Publication bias is another possible reason, with lower-quality studies simply not being published or reported. We doubt that publication bias was a significant factor, however, because of our extensive search strategy, the inclusion of "gray" literature, and the generally low level of funding for research in this field. In addition, we conducted a funnel plot using 13 studies with sufficient information for this procedure (data not shown). Analysis of

Table 3. Effect Size (ES) and Number Needed to Treat (NNT) in Studies of Homeopathy Versus Placebo[a]

Reference	ES (95% CI)	Rating Used	NNT	Rating Used
Anxiety or stress				
Bonne et al (2003)[24]	−0.07 (−0.70 to 0.55)	HARS	−47.5	50% Reduction in HARS score
Baker et al (2003)[26]	−0.43 (−1.02 to 0.17)	Revised Test Anxiety Scale		
McCutcheon (1996)[27]	0.50 (0.03 to 0.97)	Sleep loss		
	0.22 (−0.25 to 0.68)	State anxiety		
Sleep or circadian rhythm disturbances				
Lipman et al (1999)[30]	0.78 (0.35 to 1.22)	Snoring diary	2.95	Global rating
Kolia-Adam et al (2008)[35]	0.24 (−0.53 to 1.02)	Hours asleep	−5.99	Satisfaction with sleep
La Pine et al (2006)[34]	0.03 (−0.49 to 0.56)	Fatigue		
Naudé et al (2010)[31]	2.40 (1.46 to 3.34)	Sleep Improvement index		
Kumar (2010)[33]	0.24	POMS-Fatigue		
	0.17	POMS-Vigor		
Premenstrual syndrome				
Yakir et al (2001)[38]	0.94 (−0.02 to 1.90)	MDQ	1.87	Global improvement
Laister (2010)[39]	−0.17 (−0.93 to 0.58)	MDQ-Pain		
Chapman et al (1994)[37]			−5.00	Global improvement
Attention-deficit/hyperactivity disorder				
Jacobs et al (2005)[41]	−0.12 (−0.72 to 0.48)	Conners Parent Global Scale		
Frei et al (2005)[42]	0.34	Conners Parent Global Scale		
Strauss et al (2000)[43]	0.17 (−0.71 to 1.05)	Conners Parent Symptom Questionnaire		
Mild traumatic brain injury				
Chapman et al (1999)[45]	0.14	Three-part Functional Assessment Scale	3.26	Global situations
			621.00	Global activities
Functional somatic syndromes				
Weatherley-Jones et al (2004)[49]	0.40 (−0.03 to 0.83)	Multidimensional Fatigue Inventory-Fatigue	6.14	Clinically significant improvement on all primary scales
	−0.08 (−0.34 to 0.50)	Multidimensional Fatigue Inventory-Reduced Motivation		
Bell et al (2004)[50]	0.31 (−0.23 to 0.86)	Tender point palpation pain	2.84	25% Improvement on tender point palpation pain
	−0.07 (−0.61 to 0.47)	McGill sensory pain		
Fisher et al (1990)[53]			4.28	Global improvement
Awdry (1996)[48]			2.49	Global response: unchanged or slight improvement vs other categories

[a]Negative values indicate that placebo was more effective than homeopathy.
Abbreviations: HARS = Hamilton Anxiety Rating Scale, MDQ = Menstrual Distress Questionnaire, POMS = Profile of Mood States.

the funnel plot also did not support evidence of publication bias ($\chi^2_1 = 1.923$, $P = .166$).

DISCUSSION

Principal findings of this systematic review are as follows: Homeopathy had no effect over placebo in the studies of anxiety and stress reaction. There are currently no studies meeting our selection criteria for depression. There was reasonable evidence for the efficacy of homeopathy in functional somatic syndromes. Findings for other conditions were mixed and inconclusive. Sample sizes were generally small, and overall confidence in the results was graded as moderate or low, suggesting that further research could well change the estimate of effect. Mainly because of the limited number of studies in any single category and heterogeneity of the data set, we decided that meta-analysis was not meaningful. Disorders were grouped to provide some level of diagnostic homogeneity, although this clearly worked better for some disorders (eg, ADHD, PMS) than for others (eg, sleep/circadian rhythm and anxiety disorders). Possible reasons for the lack of effect in stress and anxiety include a high placebo response or spontaneous recovery for the conditions studied, clinical variability of the included syndromes, methodological problems, or some other factor. Further study of homeopathy in sleep-related disorders is warranted; a recent polysomnography study by Bell et al[54] offers some basis for believing in the activity of homeopathic remedies on sleep mechanisms. The efficacy of homeopathy for FSS looks promising, but larger well-designed studies are needed.

Functional somatic syndromes, which account for 25% to 50% of all outpatient visits in the United States,[55] are chronic, disabling conditions that are unlikely to show spontaneous improvement. They are also among the more frequently studied psychiatric disorders with respect to homeopathy. In this review, 5 of the 6 studies provided some evidence for efficacy in either fibromyalgia or chronic fatigue syndrome. The low placebo response (4%–15%) and modestly consistent rates of response to homeopathy (26%–50%) in these disorders and the larger sample size of over 200 patients may have yielded more precise estimates than in the other categories. Taking the best-case outcomes, ESs of 0.31 (pain) and 0.40 (fatigue) are comparable to the ES ranges that have been reported for selective serotonin reuptake inhibitor antidepressants of 0.39 and 0.17.[56] Other widely used psychotropic drugs for fibromyalgia have small ESs for pain and fatigue, in the range of 0.2 for pain and 0.1 to 0.3 for fatigue.[57] Consistent with the efficacy of homeopathy in fibromyalgia is a pragmatic RCT that showed benefit for homeopathy over usual treatment in primary care.[58] Relevant collateral support in this context

comes from exploratory work by Bell et al,[59,60] who found links of clinical benefit to possible mechanisms of action and predictors of response in their fibromyalgia sample. The overall NNT for homeopathy on global measures in the 4 studies that provided source information compares favorably with the NNTs of 5.0 to 9.2 (as determined for 30% relief of pain) reported in 5 studies of gabapentin and pregabalin for fibromyalgia.[57] All-cause dropout rates in 3 FSS studies were 11% for homeopathy and 10% for placebo, which compares to the published dropout rate of 21% for adverse effects with pregabalin and gabapentin.[57] As noted by others,[15,16] studies of homeopathy for fibromyalgia are currently neither sufficiently rigorous nor sufficiently plentiful to warrant a definite answer on its use, but the evidence is encouraging.

Full understanding of any treatment involves not only evidence of efficacy, but also evidence of safety. Unfortunately, only 7 studies addressed this question, and even then the assessments were minimal, but all indicated there was no difference between homeopathy and placebo, which is consistent with the general presumption about the safety of homeopathy, where side effects and aggravations of the underlying symptoms have not been found to occur more frequently on homeopathy than on placebo in a major systematic analysis.[61] In one study of ADHD,[42] there were 3 dropouts related to tics, depression, and disturbed behavior, which suggests that careful evaluations might indicate the existence of homeopathy-related adverse effects. What cannot be assessed here, however, is the "harm" caused by failing to offer an effective treatment to a condition that, if untreated, leads to disability or other morbidity. To the extent that the reports said little about safety, our GRADE-based recommendations have limitations, since safety evaluation should be taken into account when making such assessments. One surprising finding was the low rate of dropouts, which was 12% in 12 studies (range, 0%–21%). In that one of the more common reasons for early exit relates to side effects, a low dropout rate might be seen as a favorable aspect of homeopathic treatment. On the other hand, an almost total lack of side effects is often taken to imply lack of efficacy. This aspect of homeopathy has consistently been neglected in the design and reporting of clinical trials.

Limitations of this review include its inability to provide information about major depression, which is such a large health problem worldwide and for which there is quite an extensive literature on other CAM approaches. We also did not include the entire range of psychiatric problems in our review, such as dementia, alcohol and substance problems, eating disorders, or psychosis. Apart from an unrevealing Cochrane review of homeopathy for dementia, we are unaware of any systematic reviews, or even a double-blind placebo-controlled trial, of homeopathy in any of these disorders. Another consideration is that not all studies we reviewed presented their results as an intent-to-treat analysis.

In summary, our review demonstrates that well-designed and comprehensively reported homeopathic studies in psychiatry are few and far between and preclude firm conclusions about the efficacy of this treatment in any single disorder. The same holds true for safety. For anxiety and stress-related problems, particularly generalized anxiety disorder, the data are not encouraging, but most forms of anxiety remain unstudied. For fibromyalgia and chronic fatigue syndrome as a group, results suggest possible utility for homeopathy. For the other disorders, the data are insufficient in quality or quantity to generate either positive or negative recommendations. Overall, we believe the findings offer sufficient grounds to warrant further clinical trials and are compatible with the use of homeopathy to treat certain conditions.

Drug names: gabapentin (Neurontin and others), pregabalin (Lyrica).
Author affiliations: Department of Psychiatry and Behavioral Science, Duke University Medical Center, Durham, North Carolina (Dr Davidson); and Samueli Institute, Alexandria, Virginia (Ms Crawford and Drs Ives and Jonas).
Potential conflicts of interest: In the last 12 months, **Dr Davidson** has received consulting fees from AstraZeneca and Euthymics Bioscience and royalties from the Davidson Trauma Scale, Social Phobia Inventory, Connor-Davidson Resilience Scale, Guilford Publications, and American Psychiatric Press. **Ms Crawford** and **Drs Ives** and **Jonas** report no potential conflict of interest.
Funding/support: This project was partially supported by award number W81XWH-08-1-0615-P00001 (United States Army Medical Research Acquisition Activity).
Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the official policy or position of the US Army Medical Command or the Department of Defense.
Acknowledgments: The authors acknowledge the following individuals for giving their permission to cite their unpublished results: Peter Fisher, FF Hom, FRCP, Royal London Homoeopathic Hospital and University College London, United Kingdom; Elizabeth Solomon, HD, ND, DO, Department of Homoeopathy, Faculty of Health Sciences, University of Johannesburg, South Africa; Andrew Criglington, B Comm, Miers Laboratories, Wellington, New Zealand; and David Naudé, M Tech (Hom), Department of Homeopathy, Faculty of Health Sciences, Durban University of Technology, Durban, South Africa. Mr Criglington is an employee of and stock shareholder in Miers Laboratories; the other acknowledged individuals report no potential conflict of interest.

REFERENCES

1. Freeman MP, Fava M, Lake J, et al. Complementary and alternative medicine in major depressive disorder: the American Psychiatric Association Task Force report. *J Clin Psychiatry*. 2010;71(6):669–681.
2. Freeman MP, Mischoulon D, Tedeschini E, et al. Complementary and alternative medicine for major depressive disorder: a meta-analysis of patient characteristics, placebo-response rates, and treatment outcomes relative to standard antidepressants. *J Clin Psychiatry*. 2010;71(6):682–688.
3. Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? a meta-analysis of placebo-controlled trials. *Lancet*. 1997;350(9081):834–843.
4. Jonas WB, Kaptchuk TJ, Linde K. A critical overview of homeopathy. *Ann Intern Med*. 2003;138(5):393–399.
5. Linde K, Melchart D. Randomized controlled trials of individualized homeopathy: a state-of-the-art review. *J Altern Complement Med*. 1998;4(4):371–388.
6. Ernst E. Homeopathy: what does the "best" evidence tell us? *Med J Aust*. 2010;192(8):458–460.
7. Lewith G. The conundrum of homeopathy: a commentary on Rutten ALB & Stolper CF (2009). *J Eval Clin Pract*. 2009;15(6):1236–1237.
8. Cucherat M, Haugh MC, Gooch M, et al; Homeopathic Medicines Research Advisory Group. Evidence of clinical efficacy of homeopathy: a meta-analysis of clinical trials. *Eur J Clin Pharmacol*. 2000;56(1):27–33.
9. Shang A, Huwiler-Müntener K, Nartey L, et al. Are the clinical effects of homoeopathy placebo effects? comparative study of placebo-controlled trials of homoeopathy and allopathy. *Lancet*. 2005;366(9487):726–732.
10. Lüdtke R, Rutten ALB. The conclusions on the effectiveness of homeopathy highly depend on the set of analyzed trials. *J Clin Epidemiol*. 2008;61(12):1197–1204.
11. Heirs M, Dean ME. Homeopathy for attention deficit/hyperactivity disorder or hyperkinetic disorder. *Cochrane Database Syst Rev*. 2007;4:CD005648.

12. Pilkington K, Kirkwood G, Rampes H, et al. Homeopathy for depression: a systematic review of the research evidence. *Homeopathy*. 2005;94(3):153–163.
13. Pilkington K, Kirkwood G, Rampes H, et al. Homeopathy for anxiety and anxiety disorders: a systematic review of the research. *Homeopathy*. 2006;95(3):151–162.
14. McCarney RW, Warner J, Fisher P, et al. Homeopathy for dementia. *Cochrane Database Syst Rev.* 2003;1:CD003803.
15. Perry R, Terry R, Ernst E. A systematic review of homoeopathy for the treatment of fibromyalgia. *Clin Rheumatol*. 2010;29(5):457–464.
16. De Silva V, El-Metwally A, Ernst E, et al; Arthritis Research Campaign Working Group on Complementary and Alternative Medicines. Evidence for the efficacy of complementary and alternative medicines in the management of fibromyalgia: a systematic review. *Rheumatology (Oxf)*. 2010;49(6):1063–1068.
17. Cooper KL, Relton C. Homeopathy for insomnia: a systematic review of research evidence. *Sleep Med Rev*. 2010;14(5):329–337.
18. Jacobs J, Crothers D. Who sees homoeopaths? a study of patients' characteristics in a homeopathic family practice. *Br Homeopath J*. 1991;80(1):57–58.
19. Davidson JRT, Rampes H, Eisen M, et al. Psychiatric disorders in primary care patients receiving complementary medical treatments. *Compr Psychiatry*. 1998;39(1):16–20.
20. SIGN Network. *A Guideline Developer's Handbook*. Edinburgh, Scotland: SIGN; 2001. http://www.sign.ac.uk/pdf/sign50.pdf. Accessed March 8, 2011.
21. Jacobs BP, Gundling K. Introduction. In: *The ACP Evidence-Based Guide to Complementary and Alternative Medicine*. Philadelphia, PA: ACP Press; 2009. http://wdn.ipublishcentral.net/acp/viewinside/25931038387829. Accessed March 7, 2011.
22. Hedges L, Olkin I. *Statistical Methods for Meta-Analysis*. London, England: Harcourt Brace Jovanovich; 1985.
23. NNT Calculator. Evidence Based Emergency Medicine Web site. http://www.ebem.org/nntcalculator.html. Accessed August 19, 2010.
24. Bonne O, Shemer Y, Gorali Y, et al. A randomized, double-blind, placebo-controlled study of classical homeopathy in generalized anxiety disorder. *J Clin Psychiatry*. 2003;64(3):282–287.
25. Ngobese JC. *The Relative Efficacy of Homeopathic Simillimum Treatment as Compared to Psychological Counseling (Cognitive Therapy and Behavioral Therapy) in the Management of Generalized Anxiety Disorder* [mini-dissertation]. Durban, South Africa: Durban University of Technology; 2006. http://ir.dut.ac.za/handle/10321/26. Accessed April 19, 2010.
26. Baker DG, Myers SP, Howden I, et al. The effects of homeopathic *Argentum nitricum* on test anxiety. *Complement Ther Med*. 2003;11(2):65–71.
27. McCutcheon LE. Treatment of anxiety with a homeopathic remedy. *J Appl Nutr*. 1996;48(1&2):2–6. http://homeoinst.org/node/358
28. Traub G. *The Influence of Homeopathic Medicines on Thought Interference, Nervousness and Anxiety in University Students Under Examination Conditions* [M. Tech thesis]. Johannesburg, South Africa: Technikon Witwatersrand; March 2000. http://ujdigispace.uj.ac.za:8080/dspace/handle/10210/2580. Accessed Jun 21, 2010.
29. Vaithilingam H. *The Effectiveness of Homoeopathic Simillimum in the Treatment of Job Burnout in the Human Services Field* [mini-dissertation]. Durban, South Africa: Durban University of Technology; 2005. http://ir.dut.ac.za/bitstream/handle/10321/20/Vaithilingam_2005.pdf?sequence=7. Accessed June 21, 2010.
30. Lipman D, Sexton G, Schlesser J. A randomized double-blind placebo-controlled evaluation of the safety and efficacy of a natural over-the-counter (OTC) medication in the management of snoring. *Sleep Breath*. 1999;3(2):53–56.
31. Naudé DF, Stephanie Couchman IM, Maharaj A. Chronic primary insomnia: efficacy of homeopathic simillimum. *Homeopathy*. 2010;99(1):63–68.
32. Maharaj A. *The Efficacy of Homoeopathic Simillimum in the Treatment of Chronic Primary Insomnia* [M. Tech thesis]. Durban, South Africa: Durban Institute of Technology; 2005. http://ir.dut.ac.za/bitstream/handle/10321/52/Maharaj_2005.pdf?sequence-5. Accessed June 21, 2010.
33. Kumar K. No Jet Lag Scientific Test. www.nojetlag.com/jetlag6.html. Accessed February 9, 2010.
34. La Pine MP, Malcomson FN, Torrance JM, et al. Night shift: can a homeopathic remedy alleviate shift lag? *Dimens Crit Care Nurs*. 2006;25(3):130–136.
35. Kolia-Adam N, Solomon E, Bond J, et al. The efficacy of *Coffea cruda* on insomnia: a double-blind trial. *Simillimum*. 2008;21:91–99.
36. Kolia-Adam N. *The Efficacy of* Coffea cruda *200cH on Insomnia* [mini-dissertation]. Johannesburg, South Africa: Technikon Witwatersrand; 2010. http://152.106.6.200:8080/dspace/bitstream/10210/3070/1/Kolia-Adam.pdf. Accessed June 21, 2010.
37. Chapman EH, Angelica J, Spitalny G, et al. Results from a study of the homeopathic treatment of PMS. *J Am Inst Homeo*. 1994;87:14–21.
38. Yakir M, Kreitler S, Brzezinski A, et al. Effects of homeopathic treatment in women with premenstrual syndrome: a pilot study. *Br Homeopath J*. 2001;90(3):148–153.
39. Laister C-A. The efficacy of homoeopathic simillimum in the treatment of premenstrual syndrome (PMS). http://ir.dut.ac.za/bitstream/handle/10321/383/Laister_2008.pdf?sequence=4, accessed June 21, 2010.
40. Kirtland KA. *The Efficacy of* Folliculinum *in the Treatment of Premenstrual Tension* [thesis]. Durban, South Africa: Technikon Natal; 1994.
41. Jacobs J, Williams A-L, Girard C, et al. Homeopathy for attention-deficit/hyperactivity disorder: a pilot randomized-controlled trial. *J Altern Complement Med*. 2005;11(5):799–806.
42. Frei H, Everts R, von Ammon K, et al. Homeopathic treatment of children with attention deficit hyperactivity disorder: a randomised, double blind, placebo controlled crossover trial. *Eur J Pediatr*. 2005;164(12):758–767.
43. Strauss LC. The efficacy of a homeopathic preparation in the management of attention deficit hyperactivity disorder. *Biomed Ther.* 2000;18(2):197–201.
44. Cole CL. *The Efficacy of* Selenium homaccord *in the Management of Attention Deficit Hyperactivity Disorder* [dissertation]. Johannesburg, South Africa: Technikon Witwatersrand, 1998; 1–73.
45. Chapman EH, Weintraub RJ, Milburn MA, et al. Homeopathic treatment of mild traumatic brain injury: a randomized, double-blind, placebo-controlled clinical trial. *J Head Trauma Rehabil*. 1999;14(6):521–542.
46. Fisher P. An experimental double-blind clinical trial method in homeopathy: use of a limited range of remedies to treat fibrositis. *Br Homeopath J*. 1986;75(3):142–147.
47. Fisher P, Greenwood A, Huskisson EC, et al. Effect of homeopathic treatment on fibrositis (primary fibromyalgia). *BMJ*. 1989;299(6695):365–366.
48. Awdry R. Homeopathy may help ME. *Int J Altern Complement Med*. 1996;14:12–16.
49. Weatherley-Jones E, Nicholl JP, Thomas KJ, et al. A randomised, controlled, triple-blind trial of the efficacy of homeopathic treatment for chronic fatigue syndrome. *J Psychosom Res*. 2004;56(2):189–197.
50. Bell IR, Lewis DA 2nd, Brooks AJ, et al. Improved clinical status in fibromyalgia patients treated with individualized homeopathic remedies versus placebo. *Rheumatology (Oxford)*. 2004;43(5):577–582.
51. Saul W. *The Effectiveness of Homoeopathic Simillimum Treatment in Chronic Fatigue Syndrome (CFS)* [M. Tech thesis]. Durban, Johannesburg, South Africa: Technikon Natal; 2005. http://ir.dut.ac.za/bitstream/handle/10321/44/Saul_2005.pdf?sequence=16. Accessed June 21, 2010.
52. Colquhoun D. Re-analysis of clinical trial of homoeopathic treatment in fibrositis. *Lancet*. 1990;336(8712):441–442.
53. Fisher P, Huskisson EC, Turner P, et al. Homoeopathic treatment of fibrositis. *Lancet*. 1990;336(8720):954.
54. Bell IR, Howerter A, Jackson N, et al. Effects of homeopathic medicines on polysomnographic sleep of young adults with histories of coffee-related insomnia [published online ahead of print July 27, 2010]. *Sleep Med*.
55. Aaron LA, Buchwald D. A review of the evidence for overlap among unexplained clinical conditions. *Ann Intern Med*. 2001;134(9 Pt 2):868–881.
56. Häuser W, Bernardy K, Uçeyler N, et al. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA*. 2009;301(2):198–209.
57. Häuser W, Bernardy K, Uçeyler N, et al. Treatment of fibromyalgia syndrome with gabapentin and pregabalin—a meta-analysis of randomized controlled trials. *Pain*. 2009;145(1-2):69–81.
58. Relton C, Smith C, Raw J, et al. Healthcare provided by a homeopath as an adjunct to usual care for fibromyalgia (FMS): results of a pilot randomised controlled trial. *Homeopathy*. 2009;98(2):77–82.
59. Bell IR, Lewis DA 2nd, Schwartz GE, et al. Electroencephalographic cordance patterns distinguish exceptional clinical responders with fibromyalgia to individualized homeopathic medicines. *J Altern Complement Med*. 2004;10(2):285–299.
60. Bell IR, Lewis DA 2nd, Lewis SE, et al. EEG alpha sensitization in individualized homeopathic treatment of fibromyalgia. *Int J Neurosci*. 2004;114(9):1195–1220.
61. Grabia S, Ernst E. Homeopathic aggravations: a systematic review of randomised, placebo-controlled clinical trials. *Homeopathy*. 2003;92(2):92–98.

eAppendix 1 is available at PSYCHIATRIST.COM

doi:10.4088/JCP.10r06580

eAppendix 1. Results of SIGN Evaluations

Reference	Study Addresses Appropriate, Clearly Focused Question [1.1]	Treatment Group Assignment Is Randomized [1.2]	Adequate Concealment Method Is Used [1.3]	Subjects and Investigators Are Kept "Blind" About Treatment Allocation [1.4]	Treatment and Control Groups Are Similar at the Start of the Trial [1.5]	Only Difference Between Groups Is the Treatment Under Investigation [1.6]	Outcomes Are Measured in a Standard, Valid, and Reliable Way [1.7]	What % of Subjects in Each Treatment Arm Dropped Out Before the Study Was Completed [1.8]	All Subjects Are Analyzed in the Groups to Which They Were Randomly Allocated (intention-to-treat analysis) [1.9]	If the Study Is Multisite, Results Are Comparable for All Sites [1.10]
Bonne et al (2003)[24]	W	P	A	A	P	W	W	A 13% Homeopathy, 9% placebo	W	N
Ngobese (2006)[25]	A	A	A	A	P	A	W	A 21% Homeopathy, 28% placebo	P	N
Baker et al (2003)[26]	W	W	A	A	P	A	A	P 11% Total	P	N
McCutcheon (1996)[24]	W	P	A	W	A	A	P	P 8% Homeopathy, 5% placebo	A	N
Traub (2000)[28]	W	P	P	A	P	P	W	P 32% Total	P	N
Vaithilingam (2005)[29]	W	W	P	A	P	A	W	P No information	P	N
Lipman et al (1999)[30]	A	P	A	A	W	A	W	P 11% Total	P	N
1. Naudé et al (2010)[31,a] 2. Maharaj (2005)[32] 3. Combined	AWW	AAA	AAA	AAA	APA	AAA	WWW	WPW 12% Homeopathy, 6% placebo	PPP	NNN
Kumar (2010)[33]	P	A	P	P	P	A	W	P 17% Total	P	N
La Pine et al (2006)[34]	A	A	P	P	P	W	A	P 18% Total	P	N
Kolia-Adam et al[a] 1. Publication (2008)[35] 2. Thesis (2010)[36] 3. Combined	PWW	PPP	PPP	AAA	PPP	PPP	PPP	PAA 7%–20% Homeopathy, 7% placebo	PPP	NNN
Chapman et al, PMS (1994)[37]	A	A	A	A	P	W	P	A 0%	P	N
Yakir et al (2001)[38]	W	A	W	W	P	A	W	A 14% Homeopathy, 20% placebo	P	N
Laister (2008)[39]	W	W	A	W	W	W	W	P	A	N
Kirtland (1994)[40]	W	P	P	A	P	W	W	A	P	N
Jacobs et al (2005)[41]	A	W	W	W	W	W	W	A 9% Homeopathy, 14% placebo	A	N

(continued)

doi:10.4088/JCP.10r06580

eAppendix 1 (continued). Results of SIGN Evaluations

Reference	Study Addresses Appropriate, Clearly Focused Question [1.1]	Treatment Group Assignment Is Randomized [1.2]	Adequate Concealment Method Is Used [1.3]	Subjects and Investigators Are Kept "Blind" About Treatment Allocation [1.4]	Treatment and Control Groups Are Similar at the Start of the Trial [1.5]	Only Difference Between Groups Is the Treatment Under Investigation [1.6]	Outcomes Are Measured in a Standard, Valid, and Reliable Way [1.7]	What % of Subjects in Each Treatment Arm Dropped Out Before the Study Was Completed [1.8]	All Subjects Are Analyzed in the Groups to Which They Were Randomly Allocated (intention-to-treat analysis) [1.9]	If the Study Is Multisite, Results Are Comparable for All Sites [1.10]
Frei et al (2005)[42]	W	W	A	A	W	W	W	W 9% Homeopathy, 3% placebo	W	N
Strauss (2000)[43]	W	A	A	A	P	P	W	P No information given	P	N
Chapman et al, TBI (1999)[45]	W	W	W	W	W	A	W	A 20% Homeopathy, 16% placebo	W	N
Fisher (1986)[46]	P	A	P	P	P	P	W	P No information given	P	N
Fisher et al (1989)[47]	A	P	P	A	P	P	A	P No information given	P	N
Awdry (1996)[48]	A	A	A	A	A	P	P	W 6% Homeopathy, 3% placebo	P	N
Weatherley-Jones et al (2004)[49]	W	W	W	W	W	W	W	A 14% Homeopathy, 19% placebo	W	N
Bell et al (2004)[50]	W	W	W	W	W	A	W	A 13% Homeopathy, 16% placebo	W	N
Saul (2005)[51]	A	A	P	A	P	P	W	P 19% Total	P	N

[a]Where ratings were done of published, unpublished, and composite of both, the sequence was published report, unpublished thesis, and composite.
Abbreviations: A = adequately addressed, N = not applicable, P = poorly addressed, PMS = premenstrual syndrome, SIGN = Scottish Intercollegiate Guidelines Network, TBI = traumatic brain injury, W = well addressed.