A Randomized, Double-Blind, Placebo-Controlled Study of Classical Homeopathy in Generalized Anxiety Disorder

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Background: Homeopathy is commonly used for the treatment of medical and psychological conditions. Such prevalent use, however, is not supported by robust, methodologically sound research. This study evaluates the effect of homeopathic treatment in generalized anxiety disorder, a prevalent mental disorder characterized by an enduring pattern of excessive apprehension and distress and by mental and bodily complaints.

Method: Forty-four patients with DSM-IV generalized anxiety disorder participated in a randomized, double-blind, placebo-controlled 10-week trial of individually tailored homeopathic remedy. Homeopathic therapy was administered by an expert who followed the traditional routines of homeopathic diagnosis and prescription. Thirty-nine subjects completed the study (20 in the active treatment group and 19 in the placebo group). Subjects' symptoms were rated before treatment and after 5 and 10 weeks of treatment, with the Hamilton Rating Scale for Anxiety (HAM-A) as main outcome measure. Additional measures of outcome included the Brief Symptom Inventory, the Psychological General Well-Being Index, the Hamilton Rating Scale for Depression, the Beck Depression Inventory, Spielberger's State-Trait Anxiety Inventory, and a Visual Analogue Scale of subjective distress.

Results: Significant ($p < .05$) improvement in most measures, including the HAM-A, was observed in both the active treatment and placebo groups, yet no group effect was observed.

Conclusion: The effect of homeopathic treatment on mental symptoms of patients with generalized anxiety disorder did not differ from that of placebo. The improvement in both conditions was substantial. Improvement of such magnitude may account for the current belief in the efficacy of homeopathy and the current increase in the use of this practice.

(J Clin Psychiatry 2003;64:282–287)

The use of alternative medicine is increasing rapidly.[1,2] In the United States, the number of visits to practitioners of alternative medicine may exceed that of visits to primary care physicians.[2] Out-of-pocket expenditure on alternative medicine ($27.0 billion in 1997) is comparable to expenditure for all conventional medical services.[2] Homeopathy is a widely used method of alternative medicine. In Israel, homeopathy is the most prevalent alternative medicine approach,[3] with patient satisfaction rates exceeding 80%.[4]

Considerable effort has been recently directed toward assessing the preclinical and clinical factual bedrock of homeopathy. Notably, the reputed ability of a very dilute antiserum against human immunoglobulin E to trigger basophil degranulation was the subject of much heated debate,[5] with subsequent attempts to replicate this "effect" not yet successful.[6,7] Two meta-analyses[8,9] examined results and quality of clinical trials conducted in homeopathy. Both concluded that the evidence is generally favorable but not sufficient to determine efficacy in any single condition. Data from the more recent study[9] were reexamined,[10] and the impression was that studies of superior methodological quality tend to yield less favorable results, as do studies employing "classical" homeopathy.[11]

Of the diverse techniques grouped under the term *homeopathy*, "classical" homeopathy is probably closest to the guidelines proposed by Samuel Hahnemann, the founder of the discipline in the late 18th century. Briefly, classical homeopathy does not categorize medical conditions into disparate illnesses but rather addresses the complete and unique symptom picture of each patient.[12] Thus, patients who would be given a similar diagnosis

and hence similar treatment by conventional physicians may receive various and individualized medications by classical homeopaths. Moreover, all remedies given to patients are extremely diluted and contain no measurable substance.

The patient's mental state is said to be of utmost importance in classical homeopathy.[12] However, only a few controlled studies have actually examined the effect of homeopathic treatment in mental disorders. A placebo-controlled, double-blind study[13] compared administration of homeopathic remedy (from a choice of 5 possible agents) with placebo in the treatment of premenstrual syndrome. Homeopathic drug was superior to placebo in the 3-month period following treatment. In another study, greater improvement in symptoms of hyperactivity was observed 10 days after administration of homeopathic remedy, compared with placebo, in children with attention-deficit/hyperactivity disorder.[14] Open studies[15,16] report benefit from the administration of homeopathic remedies in treatment of depression, anxiety, and postoperative pain. Animal studies report an effect for highly diluted homeopathic substance on prolongation of haloperidol-induced catalepsy[17] and reduction of alcohol-induced sleep times.[18] However, the impact of these reports on the mental-health literature is seminal, and reviews of alternative medicine in psychiatric journals scarcely mention homeopathy.[19,20]

Generalized anxiety disorder (GAD) is a prevalent mental disturbance, manifest by psychic and somatic complaints.[21] The hallmark of the disorder is an enduring pattern of excessive apprehension and distress concerning events and activities that are well within the scope of everyday life. Insomnia, fatigue, restlessness, irritability, and impaired concentration are common. Physically, many signs of autonomic hyperactivity are present, such as shortness of breath and palpitations, dizziness, sweating, dry mouth, flushes, chills, and paresthesias. Patients will ordinarily first turn to their primary caregiver for treatment of these symptoms. They often undergo many simple and more elaborate diagnostic procedures that will ordinarily yield negative results. The general practitioner may then refer them to a psychiatrist, a step many patients will be reluctant to take.

Psychopharmacologic treatment of GAD consists of benzodiazepines, which provide rapid relief but may cause side effects such as sedation, fatigue, and memory impairment,[22] as well as induce tolerance and dependence,[23] and agents such as buspirone, imipramine, venlafaxine, and paroxetine, which carry a more favorable side effect profile but take longer to reach positive outcome.[24,25] Since the prospect of psychotropic medication is often intimidating, many patients with GAD either resort to alternative medicine or remain untreated even at the expense of continued distress and impairment in quality of life. Homeopathy has thus become a desirable and often-used alternative to pharmacotherapy in GAD. To test whether the efficacy of homeopathy treatment of GAD is greater than that of placebo, we invited GAD patients to participate in a randomized, double-blind, placebo-controlled trial of classical homeopathy.

METHOD

Participants

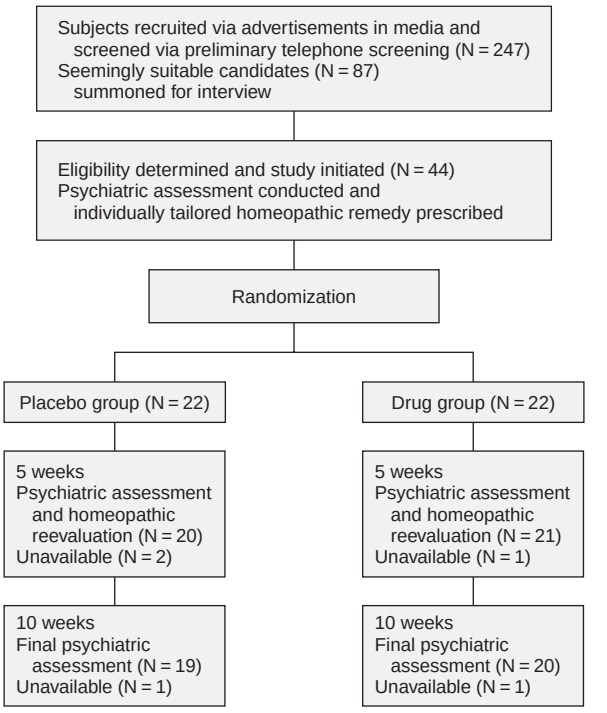
The study population, male and female volunteers aged 18 to 65 years, was recruited through advertisements in local newspaper (in Jerusalem, Israel). Participation in the study was free of charge. Candidates were first screened by a telephone interview. Seemingly suitable participants were then interviewed by a board-certified psychiatrist (O.B.) who administered the Structured Clinical Interview for DSM-IV[26] and the psychometric instruments listed below. Eligibility criteria included DSM-IV diagnosis of GAD, absence of additional DSM-IV Axis I and II diagnoses, Hamilton Rating Scale for Anxiety (HAM-A)[27] score above 20, and Hamilton Rating Scale for Depression (HAM-D)[28] score below 18. Participants were free of medication for at least 1 month before screening. Psychotherapy was allowed if initiated at least 6 months before beginning the trial. A single highly accredited classical homeopath (Y.S.) conferred homeopathic diagnosis and treatment. All participants gave written informed consent. The trial was approved by the hospital ethics committee and the Israeli Ministry of Health.

Trial Protocol

The homeopath assessed each patient and prescribed his/her unique remedy within 4 days of the initial psychiatric examination. All participants meeting entry criteria were medicated (or given placebo). It was decided a priori that the dilution of prescribed remedies would exceed 10^{-30}. Given Avogadro's constant of 6×10^{23} molecules in a gram/mole, the likelihood of finding even 1 molecule in a homeopathic preparation of the 10^{-30} potency is less than 1 in a million. The prescription was dispatched to a reliable homeopathic pharmacy, which produced 2 identical tablet bottles, one containing medication globules marked "D" (drug) and the other containing visually identical non–medication-impregnated globules marked "P" (placebo). A list of the specific compounds used in the study is available from the authors on request.

A senior member of the psychiatry outpatient clinic performed randomization, which was stratified for sex with simple random assignment within each subgroup. Participants were summoned to the outpatient clinic to collect their medication from the clinic secretary (the "P" and "D" tags were removed from each bottle). Treatment began within 1 week of the initial psychiatric evaluation. Participants received a single dose of the remedy/placebo at the beginning of the study. The secretary, psychiatrist, and homeopath remained blind to patient group assignment

Figure 1. Trial Profile



throughout the study. The code was held only by the physician responsible for randomization.

Five weeks after the beginning of treatment, participants were reevaluated by the same psychiatrist using the same rating scales as before. The homeopath also then reexamined all participants, and, according to his clinical judgment, could change the medication or alter the dose. The procedure of remedy prescription and dispatch was repeated, with participants' drug/placebo status remaining unchanged (e.g., a participant receiving placebo whose medication was changed by the homeopath continued to receive a [differently labeled] placebo). Patients whose medication/placebo was changed at mid-study received another single dose of the new remedy/placebo. Five weeks later, a psychiatric end-of-study evaluation was performed. Drug/placebo code was revealed after all participants completed the study. Placebo-treated subjects then could, if they wished, receive open-label homeopathic treatment, free of charge. This possibility was made known to all participants at recruitment.

Statistical Analysis

The main outcome measure was the HAM-A, with the HAM-D used for determination of eligibility and as an auxiliary measure of response. Given the wide range of a priori hypotheses regarding improvement in homeopathic treatment, inclusion of ancillary (self-report) outcome measures enabled evaluation of additional dimensions of mental health and well-being. These measures included the Beck Depression Inventory,[29] Spielberger's State-Trait Anxiety Inventory,[30] Brief Symptom Inventory,[31] Psychological General Well-Being Index,[32] and a visual analogue scale[33] assessing current subjective distress. Prestudy power calculation was based on findings from previous clinical drug trials in GAD[34,35]: mean pretreatment HAM-A score of 25, mean reduction in HAM-A scores of 13 in drug-treated participants and 8 in placebo-treated participants, and mean standard deviation of 8 in the changes in HAM-A score. With the use of a 5% significance level and 80% power, 30 participants would be required in each group to avoid false-negative results. However, subject recruitment was arduous and prolonged, and recruitment was stopped after inclusion of 44 participants.

Group, time, and interaction effects for each scale were examined using analysis of variance (ANOVA) with repeated measures, with medication status (drug/placebo) as grouping variable and time as repeated-measure factor. Since ANOVA with repeated measures for all 3 timepoints was the major analysis procedure, only study completers were considered. As a check, a last-observation-carried-forward (LOCF) analysis was performed for all patients for whom data were available for the mid-study assessment. Clinical response was defined as a 50% reduction in HAM-A score. The chi-square statistic was used to examine the distribution of responders in placebo- and drug-treated groups.

As an additional check, we applied multivariate analysis of variance (MANOVA) with repeated measures concurrently for all rating scales, again with medication status (drug/placebo) as grouping variable and time as repeated-measure factor.

RESULTS

Two hundred forty-seven people responded to the advertisements and were screened by telephone (Figure 1). Eighty-seven were summoned for clinical interview; 44 were found to be eligible and were randomized, with 22 participants in each group. Three participants were not available for the 5-week evaluation, and an additional 2 dropped out before the end of the study.

Thirty-nine subjects completed the study, 20 in the active drug group and 19 in the placebo group. Most patients received potencies of 1M (a dilution of 100^{-1000}), and the rest received a potency of 200CH (a dilution of 100^{-200}). The 21 patients in the active drug group who were available for the mid-study evaluation initially received 16 different remedies, 5 of which were changed at the mid-study evaluation. One remedy was prescribed again at a higher (i.e., more diluted) dose. No more than 2 patients received any single medication.

Sociodemographic measures were similar for both groups: participants' mean ± SD age was 46.1 ± 12.9

Table 1. Psychometric Scale Scores for Homeopathic Medication–Treated (N = 22) and Placebo-Treated (N = 22) Participants With Generalized Anxiety Disorder[a]

	Pretreatment		Mid-Study (5 weeks)		Posttreatment (10 weeks)		Repeated-Measure ANOVA F Value[b]		
Scale	Drug	Placebo	Drug	Placebo	Drug	Placebo	Group	Time	Interaction
HAM-A	31.4 ± 7.2	30.4 ± 7.6	18.8 ± 11.1	20.2 ± 11.0	21.7 ± 11.6	20.9 ± 9.2	< 1	19.9***	< 1
HAM-D	15.4 ± 3.9	15.4 ± 5.8	11.2 ± 3.6	11.6 ± 5.8	13.5 ± 6.9	12.0 ± 5.4	< 1	9.3**	< 1
BDI	18.2 ± 8.1	16.9 ± 7.0	15.1 ± 7.6	13.6 ± 6.6	12.5 ± 6.7	12.3 ± 8.5	< 1	10.1**	< 1
BSI	0.31 ± 0.09	0.30 ± 0.09	0.26 ± 0.11	0.26 ± 0.10	0.25 ± 0.13	0.25 ± 0.14	< 1	9.1**	< 1
PGWB	55.9 ± 14.1	56.4 ± 14.3	63.7 ± 13.6	60.6 ± 13.2	63.4 ± 17.2	63.9 ± 17.4	< 1	8**	< 1
STAI									
State	53.8 ± 9.8	50.9 ± 10.6	50.6 ± 8.5	51.1 ± 10.0	50.1 ± 9.5	47.6 ± 9.3	< 1	3.8*	< 1
Trait	51.3 ± 11.4	50.2 ± 12.7	51.5 ± 10.0	49.8 ± 11.3	50.8 ± 8.5	49.1 ± 12.5	< 1	< 1	< 1
VAS	6.7 ± 0.5	6.8 ± 0.5	5.9 ± 0.6	6.1 ± 1.7	5.9 ± 0.5	6.0 ± 2.2	< 1	23.7***	< 1

[a]All values shown as mean ± SD unless otherwise noted.
[b]F < 1 = p > .36.
*p < .05.
**p < .001.
***p < .0001.
Abbreviations: ANOVA = analysis of variance, BDI = Beck Depression Inventory, BSI = Brief Symptom Inventory, PGWB = Psychological General Well-Being Index, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, STAI = State-Trait Anxiety Inventory, VAS = visual analogue scale of subjective distress.

years, and 26 were women (13 in each group). The subjects had a mean education level of 14.6 ± 2.7 years, and most (17/22 in the active treatment group and 16/22 in the placebo group) were married.

A consistent pattern of response was observed for the HAM-A and most other rating scales: (1) a nonsignificant group main effect, (2) a significant time main effect, and (3) a nonsignificant group-by-time interaction. The main improvement in most psychometric scores occurred in the first phase of the study (i.e., between initial and week 5 assessments), with lesser change thereafter. Psychometric scale mean scores and results of ANOVA with repeated measures for each scale are presented in Table 1.

MANOVA similarly revealed a nonsignificant group effect ($F = 0.3062$, df = 8,108; $p = .95$), a significant time effect ($F = 23.80$, df = 7,109; $p < .0001$), and a nonsignificant group-by-time interaction ($F = 0.36$, df = 7,109; $p = .9$). Eight subjects in each group met criteria for clinical response, with no significant between-group difference ($\chi^2 = 0.01$, $p = .93$). Two patients in each group met standard criteria for remission, i.e., HAM-A score < 8, at both the 5- and 10-week evaluations. Results of the LOCF analysis were, for all purposes, identical to the results from the analysis of completers.

DISCUSSION

The results of this study show no clinical or statistical advantage for homeopathic therapy over placebo in the treatment of GAD and associated symptoms. Although the minimal sample size as calculated by the power analysis was not reached, given the complete absence of between-group differences, it is highly unlikely that inclusion of the missing participants would markedly alter this impression. Furthermore, even enormous sample sizes would not detect between-group differences if the trends observed thus far remain. In fact, it could be argued that in these conditions, continuation of the trial is not only unnecessary but also ethically inappropriate.

Improvement was observed in both the homeopathy and placebo groups. The magnitude of decrease in HAM-A scores resembles that of placebo-treated groups in previous drug studies of GAD.[34,35] Although our findings suggest that the effect of the homeopathic remedy is a "placebo effect," we have not ruled out the possibility that the decreases in HAM-A scores may represent a fluctuating course of the disorder[23] (this could have been controlled for by including a nontreatment group). The possibility that administration of a conventional anxiolytic medication to this cohort would result in similar decreases in HAM-A values has also not been excluded (the last 2 possibilities are examples of "failed" rather than "negative" studies). In light of our considerable placebo effect and sizable standard deviation, we assume that even administration of an established active comparator would only result in a moderate (0.25) effect size.

Study samples recruited by advertisement may differ from the help-seeking patient population (e.g., have less severe disorder or be more prone to suggestion). Specifically, the current sample was adverse to conventional pharmacotherapy (resembling, however, consumers of alternative medicine). Response rates may have been higher had participants not been informed of the possibility of placebo administration. Still, this effect would be similar for both "placebo" and "homeopathic treatment" groups and is ethically inadmissible. Conversely, it has been argued that the increased attention and social stimulation provided by research settings may even enhance placebo response (i.e., the Hawthorne effect).[36] In accordance with this approach, Walach[37,38] has written exten-

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sively about the need to refrain from equating equivalence to placebo with lack of effect. As is partly observed in our study, Walach maintains that context-related high rates of success are often obtained in complementary alternative medicine (CAM), although superiority of the agents used in CAM over placebo is seldom established. He thus argues that the overall efficacy of any given treatment should take precedence to its comparison with placebo.

The present study evaluated classical homeopathic treatment, as practiced in the community. Such a design may help refute a common objection of homeopathic practitioners to contemporary research, namely, that the efficacy of homeopathy cannot be studied by simply prescribing homeopathic remedies within an "allopathic" framework. Furthermore, homeopathic literature describes a characteristic time pattern in some patients that is associated with a favorable response.[12] This pattern first calls for an "aggravation" in the patient's condition, which is later followed by an "amelioration." The aggravation may involve physical or mental symptoms. No such aggravation was observed in any of our participants. In fact, improvement in most symptom measures occurred between the first and middle assessments, reportedly (although not actually documented) mainly within the initial 2 weeks of the study. However, our rating scales and the frequency of their administration were not designed to capture somatic symptoms, so the presence of a somatic aggravation in a minority of our subjects may have gone unnoticed.

A certain setback of this study's design lies in its dependence on a single homeopathic practitioner. Another reservation applies to the diversity of agents employed in the study. While both of these factors may prevent an exact mechanistic replication of the study, a conceptual replication, posing and answering exactly the same questions, is highly feasible. It may also be argued that the duration of this trial is brief by homeopathic clinical practice standards. We agree that, according to homeopathic conceptualization, attainment of complete "cure" would require a longer period than the duration of the current study. However, the homeopath who prescribed in the current study maintains that 1 month is sufficient to witness an initial effect of the administered medication. It is his standard clinical practice to evaluate patients after 1 month and accordingly decide whether the prescribed remedy is sufficient, should be repeated (at a similar or different dose), or should be changed.

GAD is a very "placebo-responsive" disorder. Placebo response rates in GAD have been said to increase in the last 2 decades.[34] "Worries," as described in GAD, may be eminently affected by reassurance and care. In this instance, participants were exposed to the interpersonal and ritualistic components of homeopathic practice, which may carry enough suggestive or other psychological effect to account for such results. Indeed, what this study shows is that the specific compounds used in homeopathy do not add to the healing power of the method. Bearing in mind Walach's appreciation of the efficacy of placebo within CAM, it would be interesting to compare, in future controlled studies, whether the "healing power" of placebo within CAM differs from that of placebo used in conventional clinical drug studies.[34,35] Given the possibility of a higher tendency for relapse[39] among placebo responders, a longer follow-up period in future studies would be merited.

Alternative medicine flourishes by word of mouth. We have shown marked (50%) symptomatic improvement in nearly 40% of study participants, irrespective of treatment modality. Since homeopath/patient transaction is not done within a research setting, such "effectiveness," although not different from that of placebo, may be attractive enough to create and maintain a general attribution of success to this treatment modality. Placebo response in prevalent medical conditions may, therefore, account for the current affluence in homeopathy and other modalities of alternative medicine.

Drug names: buspirone (BuSpar and others), haloperidol (Haldol and others), imipramine (Tofranil, Surmontil, and others), paroxetine (Paxil), venlafaxine (Effexor).

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