Homeopathic Treatment of Mild Traumatic Brain Injury: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

Background: Mild traumatic brain injury (MTBI) affects 750,000 persons in the United States annually. Five to fifteen percent have persistent dysfunction and disability. No effective, standard pharmacological treatment exists specifically for this problem. We designed a pilot research project to study the clinical effectiveness of homeopathic medicine in the treatment of persistent MTBI. **Method:** A randomized, double-blind, placebo-controlled trial of 60 patients, with a four-month follow-up (N = 50), was conducted at Spaulding Rehabilitation Hospital (SRH). Patients with persistent MTBI (mean 2.93 years since injury, SD 3.1) were randomly assigned to receive a homeopathic medicine or placebo. The primary outcome measure was the subject-rated SRH-MBTI Functional Assessment, composed of three subtests: a Difficulty with Situations Scale (DSS), a Symptom Rating Scale (SRS), and a Participation in Daily Activities Scale (PDAS). The SRH Cognitive-Linguistic Test Battery was used as the secondary measure. **Results:** Analysis of covariance demonstrated that the homeopathic treatment was the only significant or near-significant predictor of improvement on DSS subtests (P = .009; 95% CI −.895 to −.15), SRS (P = .058; 95% CI −.548 to .01) and the Ten Most Common Symptoms of MTBI (P = .027; 95% CI −.766 to −.048). These results indicate a significant improvement from the homeopathic treatment versus the control and translate into clinically significant outcomes. **Conclusions:** This study suggests that homeopathy may have a role in treating persistent MTBI. Our findings require large-scale, independent replication.

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INTRODUCTION

This pilot study was undertaken to assess the effect of homeopathic treatment on the persistent symptoms and disability resulting from mild traumatic brain injury (MTBI). Each year, three-quarters of a million Americans sustain an MTBI, defined by the American Congress of Rehabilitation Medicine and the National Brain Injury Association[1] as:

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a traumatically induced physiological disruption of brain function, manifested by at least one of the following:

1. any period of loss of consciousness up to 30 minutes
2. any loss of memory for events immediately before or after the accident up to 24 hours
3. any alteration in mental state at the time of the accident (feeling dazed, disoriented or confused)
4. focal neurological deficits which may or may not be transient but result in a Glasgow Coma Scale score of no less than 13–15 within 30 minutes of the accident.

The natural course of recovery from MTBI is difficult to predict. Recovery falls into two patterns—full recovery or persistence of symptoms. Most recover from the injury without sequelae; however, 5–15% experience persistent deficits beyond three months.[2,3] Complete recovery is rare among those with symptoms persisting beyond six months post-injury.[4,5] Some of the more common and disabling sequelae include: mood disorders, pain and fatigue, deficits of attention, and difficulties with information processing and new learning.[3,6–8] Effects of subtle injury to the brain overlap with structural injury in the head and neck that may contribute to symptoms such as headache and dizziness. Persistence of deficits in physical, cognitive, and affective functioning result in considerable morbidity, both social and economic, the cost of which is estimated at $3.8 billion per year.[9]

Patients with persistent MTBI are difficult to evaluate by current radiological or neuropsychological assessment tools for several reasons:

1. patients are heterogeneous vocationally, educationally, and socially[10,11]
2. current imaging techniques are insensitive to the diffuse microscopic type of injury that characterizes MTBI[12–14]
3. although there are many common symptoms in a group of MTBI patients, the individual symptom complexes can be quite variable[2]
4. current neuropsychological evaluation tools place cognitive performance in broad categories of age-related population norms, but, without testing pre-injury for comparison, they fail to identify loss of function in an individual who had functioned at a "superior" level and is performing at the "average" level post-injury.[15–17]

These complexities have limited the scope of research and the availability of validated measures for dysfunction seen in MTBI patients.

Persistent MTBI patients are also very difficult to treat. Current treatment employs a combination of rehabilitation therapies aimed at helping patients to develop compensatory strategies for persistent deficits and using medications[12,18,19] that address the variety of MTBI-related complaints. Because patients rarely present with a single symptom, polypharmacy is often required, and medications used include nonsteroidal anti-inflammatory agents, narcotics, muscle relaxants, antivertigo agents, psychostimulants, and antidepressants. Pharmacological treatment of one symptom may exacerbate other deficits, disrupting the fragile balance of post-trauma skills.[11,19] Clinicians must weigh benefits against the risk of adverse effects. The limitations of current pharmacological approaches in MTBI are reflected in the absence of any published studies of pharmacological treatment since 1993.

Benefit from homeopathic medicine has been reported in published cases of patients suffering from the chronic effects of concussion and head injury.[20–22] Although homeopathy has only limited recognition in the United States, it is popular throughout Eastern and Western Europe, many countries

in South America, South Africa, Australia, New Zealand, and the Indian subcontinent. Eisenberg estimated that 700,000 Americans used homeopathic medicines in 1990,[23] a number that increased to 3.4 million in 1997.[24] Four metaanalyses[25–28] have reviewed the status of homeopathic research, including 189 clinical trials. Although single studies have demonstrated the efficacy of homeopathy in various clinical conditions, including asthma,[29] allergy,[30] diarrhea,[31] influenza,[32] fibrositis,[33] and depression,[34] issues of quality, reproducibility, and a mechanism of action for homeopathic medicines limit the conclusions that can be drawn from this research.[27] In 1992, Congress created the Office of Alternative Medicine (OAM) at the National Institutes of Health to fund research exploring the potential efficacy of complementary/alternative medicine (CAM). This pilot study, supported by one of the 30 initial grants awarded by the OAM, is the only federally funded study of homeopathy in the treatment of any clinical condition, and it is the first randomized, double-blind clinical trial testing the efficacy of homeopathy in MTBI.

Homeopathy is based on the premise that specific "homeopathic" substances act to treat disease or injury by facilitating the body's natural healing processes. The homeopathic therapeutic system was articulated 200 years ago by Samuel Hahnemann.[35,36] Homeopathy's two fundamental principles, the "law of similars" and the "minimum dose," challenge conventional medical understanding. The law of similars states that a substance can cure the same symptoms that it produces, when given to healthy human subjects in "homeopathic drug provings" (HDPs).[37–39] The homeopathic prescription is individualized to the patient, rather than to a specific diagnosis. Consequently, a different medicine may be prescribed for each patient with a single diagnosis; or, conversely, the same medicine to patients with widely varying diagnoses. For instance, the well-known constellation of symptoms produced by Belladonna (atropine)—red, hot, dry, dilated pupils, agitation, delirium—could be used to treat a febrile child, no matter what the microbiological etiology, or an adult presenting with cluster headaches. Homeopathy differs from the conventional models of pharmacological disease treatment: replacement therapy (insulin, thyroid), isopathy (immunization or allergy desensitization), or allopathy (treatments that remove or oppose the manifestations of disease).[40]

Homeopathy uses medicines in "infinitesimal doses." The medicines are produced by serially agitated dilution (SAD). One part of the original material, derived from plant, mineral, or animal sources, is serially diluted and agitated in distilled water or pharmaceutical alcohol at a ratio of 1:99 (C or centesimal potency) or 1:9 (X or decimal potency) to dilutions of 3X (10^{-3} molar) to 100,000C ($10^{-200,000}$ molar).[41] The final solution is sprayed on sucrose pellets that are administered sublingually. The dilution used in this study was 200C (10^{-400} molar).

A specific mechanism of action for homeopathic medicines has not been identified. Because the probability that the number of molecules of the original substance approaches zero in dilutions beyond 10^{-23} molar, homeopaths postulate that changes in the structure of the diluent water[42,43] carry information that can affect biological systems.[44,45] Homeopathic potencies appear to act like catalysts, or pheromones, stimulating autoregulatory pathways and generating multisystem therapeutic effects.[40] The United States Homeopathic Pharmacopoeia was part of the original act of 1938, under the authority of the United States Food and Drug Administration (USFDA), and is referenced in the legal definition of a drug in every state and by Medicare. The USFDA regulates the production of homeopathic medicines, using guidelines

developed by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS).[46] Most are classified in the over-the-counter (OTC) category[47] and regulated separately from herbal and dietary supplements.

The decision to investigate homeopathy as a treatment of MTBI is justified for a number of reasons. First, published clinical case reports[20–22] suggest efficacy of homeopathic medicines in MTBI. Second, a single homeopathic medicine can simultaneously affect the full range of physical, emotional, and cognitive functions affected by the brain injury. Third, homeopathic medicines have a relatively low incidence of side effects.[40] Finally, the individualized nature of the homeopathic prescription, based on a patient's subjective symptoms, makes this approach sensitive to and adaptable to the variable presentations of MTBI patients.

METHODS

Subjects and enrollment

Subjects were recruited by a letter sent to all patients previously evaluated and treated at the Adult Head Injury Clinic at Spaulding Rehabilitation Hospital (SRH). Letters were also sent to rehabilitationists and neurologists in the Boston area who treat patients with MTBI. We received approximately 100 responses. Sixty-one subjects were enrolled (57 from SRH and 4 referred from other sources). The preestablished inclusion criteria were:

a) symptoms consistent with the diagnosis of MTBI, confirmed by review of medical records
b) time since the original injury of at least three months
c) age 18 or older
d) competence to give informed consent
e) ability to transport self to the study site.

Exclusion criteria included:

a) current use of medications for conditions or symptoms not associated with MTBI—including conventional, homeopathic, herbal, etc. (exceptions were NSAIDs, insulin, thyroid hormone, and vitamins)
b) current use of "energy therapies" known to interfere with the action of homeopathic remedies, including acupuncture, ultrasound, and therapeutic radiation
c) current pregnancy or pregnancy planned for the coming year
d) current use of hormonal contraception
e) inability to discontinue substances (oral or topical) known to antidote homeopathic remedies, such as coffee and aromatic substances (eg, camphor, menthol and eucalyptus)
f) current acute phase of a major psychiatric disorder
g) current alcohol or substance abuse.

All subjects had a diagnosis of MTBI, consistent with the ACRM definition, confirmed by history taken by the director of the SRH outpatient head injury clinic (EW); the mean duration since injury for the sample studied was 2.93 years (SD 3.1, range 4 months to 16 years). The patients' symptoms resulted from traumatic brain injuries incurred in a variety of settings, mostly automobile accidents and falls. Of the 61 subjects who met the eligibility criteria, most had been treated previously, using the range of conventional modalities, including physical, occupational, speech/language, and pharmacological therapies. Four subjects had not received any previous rehabilitation or pharmacological treatment. Thirteen patients (21%) had previously used some form of alternative therapy for any reason, including MTBI, a proportion that is lower than the 42.1% reported in the general population in the United States.[23,24] None had received homeopathic treatment for MTBI symptoms. Twenty-nine subjects (48%) were currently taking prescription medications for their MTBI symptoms; these were continued during the study. As evidenced by the initial mean scores on the Symptom Rating Scale

(SRS, 3.02) and Difficulty with Situations Scale (DSS, 2.97), the average patient in the study had persistent symptoms that significantly limited their functioning, at least some of the time, despite having received the range of rehabilitation therapies.

Informed consent from each subject, using a form approved by the Human Subjects Committee of the SRH in Boston, was obtained for participation in the study. Each subject then completed the self-rated functional assessment and a battery of cognitive-linguistic tests administered by a speech and language pathologist (TO-P) and designed to assess the subject's baseline cognitive ability and pain symptoms, as well as a one-hour homeopathic evaluation conducted jointly by the homeopathic physician (EC) and staff psychiatrist (RW).

The homeopathic medicine appropriate to each case was chosen, using a classic homeopathic process.[39] Characteristic symptoms for each patient were determined; these symptoms were then cross-referenced with homeopathic medicines known to elicit or cure these symptoms, a process called *repertorization*, performed using a computerized repertory program;[48] and the single medicine most similar to the patient's case was determined by study of relevant materia medica by the homeopathic physician (EC) and the staff psychiatrist (RW). While taking the homeopathic medications, subjects were asked not to use coffee or aromatic substances (eg, Ben-Gay, Tigerbalm, menthol, eucalyptus) known to antidote homeopathic medicines. Medications prescribed for MTBI symptoms were continued, as were any current occupational, speech, or physical therapies. Subjects returned monthly for four months to assess progress and adjust homeopathic medication.

Measures

At the time that the study was designed and implemented, there was no validated measure in use that was both sensitive to the range of dysfunction seen in a heterogeneous population of MTBI patients and able to detect changes resulting from treatment. Therefore, we chose as our predetermined, primary outcome measure a patient-rated, three-part, functional assessment tool developed by the clinical staff at the SRH, Speech-Language Pathology Department (SRH-SLPD). Along with performance on objective standardized tests, this assay is used at SRH to establish therapy goals and was judged by the staff as a useful and reliable assessment tool, although it had not been validated in published trials.

The functional assessment is composed of three subscales: the SRS assesses 34 physical, cognitive, and affective symptoms of traumatic brain injury (see Table 1); the DSS assesses the functional disability associated with 18 day-to-day situations (see Table 2); and the Participation in Daily Activities Scale (PDAS) evaluates daily function in 13 common activities: watching TV, doing crafts, exercising, reading, playing games, traveling, shopping, volunteering, cooking, attending movies/theater, socializing, dancing. All three scales employ a 1–5 Likert scale: 1 ("never"), 2 ("rarely"), 3 ("sometimes"), 4 ("most of the time"), and 5 ("always"). Patients rated each item in response to the instruction, "Please rate the degree to which the following apply to you now."

The secondary outcome measure used was the SRH Cognitive-Linguistic Test Battery, which includes selected elements of the Woodcock-Johnson tests of Cognitive Abilities—Revised[49] (a. Analysis-Synthesis Subtest, b. Visual-Auditory Learning Subtest). Additionally, a measure of social support, the Provision of Social Relations (PSR) scale,[50] and questionnaires to determine routine demographic information and previous use of homeopathy and other alternative therapies were administered at intake.

All subjects (N = 50 in the analysis sample) were administered the functional assess-

Table 1. Mean scores on the Symptom Rating Scale

Symptom	Treatment		Control	
	Pre	Post	Pre	Post
1. Short term memory problems	3.96	3.41	3.61	3.56
2. Short attention span	3.81	3.31	3.82	3.41
3. Slow thinking	3.96	3.23	3.35	3.26
4. Headache	3.69	3.26	3.61	3.39
5. Mental fatigue	3.85	3.37	3.35	3.17
6. Sleep disturbances	3.63	3.19	3.59	3.43
7. Impatience	3.70	2.74	3.18	3.04
8. Frustration	3.56	3.96	3.45	3.30
9. Distractibility	3.26	3.03	3.26	3.36
10. Withdrawal from social activities	3.26	2.67	3.48	3.26
11. Anxiety	3.35	2.89	3.32	3.32
12. Irritability	3.35	2.89	3.30	3.30
13. Confusion	3.35	3.07	3.14	3.14
14. Reading problems	3.15	2.59	3.30	3.04
15. Lack of motivation	3.19	2.85	3.26	3.17
16. Drowsiness	3.00	2.65	3.23	3.04
17. Depression	3.96	2.63	3.18	2.96
18. Anger	3.07	2.30	2.96	2.91
19. Memory loss for the accident	2.68	2.63	3.18	2.68
20. Feelings of helplessness	2.81	2.31	3.00	2.78
21. Poor judgement	2.85	2.44	2.86	2.50
22. Writing problems	2.70	2.59	2.95	2.87
23. Fearful	2.67	2.52	2.70	2.52
24. Cry easily	2.67	2.30	2.52	2.52
25. Explosive temper	2.44	2.22	2.83	2.73
26. Blurred vision	2.30	2.30	2.82	2.87
27. Ringing in the ears	2.56	2.30	2.45	2.23
28. Hearing problems*	2.44	2.44	2.52	2.26
29. Fear of "going crazy"	2.19	2.11	2.41	2.39
30. Guilt	2.43	2.11	2.43	2.09
31. Nausea	2.30	2.04	2.04	2.23
32. Inconsideration	2.33	1.69	1.96	1.96
33. Vomiting	1.44	1.22	1.39	1.57
34. Seizures*	1.43	1.31	1.43	1.43

The first ten symptoms (those with a median of 4 = most or all the time) were used in the post-hoc analysis.
*Two symptoms, hearing problems and seizures, were removed from the analysis, due to negative correlations in the reliability analysis.

Table 2. Mean pre- and posttreatment scores on the Difficulty in Situations scale

Situation	Treatment		Control	
	Pre	Post	Pre	Post
Reading technical or work-related information	3.60	2.85	3.68	3.32
Working	3.35	2.96	3.80	3.14
Socializing in large groups	3.41	2.85	3.50	3.35
Following instructions	3.44	2.78	3.22	3.13
Reading novels	2.96	2.27	3.23	3.04
Writing letters	2.92	2.60	3.17	3.04
Cleaning house	2.92	2.38	3.18	2.96
Dealing with finances	2.85	2.44	3.13	3.48
Following a schedule	3.00	2.74	2.83	3.04
Shopping	2.96	2.52	2.91	3.13
Reading newspapers/magazines	2.85	2.19	2.86	2.65
Making/keeping appointments	2.78	2.41	2.78	3.00
Driving	2.73	2.41	2.78	3.04
Socializing in small groups	2.78	2.35	2.52	2.83
Meal preparation	2.50	2.30	2.50	2.89
Talking on the phone	2.63	2.44	2.30	2.74
Listening to radio/watching TV	2.41	2.37	2.35	2.43
Eating in restaurants	2.40	2.30	2.22	2.52

ments, cognitive-linguistic tests, PSR scale (n = 49), and alternative medicine questionnaire (n = 46) prior to randomization and receiving the study medication. After initial evaluation (pretest), all subjects were randomly assigned to either the treatment (homeopathic) or control (placebo) groups and began taking the prescribed treatment within one week. Patients were evaluated monthly by the homeopathic physicians for clinical improvements in the following patient-reported criteria: their overall mental and emotional state, their level of energy or well-being, and specific symptoms or functional complaints. There was no attempt to quantify these patient impressions, nor were measurements of the primary or secondary outcome variables administered at the interim visits. After the termination of four-month treatment, the initial functional and cognitive-linguistic assessments were repeated (posttest) on the subjects completing the study.

Medications

Eighteen homeopathic medications (see Table 3) were selected for use in this study, based on the similarity of drugs' proving symptoms with the symptoms of people with MTBI,[48] the published experience of physicians using these remedies in cases of head injury,[20–22] and the author's (EC) observation of efficacy in cases of head injury. The homeopathic prescription is based on the patient's individual pattern of symptoms. For instance, *Nux vomica* is indicated in patients who are oversensitive to medication, irritable, overly chilly, and who suffer from headaches that are aggravated by stress; whereas *Papaver somniferom* is prescribed for people whose MTBI was associated with an experience of

Table 3. Eighteen homeopathic medications

Homeopathic Medicines

The 18 study medicines are presented with their common or chemical names, as well as their "keynote symptoms."

Argentum nitricum (Silver nitrate, $AgNO_3$). Anticipation, impulsiveness, agoraphobia, claustrophobia, vertigo, and photophobia.

Arnica montana (Leopard's Bane). Sore, bruised sensations, denial of illness, hopeless indifference, vertigo, head feels hot or enlarged, and diplopia.

Aurum metallicum (Gold, Au). Suicidal depression, feeling of neglecting one's duty, music ameliorates, violent headaches often with chest oppression, and photophobia.

Baryta carbonica (Barium carbonate, $BaCO_2$). Slow comprehension, irresolution, lack of confidence, feels people are ridiculing, and numbness of parts lain on.

Calcarea carbonica ($CaCO_2$) Flabby, fear of insanity and being observed, chilliness, profuse perspiration, worse on exertion, and sleeplessness from cares.

Cicuta virosa (Water hemlock) Convulsions, cramps, strabismus, objects in the vision appear to approach and recede, tinnitus, childish behavior, estrangement, and want of confidence in mankind.

Cocculus indica (Indian cockle) Worse loss of sleep, reaction time slowed, nausea from sight or smell of food, car sickness, weakness, numbness, trembling, empty and hollow sensation.

Helleborus niger (Snow-rose) Stupor, staring/thoughtless, slow, forgetful, feels doomed, what the patient sees, hears or tastes makes no impression on the mind, and worse 4–8 p.m.

Hyoscyamus niger (Henbane) Suspicion, violent outbursts, loquacity or silent disposition, shamelessness, playing with fingers, twitchings, jerks, and cramps.

Hypericum perforatum (St. John's Wort) Mistakes in writing, omitting letters, injuries to nerves-attended with headache, vertigo, convulsions, neuralgic pains worse with change of weather.

Lachesis muta (Bushmaster snake venom) Overactivity, loquacity, vivid imagination, passionate and intense, better discharges, especially menses, left-sided complaints, and worse after sleep.

Natrum muriaticum (NaCl) Defensive, closed, cautious, dwells on past, disagreeable occurrences, silent grief, averse to consolation, headaches, desire for salt, worse with heat, sun, and at the seaside.

Natrum sulphuricum ($NaSO_4$) Objective, realistic, no delusions, sadness and suicidal tendency, headaches, photophobia, vertigo, worse, dampness, aggravated in the morning after rising, and at 4–5 a.m.

Nux moschata (Nutmeg) Dreamy, confused, slowness of response, overpowering sleepiness, sensation of extreme dryness of mouth and throat, yet no thirst.

Nux vomica (Poison-nut) Ineffectual urging [work, stool, micturition], fastidious, ambitious, unrefreshed, irritable, depressed, chilly after over medication, use of stimulants, and cramps.

Papaver somniferum (Opium) Disassociation after fright, flashbacks, unaffected by external impressions, or boldness and fearlessness, somnolence, snoring respiration, and constipation.

Silica (SiO_2) Obstinate, fixed ideas, lack of confidence, fastidious, occipital headaches, sensitive to noise, drafts, and slowness.

Sulphur (S) Self-centerd, theorizing, no depth or focus; lazy, messy, warm-blooded, burning pains and sensations, offensive, excoriating discharges, desire for sweets and spicy food, and itching.

fright and results in a significant degree of somnolence or dissociation, often with frequent flashbacks of the traumatic event.

The FDA provided investigational new drug (IND) clearance for the medicines used in this study. The medicines were manufactured by Laboratoires Boiron in Norwood, Pennsylvania. Two lots (A and B) were generated—the homeopathic medicine and an identically appearing placebo; both lots contained 70 unit-dose vials of each of the 18 medicines. Each vial was labeled "Study Remedy 1/*X*/*Y*," with *X* a number from 1 to 18 and *Y* the lot designation, A or B. The code designating the allocation of Lot A or B to active or placebo was kept at a locked safe at the manufacturer's facility. A third lot (C) of unmedicated pellets, labeled "Study Remedy 2" was packaged in multidose vials.

A single medicine was selected by consensus of the two physicians, based on the individual characteristics of the patient. The study nurse was informed by phone of the name of the medicine. Assignment to treatment arm was made by the study nurse, using a table of random numbers from a standard medical text.[51] According to the randomization for each subject, the study nurse picked a vial of the selected medication from either Lot A or B and mailed it, along with a vial from Lot C, to the subjects. Receipt and understanding of administration instructions was confirmed by a phone call within three days. Study Remedy 1 was administered sublingually in a single pulsed dose, using two possible protocols, depending on subjects' concurrent use of conventional medications. Patients not currently prescribed conventional medications took three individual doses at twelve-hour intervals; patients taking conventional medicines took one dose daily for seven days. The longer administration period used for subjects on conventional medicines was designed to compensate for the potential antidoting effect of allopathic medications.

Following either of these dosing regimens used for Study Remedy 1, all patients took a daily dose of Study Remedy 2 until the next follow-up visit. Study Remedy 2, a separately packaged placebo used in both the active and control groups, was included in the protocol to improve compliance by creating conditions to which patients were accustomed—taking a daily dose of a prescribed medicine.

Subjects were reassessed by the homeopathic physician at monthly follow-up visits. If the initial prescription resulted in little or no improvement, as determined by a complete review and assessment of change for each symptom that the subject had reported, the initial medicine was repeated or the prescription was changed to a second of the 18 medicines, taken from the same Lot—A or B—as the initial prescription. If improvements were noted, the initial prescription was left unchanged and the subject was continued on Study Remedy 2.

Blinding

Concealment was assured because a study nurse (RL) assigned patients to Lot A or B, using a random number list provided by the study statistician (MM). The nurse had sole access to the medications. Her contact with patients was limited to phone confirmation of receipt and instructions for administration. Her contact with the clinicians was limited to communication of the identity of the subject and medicine to be prescribed. The prescribing physicians did not see the vials of prescribed medication and were not aware to which lot subjects had been assigned. Furthermore, patients, physicians, study nurse, and statistician were blinded to the designation of Lot A or B as the active or placebo condition. Data entry was done blindly by a research assistant (PC) not otherwise involved

in the study. The code was broken only after all data analyses were complete. Compliance with the instruction for medication use was determined by patient self-reporting in follow-up visits.

Statistical analysis

During protocol development, we predicted a moderate to large treatment effect, based on past homeopathic clinical experience with minor head injury. An analysis of the statistical power for this experiment[52] indicated a high probability of detecting a treatment effect on at least one of the dependent variables. Assuming a minimal sample size (n = 25 per group) and only a moderate effect size ($f^2 = .15$), the power is equal to .75 to detect a treatment effect in any of the five outcome variables. With a slightly larger sample size (n = 30 per group), the power increases to .83. If the treatment effect was large ($f^2 = .35$), with a sample size of 25 per group, the power is .98. We intended to enroll 70 patients—35 per group.

According to the protocol, the intention to treat analysis assumed that dropouts would be unaffected by treatment and assigned a posttest score equal to their pretest score. We planned a regression analysis with group (placebo/homeopathic) predicting change scores on the primary outcome measures. Because there are no published reports of the reliability of the primary outcome measure, an initial analysis was planned to determine the combination of items on each subscale that produced the most reliable measurement.

For purpose of analysis, we computed a scale score for each patient on each of the three subscales by averaging the patient's ratings on all of the items within each subscale. For example, the subjects' ratings of the 32 symptoms on the SRS in the pretest were averaged to create the pretest SRS score. Change scores, generated by subtracting the pretreatment score from posttreatment score for each of the dependent measures, were computed for each subject. Univariate analyses were planned to compare these change scores between homeopathic and placebo groups on the three patient-rated functional assessments and cognitive-linguistic tests using *t* tests for continuous variables and chi-square tests or Fisher's exact tests for discrete variables.

To control for the possibility of increased Type I error resulting from multiple significance tests, we planned an initial multivariate analysis of variance (ANOVA). For significant univariate findings, we planned a series of analyses of covariance (ANCOVAs), testing the effect of the homeopathic treatment on the various posttest scores, controlling for the respective pretest scores. We planned to assess the effects of additional covariates, including age, sex, educational level, years since injury, concurrent use of conventional medications, prior experience with alternative medicine, and social support. To assess the differential effect of homeopathic treatment on patients with different durations of injury, we planned a second ANCOVA, adding to the model an interaction term (years since injury multiplied by group [0 = placebo, 1 = homeopathic]). All calculations were performed using SPSS (Statistical Package for the Social Sciences) for Windows.[53]

RESULTS

Patient characteristics

On the pretest, no significant differences existed between the active and placebo groups on demographic variables or on the presumed effects of head injury, as measured by functional assessments or cognitive-linguistic variables (see Table 4).

Table 4. Initial demographic and clinical characteristics of patient sample

Variable		Treatment Group (SD)	Placebo Group (SD)	*P*
Initial sample size [n = 61]		33	28	
Analysis sample size [n = 50]*		27	23	
Age (in years)	Mean	42.7 (11.3)	43.5 (12.3)	.80
	Range	(18–72)	(18–75)	
Years since injury	Mean	3.18 (3.1)	2.73 (3.3)	.62
	Range	(0.5–14)	(0.5–16)	
Gender	Males	11 (41%)	13 (56%)	.27
	Females	16 (59%)	10 (44%)	
Education	Less than H. S.	3 (12%)	4 (17%)	.07
	High school	4 (15%)	1 (4%)	
	Some college	8 (34%)	10 (44%)	
	College graduate	5 (19%)	8 (35%)	
	Graduate degree	6 (23%)	0 (0%)	
Concurrent use of conventional Rx		13 (48%)	16 (70%)	.13
Prior experience with alternative medicine [n= 46]		4 (17%) [n = 24]	9 (41%) [n = 22]	.07
Social support mean (SD) [n = 49]		2.19 (.90) [n = 26]	2.08 (.18) [n = 23]	.67
Pretreatment measures of function mean (SD)	Activity	2.34 (.56)	2.16 (.46)	.21
	Symptom rating scale	3.02 (.59)	3.00 (.66)	.91
	Ten most frequently reported symptoms	3.69 (.60)	3.46 (.68)	.21
	Difficulty with situations	2.97 (.93)	2.98 (.79)	.96
	Linguistic	5.97 (3.6)	5.34 (3.1)	.51
	Memory	7.74 (5.5)	7.95 (5.0)	.89
	Cognitive	3.50 (2.1)	3.97 (3.2)	.54

*The "N" for all data is the analysis sample size (50), unless otherwise indicated.

Reliability analyses

Internal consistency

We conducted internal consistency reliability analyses on the SRS, the DSS Scale, and the PDAS. All items on the PDAS were used; the Cronbach's alpha was .78. The reliability analysis of the SRS indicated that the responses to two of the 34 symptoms, hearing problems ($r = -.13$) and seizures ($r = -.01$), were not

consistent with responses to the other items; therefore, these two items were excluded from subsequent analyses. The scale composed of the remaining 32 items, reported in Table 1, had a Cronbach's alpha of .93, demonstrating very high reliability. Table 2 shows the pretreatment and posttreatment average scores reported on the DSS. One item on this subscale, listening to radio and watching TV, was excluded, subsequent to reliability analysis, which demonstrated it to be uncorrelated to the other activities in the scale. The DSS, composed of the remaining 17 situations, had a Cronbach's alpha of .96.

Descriptive analyses

A summary of the changes in the three primary and three secondary outcome measures is presented in Table 5. Improvements over time were not significantly different between the groups' scores on the PDAS ($P = .862$) or the Cognitive-Linguistic Screening Test Battery tasks: Linguistic ($P = .129$), Memory ($P = .487$), and Cognitive ($P = .687$). The homeopathic treatment group showed greater improvement than did the placebo group for the DSS ($P = .009$) and the SRS ($P = .058$) (see Table 5).

Our data revealed the limitations of the standardized cognitive, linguistic, and memory tests to assess changes resulting from treatment. The average percentile change (posttest minus pretest) in each of these three tests for each subject was computed. We correlated these change scores with the amount of change on the self-reported primary measures. The percentile improvement (or decline) in the cognitive, linguistic, and memory scores was unrelated to each other or to the improvement in the self-reported measures. In contrast, improvement in the self-report measures, particularly on the SRS and DSS, showed significant correspondence with each other.

Our analyses focused on the scales of the three primary dependent variables—the SRS, the DSS, and the PDAS. Subjects' posttest scores on these scales were all significantly intercorrelated, with symptoms and difficulty functioning showing the highest relationship ($r = .74$, $P < .01$). The PDAS correlated significantly with these two variables, but at a

Table 5. Pretest and posttest scores for primary and secondary outcome measures

	Treatment			Placebo			
Variable	**Pre**	**Post**	**Change**	**Pre**	**Post**	**Change**	***P***
Symptoms (SD)*	3.02 (.59)	2.61 (.65)	−.40 (.57)	3.0 (.66)	2.87 (.71)	−.13 (.39)	.058
Situations (SD)*	2.97 (.93)	2.52 (1.03)	−.45 (.63)	2.98 (.79)	3.02 (.97)	.04 (.67)	.009
Activity (SD)*	2.34 (.56)	2.60 (.50)	.26 (.71)	2.16 (.46)	2.44 (.66)	.28 (.42)	.862
Top 10 Symptoms (SD)*	3.69 (.60)	3.11 (.70)	−.58 (.70)	3.46 (.68)	3.32 (.93)	−.14 (.50)	.015
Cognitive (SD)**	31.3 (16.3)	41.0 (20.4)	9.7 (11.9)	31.0 (18.8)	39.4 (22)	8.3 (11.3)	.687
Linguistic (SD)**	46.4 (23.5)	49.3 (23.0)	4.1 (16.5)	43 (21.3)	51.6 (23.9)	10.6 (11.5)	.129
Memory (SD)**	43.7 (27.5)	55.3 (28.9)	11.7 (16.5)	41.2 (26.4)	50. (27.8)	8.8 (12.1)	.487

Data are reported as mean (standard deviation).

*Data reported as mean score on 1–5 Likert Scale.

**Data reported as mean percentile.

P values refer to comparison of the change scores, using a *t* test.

lower level: ($r = -.57$, $P < .01$) with the DSS ($r = -.52$, $P < .01$) and with the SRS.

Multivariate analyses

To control for the possibility of increased Type I error resulting from multiple significance tests, we conducted a multivariate ANOVA, testing the effect of treatment group (homeopathic versus placebo) on change scores (posttest score minus the pretest score) on the three primary dependent variables: the SRS, the DSS, and the PDAS. The Wilks' Lambda for the effect of treatment group was .841 ($F_{(3,46)} = 2.89$, $P = .046$). Following this significant multivariate effect, the three primary dependent variables were tested with separate factorial ANCOVAs. For each analysis, the posttest score for the variable was specified as the dependent variable, with group (homeopathic or placebo) as a between-subjects variable and with the corresponding pretest score as a covariate.

Although the effect of homeopathic treatment was not significant for the PDAS ($F_{(1,47)} = .195$, $P = .660$), there was a significant effect of homeopathic treatment on the DSS ($F_{(1,47)} = 7.34$, $P = .009$; 95% CI −.895 to −.15) and an effect close to significance on the SRS ($F_{(1,47)} = 3.77$, $P = .058$; 95% CI −.548 to .01). Although subjects in both the treatment and the placebo groups improved over the course of the study, with the exception of a slight deterioration of function in the control group (mean 2.98–3.02), the subjects in the homeopathic treatment group improved significantly more.

When additional covariates were included in the models, including age, sex, education, social support, previous use of alternative medicine, or years since the accident, none significantly predicted posttest scores on any of the three primary dependent variables. For the SRS, the coefficients for all of these covariates were insignificant ($P > .25$) and were excluded from the final model. For the DSS, in addition to the effect of group, only social support had a coefficient approaching significance ($P = .144$).

All but four patients had had previous conventional treatment; the lack of variability in this factor suggests that previous conventional treatment was unrelated to outcomes. Subjects' current use of conventional medications was significantly correlated with their pretest scores on the SRS ($r = .28$, $P = .043$), the PDAS ($r = .36$, $P = .015$), and the DSS ($r = .38$, $P < .001$). These findings indicate that the subjects with a higher level of initial symptoms and more difficulty in activities, such as going to work, were more likely to be using medication at the start of the study. Current use of conventional medications was correlated with change scores on the three functional scales; use of medication was weakly associated with less improvement overall for the PDAS ($r = .18$, $P = .211$), the DSS ($r = .04$, $P = .78$), and the SRS ($r = -.13$, $P = .37$), although these correlations were not statistically significant.

Post-hoc analysis of the Symptom Rating Scale

Because the SRS included symptoms with very low incidence (eg, vomiting, seizures), a "basement effect" was suspected. Therefore, we selected all of the symptoms that had a median pretest score of 4, indicating that at least half of the subjects reported experiencing the symptoms at least "most of the time." Ten symptoms (see Table 1) fell into this category. An ANCOVA predicting posttest scores on a scale composed of these ten items (SRS-10), testing the effect of treatment group and controlling for pretest scores on the SRS-10, showed a significant group effect ($F_{(1,47)} = 5.21$, $P = .027$; 95% CI −.766 to −.048). This result lends support to the conclusion that the homeopathic treatment produced a meaningful reduction in subjects' significant symptoms. When additional covariates were

entered into the model, including age, sex, education, previous experience with alternative medicine, social support, and years since injury, none of the covariates were significant, (all $P > .25$), so they were excluded from the final model.

Assessment of outlier effects

An examination of the distributions of the pretest and posttest scores for the three primary dependent variables showed only minor deviations from normality. Tests of the assumptions of the multivariate statistical analyses that we conducted (Box's Test of Equality of Covariance Matrices and Levene's Test of Equality of Error Variances) showed no significant violation of assumptions. Given the relatively small sample size analyzed (N = 50), a small number of outliers in the data could have biased the results, overestimating the actual treatment effect. We used the exploratory data analysis procedures provided in SPSS to identify any outliers and far-outliers[53] for three dependent variables: the DSS, the SRS, and the SRS-10. The following outliers were identified: For DSS, there were three outliers in the placebo group and two in the homeopathic; for the SRS-10, there were two in the homeopathic group and none in the control; for the SRS, there were two in the homeopathic group and none in the control. The small number of outliers was removed, and the ANCOVAs were recomputed. In each case, the homeopathic treatment increased in statistical significance compared to the analysis with the full scale—for the SRS ($P = .03$), for the SRS-10 ($P = .002$), and for the DSS ($P = .0008$.)

Effect size/clinical significance

To give meaning to these statistically significant results of homeopathic treatment, we attempted to determine the magnitude of the effects. Cohen[54] suggests the following parameters for interpreting effect size (f^2): small effect = 0.02; medium effect = 0.15; and large effect = 0.35. We calculated effect sizes (f^2) for observed reductions in the three dependent variables: DSS = .16; SRS = .08; and SRS-10 = .11. These findings indicate that the observed changes represent medium-range effects of homeopathic treatment.

Because our data are continuous rather than discrete, we have reported effect sizes (f^2) in terms of variance explained, as Cohen[54] has recommended. Because odds ratios are often used in the reporting of clinical trials, we computed odds ratios by counting the number of subjects who were either improved, unchanged, or worse on the SRS, DSS, and SRS-10 scales, using the following criteria, respectively: *improved* means a median change score ≤ -0.1; *unchanged* > -0.1 to < 0.1; *worse* ≥ 0.1. For the PDA positive change score (see Table 6).

The clinical significance of the homeopathic treatment is reflected in the changes that subjects reported. These ranged from mild subjective changes to larger improvements, reflected in several subjects reporting that they had returned to work or to more normal functioning. These changes were reflected in improvements on specific items on the DSS. The largest improvements ($\geq -.5$) in the homeopathic condition were seen in items measuring reading technical or work related information ($-.74$); following instructions ($-.67$); reading newspapers ($-.65$); reading novels ($-.60$); doing house cleaning ($-.54$); socializing in small groups ($-.50$); and socializing in large groups ($-.50$).

Effect of duration since injury on treatment

An interaction term was computed by multiplying the length (in years) since injury by a dummy variable for the group (placebo = 0; homeopathic = 1) and was added to the ANCOVA model. Analysis of the interaction effect of the duration since injury and whether

Table 6. Outcome status on Scales Measuring Symptoms, Difficulty in Situations, Activity, and Ten Most Frequent Symptoms

	Symptoms		Situation		Activities		10 Symptoms	
	Homeopathic	Control	Homeopathic	Control	Homeopathic	Control	Homeopathic	Control
Better*	22	14	23	12	20	17	21	12
Unchanged/Worse	5	9	4	10	7	6	6	11
Odds Ratio	1.34		1.51		1.05		1.49	

*Better is a negative change score (<−.01) for symptoms, situation, ten symptoms, and a positive change score for activities.

or not subjects received homeopathic treatment suggests that homeopathy can have meaningful effects on subjects who are many years post-injury. In all three ANCOVAs predicting the posttest score, controlling for the pretest score and social support at the time of the posttest, this interaction term was significant for reduction in symptoms ($F_{(1,45)} = 14.8$; $P < .001$) and for reduction in difficulty functioning ($F_{(1,45)} = 4.17$; $P = .047$), and approached significance for activities ($F_{(1,45)} = 3.28$; $P = .077$).

To illustrate the meaning of the interaction between treatment and years since injury, we looked at the change scores for the SRS in three groups defined as one year or less, between one and three years, and three years or more since injury (Table 7). Subjects whose injury occurred one year or less from the beginning of the study showed improvement in both the homeopathic and placebo groups. Subjects in the placebo group who were one to three years post-injury at the onset of the study showed no further improvement; and placebo subjects who were three years or more post-injury showed an increase in symptoms. The relative benefit of effect of homeopathic treatment appeared to increase with duration since injury, a finding that holds promise for patients with persistent MTBI and for whom current treatment options are limited.

Table 7. Treatment effect on symptoms by time since injury

Duration	Tx Group	N	Mean change score (SD)
≤1 yr	Placebo	7	−.386 (.181)
	Homeopathic	6	−.177 (.195)
>1 <3 yrs	Placebo	11	−.02 (.144)
	Homeopathic	13	−.343 (.133)
≥3 yrs	Placebo	5	.119 (.214)
	Homeopathic	8	−.675 (.169)

Subjects lost to study

The ten subjects who withdrew were distributed equally between groups: six from homeopathic and four from placebo (see Fig 1). Five subjects (three from the active group and two from the placebo group) withdrew after the initial visit for personal reasons communicated to the investigators. Three subjects (two active and one placebo) withdrew after one or two visits: One became pregnant and was withdrawn according to the study's human subjects protocol, one became homeless and was lost to follow-up, and one could not arrange transportation. Two subjects, one from each group, did not present for the final assessments. One subject, assigned to the placebo group, was eliminated from the final analysis because he inadvertently received a dose of active medicine.

We performed an "intent-to-treat" analysis by including these 11 subjects. We did not collect data intermediate to the pre- and posttest measurements, making it difficult to assess whether the dropouts were responding differently to the treatment or placebo than were the remaining subjects. Therefore, given the general trend toward improvement in both groups, we conducted the intent-to-treat analysis, assuming that subjects withdrew because they did not improve. The findings of this analysis were virtually identical to the results without the dropouts. A regression analysis predicting change scores on the three primary functional scales found significant

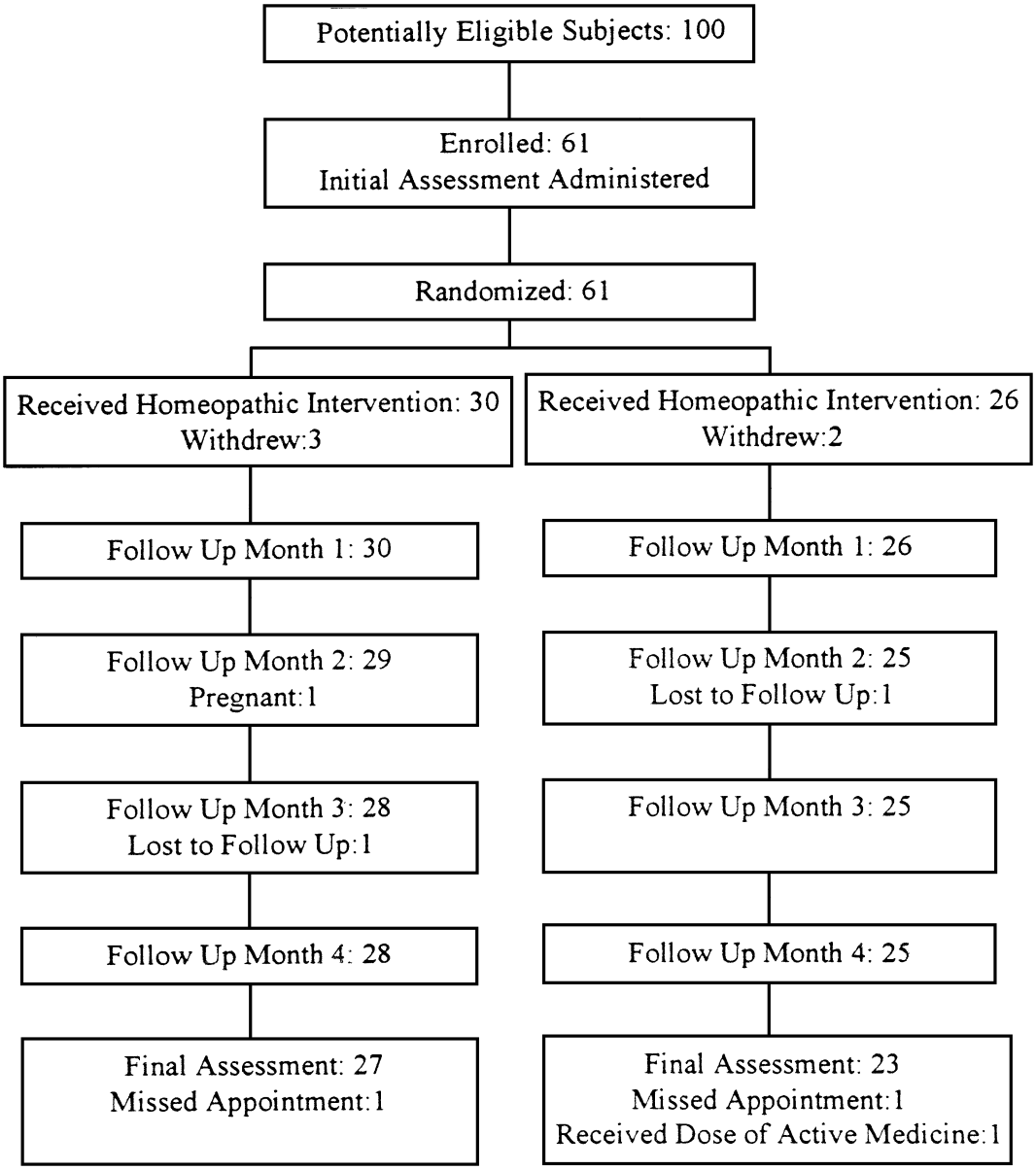

Fig 1. Accrual of subjects with mild traumatic brain injury. Approximately 100 patients expressed interest in participating in the study; 61 subjects met all of the eligibility criteria; 50 subjects completed the study.

effects of homeopathic treatment on the SRS ($t = 2.04$, $P = .046$); on the DSS ($t = 2.49$, $P = .017$); and for the SRS-10 ($t = 2.76$, $P = .008$).

Adverse reactions to medicines

Adverse reactions were rare. One subject from each group reported increased depression. One reported nausea and dizziness after taking doses of the active medicine; another reported ten days of nausea and vomiting, with a slight fever after the initial active dose. One active subject reported an initial three-week intensification of cognitive complaints, followed by a significant reduction of symptoms. The woman who was withdrawn from the study due to pregnancy had no adverse outcomes in the pregnancy and delivered a healthy, full-term infant.

DISCUSSION

This study makes a significant contribution to both the assessment and treatment of persistent MTBI. This was the first clinical trial to evaluate the efficacy of homeopathy as therapy for persistent MTBI. The treatment group subjects reported a highly significant reduction on scales measuring difficulty functioning in situations commonly encountered in daily life and a significant decrease in the reported frequency of ten most commonly reported symptoms of MTBI.

The study provided initial validation of an instrument for the assessment of the subjective complaints, which are the hallmark of disability following MTBI. This tool appears to be sensitive to changes resulting from treatment. Reported change on these functional scales correlated with patient reports of improved function. For instance, the mean change for the treatment group of −.74 on the DSS (eg, a change on a 1–5 Likert Scale from "most of the time" to "some of the time") for the item "reading technical information" reflected clinical improvements sufficient for several subjects who had been unable to work for years to return to work. Analysis of the effect of duration since injury suggested that homeopathy can be effective in reducing symptoms in even those whose injury is remote in time. It is an exciting possibility that single homeopathic agents, prescribed based on individual patient characteristics, can stimulate significant improvements in patients with persistent MTBI whose symptoms and functional status had been static for years.

The cognitive-linguistic test battery was employed in this study in an attempt to find a more objective measure of disability that is sensitive to change from treatment. This battery demonstrated baseline deficits and improved cognitive functioning in both groups, but the battery did not detect significant differences in outcome between the treatment and control groups, consequent to treatment. At least three explanations are possible for this finding: (a) individuals within a group of MTBI patients have variable deficits on the cognitive, linguistic, or memory subtests, as evidenced by the lack of correlation that we observed among the change scores on these three tests—this variability may lead to a loss of sensitivity for the full battery, rendering it unable to detect the changes observed on the functionally based, patient-rated scales; (b) learning effects of retesting negated any true effects of treatment; or (c) reported subjective benefit of homeopathic treatment on symptoms and difficulty functioning was due to placebo effects. This latter explanation is unlikely, given the randomized, placebo-controlled design.[29] Modifications in the cognitive-linguistic test battery may yield a more sensitive tool for future studies.

Side effects and possible drug interactions are concerns that all clinicians have about any new therapy. The phenomenon of symptom aggravation in the initial phase of homeopathic treatment is believed by homeopaths to have positive prognostic significance.[55] Homeopathic prescribers hold the belief that

conventional medicines interfere with or antidote the action of homeopathic medicines. Our study was deliberately designed to test this assumption, assuming that homeopathy can be used as a complementary rather than an exclusive therapy in MTBI patients. Our data indicate the following:

- Homeopathic treatment was associated with minimal side effects in 10% of the subjects, including an initial symptom aggravation in one subject.
- Previous use of conventional medicines, though correlated with a higher initial level of symptoms and difficulty functioning, had no effect on the outcome of subsequent homeopathic treatment.
- Use of homeopathic medicines concurrently with conventional medicines was effective and safe.
- Concurrent use of allopathic medications may have minimal dampening effect on homeopathic treatment outcomes. This effect may require adjustments in the homeopathic prescribing routine.

The observations regarding the interactions between conventional and homeopathic medications should be viewed as possible trends, requiring confirmation with a larger sample size and research protocols specifically designed to examine these issues.

Clinical trials with blinding and placebo control are typically designed to test a single medicine or well-defined intervention. Applying this methodology to homeopathy generates challenges for both homeopaths and methodologists. We had to accommodate the individualized nature of homeopathic prescribing. This meant that, for each subject, we could theoretically have chosen any one of the 1,242 FDA-approved homeopathic medications, each of which is available in a variety of potencies (3X to 100,000C). This need for flexibility was balanced by the need for concealment in a blinded, clinical trial—to deliver preprepared batches (70 vials of each medicine in both verum and placebo) to a secure site from which they could be dispensed without the awareness of the treatment team. The use of multiple medications makes interpretation of treatment effects more difficult for methodologists and clinicians used to single-agent trials. This study tested the homeopathic method in patients with MTBI, rather than a single medicine. Our compromise to use only 18 medicines in a single potency (200C) may have reduced the effect size of the treatment. If homeopathic assessment led to the choice of a medication outside one of the predesignated 18, as occurred in several instances, the treatment outcome would likely be failure. Future clinical trials of homeopathy should avoid limiting the number and potency of homeopathic medicines available.

When we looked at the effect of time since injury on treatment response, our results suggest two things—that there continues to be significant spontaneous recovery from MTBI up to one year and that the relative effect of homeopathic treatment appears to increase with time since injury. On the other hand, the four-month treatment period was probably insufficient to achieve the maximum response to homeopathy in a population with a mean duration of three years since injury. It is a homeopathic axiom that the longer a condition has existed, the longer will be the period of treatment before achieving maximal response, estimated at one month of treatment for every year that a condition has existed.[55] The four-month duration of treatment for a condition with a mean time since injury of three years meant that some subjects were inadequately treated. The question of the time needed to reach the maximal effect of homeopathic treatment can be settled only in a study with a longer period duration of treatment.

In summary, this study was a successful collaboration between two groups of specialists: homeopathic and rehabilitationist. This pilot study made a significant step in refining an assessment tool sensitive to the full

range of disturbances resulting from MTBI. We demonstrated a reasonable internal reliability and responsiveness of the tool and clarified the need for additional modifications and validation. Our results suggest that homeopathy—alone or used concurrently with conventional pharmacological and rehabilitation therapies—may be effective in treating patients with persistent MTBI, a clinical entity for which current treatment has limited effectiveness. The limitations imposed by the design of this pilot study, including the number and potency of homeopathic medicines and duration of treatment, may have led to an underestimate of the actual benefits of homeopathic treatment. Further exploration of homeopathy's role in the treatment of MTBI is needed, including basic science studies to define the mechanism for the action of homeopathy. The results of this pilot study warrant a definitive clinical trial with a larger number of subjects, a longer duration of treatment, and use of the full complement of homeopathic medicines.

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