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Individual Differences in Response to Randomly Assigned Active Individualized Homeopathic and Placebo Treatment in Fibromyalgia: Implications of a Double-Blinded Optional Crossover Design

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ABSTRACT

Objective: To assess individual difference characteristics of subgroups of patients with fibromyalgia (FM) patients with respect to the decision to stay in or switch from randomly-assigned verum or placebo treatment during an optional crossover phase of a double-blinded homeopathy study.

Design: Double-blinded, randomized, placebo-controlled, optional crossover clinical trial.

Participants: Fifty-three (53) community-recruited patients with FM entered the optional crossover phase.

Intervention: Two homeopaths jointly selected an individualized homeopathic remedy for all patients. The pharmacy dispensed either verum LM remedy or indistinguishable placebo in accord with randomized assignment for 4 months and the patient's optional crossover decision for an additional 2 months.

Outcome measures: Patients completed a battery of baseline state/trait questionnaires, including mood, childhood neglect and abuse, and trait absorption. They rated global health (whole person–centered) and tender point pain on physical examination (disease-specific) at baseline, 3 months, and 6 months.

Results: Rates of optional crossover from verum to placebo or placebo to verum were comparable ($p = 0.6$; 31%, and 41%, respectively). The switch subgroups had greater baseline psychologic issues (emotional neglect in placebo-switch; depression and anger in verum-switch). The verum-stay subgroup scored highest on treatment helpfulness and included all six exceptional responders who fell, prior to crossover, into the top terciles for improvement in both global health and pain. Patients staying in their randomly assigned groups, active or placebo ($n = 34$), scored significantly higher in trait absorption than did those who switched groups ($n = 19$).

Conclusion: Individual difference factors may predict better and poorer responders with FM to specific and nonspecific effects of homeopathic and placebo treatment.

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INTRODUCTION

The patient-centered nature of complementary and alternative medicine (CAM) and integrative medicine (IM) poses many complex challenges for the design, interpretation, and clinical application of efficacy and effectiveness studies. Conventional quantitative methodologies for randomized controlled trials (RCTs) in clinical research focus on group averages and facilitate the ability to make broad, public health-related decisions about specific treatments (Jonas, 2001). However, such data often fail to provide practitioners or patients with guidance for tailoring individualized treatment programs (Aiken, 2003). Patient preferences play a role in the decision to use CAM/IM (Astin, 1998; Ratcliffe et al., 2002; Sirois and Gick, 2002). However, factors that may contribute to an individual's treatment decisions remain largely unexamined. Moreover, a patient may choose a particular intervention, but the therapy may or may not have optimal potential for providing clinical benefits.

For example, Owens et al. (1999) demonstrated that the personality trait of absorption—a tendency to focus one's attention wholly within an experience—correlates with use of greater numbers of CAM modalities in patients with chronic pain and those with cancer. Absorption is higher in women and is in part genetically determined (Tellegen et al., 1988). Greater hypnotizability (Gliskey et al., 1991), intrinsic religiosity (Levin et al., 1998), involvement in meditation training (Rivers and Spanos, 1981), reported experiences of psi phenomena (Nelson, 1992), and somatization (Wickramasekera, 1994) all correlate with higher levels of absorption. Such findings suggest the testable hypotheses that persons who are high in absorption might be more likely to choose CAM treatments, adhere best to them, and perhaps respond well in general. However, one earlier study found that high absorbers with vascular headaches improved more with guided imagery than with biofeedback, whereas low absorbers exhibited the opposite response pattern. Patients with tension headache high in absorption responded to biofeedback, while those low in absorption responded to neither intervention (Neff et al., 1983). Thus, individual differences in personality interacted with both the diagnosis and the type of CAM intervention in predicting outcomes.

The relevance of absorption to CAM treatments other than mind–body interventions requires evaluation. For instance, Walach (2000) has proposed that one way in which homeopathy may exert its effects is through the symbolic properties of the remedy. High absorbers respond physiologically more strongly than low absorbers not only to relaxing imagery (Gregerson et al., 1996), but also to aversive stimuli (Challis and Stam, 1992; Zachariae et al., 2000). As a result, high absorbers might show greater remedy responsivity, for better or worse in terms of outcomes.

Walach (2003) has further proposed a weak quantum macroentanglement model to account, in part, for the appearance of homeopathic remedy-specific symptoms in placebo-treated individuals during certain double-blinded homeopathy studies. Entanglement in physics is the quantum mechanical construct used to account for the reliable empirical observation of nonlocal effects seen at the subatomic level. Change in one element of a closed system occurs simultaneously in another part of the same system, independent of the distance between the parts. Persons high in absorption might show increased capacity to merge their attention into the entangled closed macrosystem of the study protocol of which they are a part. Past research already shows that high absorbers report experiencing nonlocal events more often than do low absorbers (Kennedy et al., 1994). Thus, high absorbers might respond more strongly to their active or placebo treatment compared to low absorbers.

Patient expectancy (Peters, 2001) and other psychologic traits such as coping style, spiritual beliefs, self-efficacy, locus of control, and/or social desirability response sets could also influence perceived outcomes during treatment. In addition, a growing literature indicates that affective disturbance results in poorer patient adherence with conventional treatments in a variety of chronic conditions (Ciechanowski et al., 2000; Katon, 2003; Starace et al., 2002; Wang et al., 2002). Past life trauma history (Boscarino, 1997; Felitti et al., 1998; Russek and Schwartz, 1997) or depression (Katon, 2003; Unutzer et al., 2002) also can lead to poorer medical outcomes. CAM clinical research has not as yet addressed similar issues.

Psychosocial characteristics that attenuate capacity to form an alliance with a provider, as documented previously in psychotherapy research (e.g., early life abuse or neglect) may limit the ability to respond to provider-related nonspecific effects (Eltz et al., 1995). In conventional medicine, positive alliance with the provider not only encourages adherence to treatment, but also leads to better outcomes and greater patient satisfaction with care (Kane, 1997). Although patient–provider relationships are often cited as being better in CAM than conventional medicine, few CAM studies have quantified patient satisfaction with the provider to determine its role in CAM outcomes.

Health services research studies may serve better than a typical RCT to address many questions concerning individual differences in CAM patient preferences and decision-making. However, Ernst and Resch (1995) previously proposed a methodological strategy within a double-blinded RCT that could provide useful, albeit indirect, data about patients' perceptions of their treatment and responses to verum and to placebo. They suggested the inclusion of a patient-chosen, optional crossover decision in an RCT. Optional crossover provides an additional comparison of active and placebo treatment effects via analysis of the final number of patients who place themselves into the verum group by the end of the study. Although the original intent of the optional crossover design was to offer an additional treatment-related clinical endpoint, examining factors in the patients' decisions to stay in or to switch from a randomly as-

signed, double-blinded group assignment could also offer new insights toward understanding how to improve patient-centered treatment planning. A novel advantage of this approach would be the ability to assess individuals choosing either to stay on placebo or to switch from active treatment who were not aware of the true nature of the intervention they had been receiving.

In studying optional crossover outcomes, classical homeopathy offers a model CAM system involving a single intervention for the entire bio-psycho-social-spiritual symptom pattern of the individual. Physical double-blinding of homeopathic treatment materials for active and placebo is much easier than in systems such as acupuncture, osteopathy, or massage. However, despite basic and preclinical evidence to the contrary (Elia and Niccoli, 1999; Jonas et al., 2001; Rey, 2003; Ruiz-Vega et al., 2002), skeptics often question whether or not homeopathy can be anything other than a placebo because of the level of serial dilution of the homeopathic source materials (Vandenbroucke, 1997). Fibromyalgia (FM) is an appropriate model of a chronic pain disorder for this research because of its system-wide symptomatology, association with early life trauma (Walker et al., 1997), high levels of CAM utilization (Nicassio et al., 1997; Pioro-Boisset et al., 1996), previously demonstrated responsivity to homeopathy (Fisher et al., 1989), and limited responsiveness to conventional treatment.

We have recently reported significantly greater mean improvements in tender-point pain, global health, and quality of life in patients with FM on active/verum versus placebo during a 4-month double-blinded, RCT of individualized homeopathic medicine (Bell et al., 2004a). The purpose of the present study was to extend the analysis and evaluate individual difference factors in the optional crossover decision of patients with FM at the 4-month point of the study. Specifically, we tested the hypothesis that a patient's decision to stay in or switch groups will relate to individual differences in baseline characteristics such as trait absorption and other psychologic variables, as well as to patient-perceived benefit from treatment.

MATERIALS AND METHODS

Design

The study was a double-blinded parallel group design of randomly assigned active (verum) versus placebo individualized homeopathic treatment for 4 months, followed by an additional 2-month optional crossover phase (Ernst and Resch, 1995). The optional crossover took place under continuing double-blinded conditions, in which participants could elect to switch from their initially randomly assigned group to the other group. Further details of the design and procedures are given elsewhere in a report on the precrossover clinical findings for active versus placebo groups (Bell et al., 2004a). Liquid forms of the medicines (LM potencies; see below) were chosen to provide daily oral treatment. LM potencies (De Schepper, 1999) are reported to counteract antidoting effects of concurrent conventional medications and to allow individualized dose adjustments for the expected subset of FM patients with high levels of chemical and drug hyperreactivity/sensitivity (Slotkoff et al., 1997).

Upon baseline enrollment, all patients completed a set of state-trait questionnaires (see Measures below). At baseline, 3 months, and 6 months, patients underwent conventional medical history and physical examination for tender point pain rating status by a conventional provider uninvolved in their clinical care (rheumatologist or physician's assistant). The same assessor performed baseline and follow-up examinations for a given patient. In addition to the medical evaluations, patients' electroencephalographic responses to double-blinded olfactory-administered test doses of their treatment solution and placebo were recorded in our Tucson, AZ-based laboratory (Bell et al., 2004a, 2004b). Baseline evaluations included conventional provider assessment of chronic fatigue syndrome criteria (Fukuda et al., 1994). At baseline, 2 months, 4 months, and 6 months, patients presented for evaluation and follow-up visits at the Phoenix, AZ-based homeopathic offices. Two experienced homeopaths concurrently interviewed every patient at each visit and had to agree on a remedy selection with a high confidence rating ($\geq$ 7/10). The study was reviewed and approved by the Institutional Review Board of the University of Arizona, Tucson, AZ.

Participants

Volunteer men and nonpregnant women with medically confirmed FM were recruited from the greater Tucson and Phoenix communities (these cities are approximately 120 miles apart in the largely rural state of Arizona) by media announcements, newspaper advertisements, flyers in local health food stores, and word-of-mouth in patient support organizations. To be eligible for the study, patients had to meet the following criteria: (1) prior physician diagnosis of fibromyalgia, (2) stable conventional medication doses and any other CAM treatments for at least 2 months prior to enrollment (steroid drugs were an exclusion criterion), (3) FM criteria scores on a 15-item, 4-point Likert symptom screening questionnaire (Wolfe et al., 1990), and (4) confirmation of the FM diagnosis on rheumatologic physical examination using the 1990 American College of Rheumatology criteria (Wolfe et al., 1990). Two patients with physician diagnoses of FM had less than 11 of 18 positive tender points on initial examination, but both met the diagnostic cutoff on the second rheumatologic examination. To minimize confounds in the psychophysiologic component of the study, patients could not have a history of alcohol or drug abuse, current narcotic analgesic, benzodiazepine or antihypertensive medication use, or nasal trauma. For patient safety, anaphylaxis

history, diabetes, serious neurologic, heart, lung, liver, or kidney disease, psychosis and active suicidality were also exclusion criteria.

Intervention

The homeopaths knew the identity of the remedy they intended for treatment. However, active LM potencies (1/50,000) or placebo were actually dispensed by mail directly to the patient by an Food and Drug Administration (FDA)-regulated homeopathic pharmacy, Hahnemann Laboratories, San Rafael, CA. The dispensing procedure followed a random assignment protocol (individualized active or placebo) in complete blocks of six, as developed by the study methodologist using www.randomizer.org. Each active or placebo bottle was 16-fluid ounces and contained 20% alcohol-distilled water solvent. Active and placebo bottles were indistinguishable. For blinding, bottles were numbered, and the label did not include any remedy- or placebo-identifying information. Patients succussed (vigorously shook) their treatment solution bottle against a telephone book 10 times, diluted 5 to 15 mL in 4-fluid ounces of water, then took 5–15 mL, of the dilution by mouth on a daily basis. The range for doses derived from variability in each patient's sensitivity to the treatment solution. Homeopaths were instructed to treat each participant as if they were receiving active treatment. They were also permitted to change remedy prescriptions and adjust dosing regimens at any visit or between visits if clinically indicated. After the optional crossover, they were asked to recommend the remedy with which they wanted to treat at that point in time. The remedy recommendation could have been the original remedy choice or a different remedy. All patients started the study on an LM 1 potency and progressed sequentially in an individualized way up to LM 2, then LM 3, and so on. No LM potencies were skipped in the sequence for any patient.

Hahnemann Laboratories followed Hahnemann's original method of remedy preparation within the guidelines of the *Homeopathic Pharmacopoeia of the United States.* This homeopathic pharmacy made an initial preparation of a 3c potency $([1/100])^3$ dilution factor, with 20 succussions for each of the three dilution steps), which was then diluted in the 1/50,000 ratio in liquid solvent for the LM 1 step and beyond. If the source material was soluble, the 3c step was made directly in an alcohol-distilled water solvent dilution. With plants, the source material was mother tincture for the 3c step, made from maceration (chopping) of the plant parts, soaking in alcohol/water, and filtering. If the source material was insoluble, the 3c step was made by trituration in lactose to a 3c potency and then preparation with the 1/50,000 ratio in liquid solvent for the LM 1 step and beyond. Pharmacy preparation of each LM potency (1, 2, 3, etc.) always included 100 succussions for each dilution step. Placebo materials sent out from Hahnemann Laboratories were the same solvent material used for making the remedy dilutions, but the solvent for placebo was not prepared as an LM with dilution or succussion steps. From their treatment solution stock bottles, all patients on either verum or placebo prepared their daily oral doses under the double-blinded protocol in the same manner, performing succussion and dilution as described above.

Prior to the 4-month homeopathic visit, patients mailed a postcard directly to Hahnemann Laboratories to indicate their preference either to stay with their originally assigned condition or to switch to the other group at the 4-month point. Bottles dispensed thereafter reflected the patients' choice to stay in or switch groups. Only the methodologist and pharmacist had access to the randomization code during the study. All clinicians and research staff interacting with and assessing patients were kept blinded as to group assignments and bottle contents for the duration of the study.

Measures

At baseline, patients completed the following self-report questionnaires: (1) a rating of expectation of benefit from treatment (0–10-point scale, anchored at the extremes, with 0 = not at all helpful and 10 = extremely helpful); (2) the Bell Chemical Intolerance Index (Szarek et al., 1997); (3) the Profile of Mood State scale (POMS; Educational and Industrial Testing Service, San Diego, CA); (4) the modified Childhood Experiences Scale on Abuse and Neglect (Bernstein et al., 1994); (5) Tellegen Absorption Scale (Tellegen and Atkinson, 1974); (6) the Barsky Somatic Symptom Amplification Scale (Barsky et al., 1990); (7) the 13-item short form of the Marlowe-Crowne Social Desirability Scale (Reynolds, 1982); (8) the Lorig Self-Efficacy Scale (Lorig et al., 1996); (9) the Active and Passive Coping Scale (Brown and Nicassio, 1987); (10) the Multidimensional Health Locus of Control (Lau and Ware, 1981); (11) the JAREL [JoAnn-Ruth-Eileen-Loretta] Spirituality Scale (Hungelmann et al., 1996) (also completed at 3 and 6 months); and (12) the Quality of Social Support scale (Goodenow et al., 1990). At 3 and 6 months, patients completed the Patient Satisfaction Scale with regard to the homeopaths involved in their treatment (DiMatteo and Hays, 1980). At the 4-month optional crossover point and 6-month end-of-study point, patients rated the perceived helpfulness of the treatment (0–10-point scale, anchored at the extremes, with 0 = not at all helpful and 10 = extremely helpful).

Homeopaths report that their medicines treat the person with a given diagnosis, not the diagnosis *per se* (Bell et al., 2003). They evaluate change not only in the presenting complaint, but also in the person as a whole (Rowe, 1998; Vithoulkas, 1980). Consequently, to define "exceptional," "intermediate," and "poor" clinical responders for purposes of this phase of the study, change scores from baseline were computed for the 3-month and 6-month follow-up visits for both the primary disease-specific outcome variable, mean tender point pain on examination (Wolfe et al., 1990) and

the primary patient-centered (not disease-specific) outcome variable, Global Health Rating Scale (GHRS) total scores (sum of a three-item, five-point Likert rating of current health, health compared to peers, and health compared to the previous 6 months) (Bell et al., 1998).

Analysis

The original study was planned as a feasibility assessment that would provide adequate power (0.8) for a large effect size (d = 0.8) prior to crossover on the most sensitive measure of pain (i.e., mean tender point pain on palpation examination; Jensen et al., 2000), at an α of 0.05. We compared the four subgroups formed by the optional crossover procedure (verum-stay, verum-switch, placebo-switch, placebo-stay) with one-way analyses of variance and *post hoc* Tukey tests and tested for differences in baseline characteristics and clinical status using χ^2 tests. We evaluated the individual difference variables predicting the decision to switch or stay in the original randomized group assignment, using backwards logistic regression techniques.

Patients within the subgroups were classified at the 3-month and 6-month evaluation points as falling into terciles (thirds) for their change scores on each of the two clinical outcome variables (tender point pain, global health rating) within the overall sample. Exceptional responders were those persons in the highest tercile of improvement for both variables. Intermediate responders were in the highest tercile of improvement on only one of the two variables. Poor responders did not fall into the top tercile of improvement for either outcome variable.

In view of the preliminary nature of this element of the study, statistical significance was set at $p < 0.05$ (two-tailed) without Bonferroni correction to avoid a Type II error in evaluating individual differences between subgroups (Rothman, 1986). The total number of baseline variables examined is shown in Tables 1 and 3. Treatment helpfulness ratings at 4 months and 6 months were compared using a general linear model approach for repeated measures, including covariates as indicated by baseline subgroup differences (i.e., baseline POMS depression, anger-hostility, childhood neglect, and conventional medication usage [antihistamines, expectorants]). The data were also evaluated for individual differences between the combined groups who chose to stay in or to switch groups. Samples from the two cities (Phoenix, $n = 27$; Tucson, $n = 26$) did not differ on baseline variables and were combined for all analyses. For randomly missing items from questionnaires, mean substitution was used to retain the scale in the subject's dataset. However, as detailed in the Results section, some subjects failed to complete questionnaires and/or follow-up tender point pain examinations at certain time points. Because of the optional crossover design, only subjects who completed a questionnaire at a given time point were included in the relevant outcome analyses. Missing data procedures such as last observation carried forward are not appropriate in the setting of an optional crossover design.

Analyses involving the postcrossover decision point are reported without three patients who had expressed a clearcut choice to stay or switch at the 4-month time point and completed the study but the implementation of their choice was compromised. Because of pharmacy error, one patient who wanted to switch from placebo to verum was kept on placebo and one patient who wanted to stay on verum was switched to placebo. A switch from placebo to verum was initiated for a third patient, but she requested resumption of the pre-crossover treatment condition (started on placebo, switched to verum, perceived clinical deterioration, and switched back to placebo) early in the crossover phase.

RESULTS

Sample characteristics

After telephone screening, 90 patients with FM were judged potentially eligible for the study. From those patients, 62 met published FM diagnostic criteria and homeopathic agreement for remedy selection and were subsequently randomized. Persons who chose not to participate typically cited reluctance to make the required trips between Tucson and Phoenix, or unwillingness to complete the extensive questionnaire and laboratory components of the study. Verum and placebo groups did not differ in proportion of dropouts prior to crossover (total dropout $n = 9$) (see also Bell et al., 2004a).

For purposes of the present study (Fig. 1), 53 patients completed the 3-month follow-up assessments and made an optional crossover decision at 4 months (14.5% dropout rate

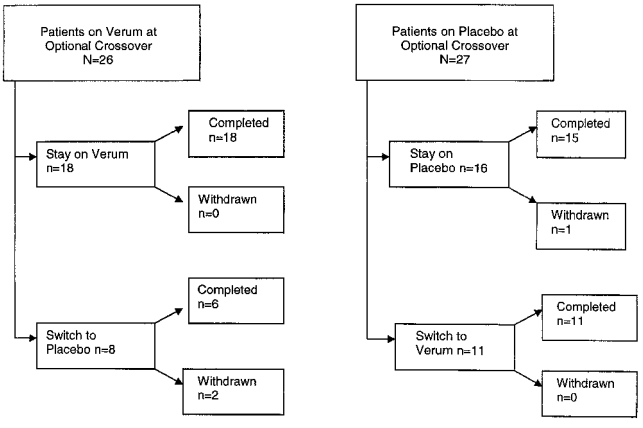


FIG. 1. Patient flow-chart in optional crossover phase of study (months 4–6). Treatment completers did not necessarily complete all questionnaires; see sample sizes for each analysis. Dropouts cited lack of time to participate in study and painful electroencephalograph hook-up in laboratory sessions as reasons for withdrawal.

prior to optional crossover). One patient (who ended up in the verum-switch subgroup) had failed to complete the baseline questionnaires (including the global health ratings), but did participate in the baseline tender point pain assessment and the rest of the study. She is included because of the availability of demographic data, her original randomized group assignment, and her optional crossover decision. However, as a result, subgroup comparisons involving baseline questionnaires reflect an $n = 52$.

The proportions of verum and placebo patients who chose to switch groups after 4 months did not differ significantly (41% of placebo and 31% of verum, Fisher's exact test $p = 0.6$, ns). A total of 3 patients dropped out after crossover, one from the placebo-stay, and 2 from the verum-switch subgroups. One patient completed the full homeopathic treatment protocol but not the final questionnaires or laboratory visit/tender point pain assessment. The 3 patients with compromised implementation of their optional crossover decision described above were excluded from outcome analyses for the 6-month time point. Thus, although 53 patients made an optional crossover decision and 50 completed 6 months of treatment, particular follow-up analyses reported reflect only cases with valid and complete data for the relevant time points.

The primary reasons for study dropouts were related to time and travel demands of the study, or excessive pain experiences during electroencephalographic (EEG) laboratory hook-up procedures (rubbing scalp to lower skin resistance for standardized recordings; Bell et al., 2004b; Bell et al. this issue, pp. 285–299). No participant reported an adverse drug reaction to a treatment solution as a reason for dropping out.

Table 1 shows the baseline demographic characteristics of patients who ended up in the four different optional crossover subgroups. Subgroups were comparable for age, gender, self-reported ethnicity, marital status, education, criteria score for chronic fatigue syndrome (Fukuda et al., 1994), chemical intolerance levels, and duration of FM. Rheumatologist and homeopath ratings for baseline global severity of illness did not differ between subgroups. Initial expectation of benefit from treatment was no different between subgroups as rated by patients, rheumatologist, or homeopaths (although the patients overall were the most optimistic raters of possible benefit). Overall, patient expectation of benefit ratings did not correlate with either rheumatologist ($r = 0.21$, ns) or average homeopath ($r = -0.05$, ns) expectations of benefit. However, the allopathic and homeopathic clinicians' expectations did correlate significantly with one another ($r = 0.45$, $p = 0.006$).

More patients in the verum-stay ($n = 5$) and verum-switch ($n = 3$) subgroups reported using antihistamine and/or expectorant drugs at baseline, versus none of the placebo-stay or placebo-switch patients. Subgroups did not differ at baseline on rates of utilization of conventional or CAM health care services, medications other than the antihistamines and expectorant drugs, or nutritional supplements.

Initial homeopathic remedy choices over the whole sample were highly individualized, but to the same degree across subgroups (Table 2). The homeopaths ended up recommending significantly fewer different remedies ($p < 0.05$) over the course of the study for the verum-stay subgroup (1.2 standard deviation [SD] 0.4) than they did for the placebo-switch subgroup (1.9 SD 0.8). As described in Methods, all patients started at an LM 1.0 dose (dilution factor 1/50,000). Subgroups did not differ significantly in LM "dose" reached by the time of optional crossover (LM mean "dose" for sample = 2.4 SD = 0.9; i.e., $[1/50{,}000]^{2.4}$). The placebo-stay and verum-stay subgroups ended their 6 months in the study at comparable LM "doses" (i.e., mean = 4.4 SD = 1.7). Dropouts within subgroups did not differ from one another significantly on baseline characteristics.

Table 3 summarizes state/trait variable findings at baseline. The subgroup that elected to switch from placebo to verum scored significantly higher on childhood emotional neglect than did either the placebo-stay or verum-stay subgroups. The verum-switch group was significantly higher than all other subgroups for baseline POMS anger-hostility and greater than the placebo-stay subgroup for baseline POMS depression. The four subgroups showed trends ($p \leq 0.10$) to diverge from one another on the childhood physical neglect subscale and Tellegen Absorption Scale. The placebo-switch subgroup was higher for physical neglect and lower for absorption in comparison with the placebo-stay subgroup. Subgroups did not differ significantly for scores on any other state or trait measure.

Treatment outcome status

Figure 2 illustrates significantly greater treatment helpfulness ratings by the verum-stay subgroup than the two switch subgroups, with a main effect averaged over both pre- and post-crossover follow-ups ($F(3,30) = 3.4$, $p = 0.03$). Overall, patients' ratings of perceived treatment helpfulness at 6 months correlated with their own original expectation of helpfulness ratings ($r = 0.38$, $p = 0.05$) as well as both rheumatologist ($r = 0.68$, $p < 0.001$) and averaged homeopath ($r = 0.73$, $p < 0.001$) ratings of actual perceived helpfulness at 6 months. The allopathic and homeopathic clinicians' ratings of perceived helpfulness before crossover (3-month laboratory session rating for allopath versus 4-month visit rating for homeopaths) ($r = 0.59$, $p < 0.001$) and after crossover at 6 months ($r = 0.74$, $p < 0.001$), correlated significantly with one another.

Figure 3 shows percentages of each subgroup falling into each of the three possible responder categories prior to the optional crossover decision. The four subgroups differed significantly in proportions of exceptional, intermediate, and poor responders ($\chi^2(6) = 14.5$, $p = 0.025$). Thirty-five percent (35%) of the verum-stay subgroup ($n = 6/17$) fell into the exceptional responder category, versus none of the other three subgroups. In contrast,

Table 1. Baseline Descriptive Characteristics (Unadjusted Means, SD) of Subgroups Generated by Patients' Original Random Assignments and Subsequent Optional Crossover Decisions after Four Months of Treatment

	Placebo-stay (P-P) (n = 16)	*Placebo-switch (P-V) (n = 11)*	*Verum-switch (V-P) (n = 8)*	*Verum-stay (V-V) (n = 18)*
Age (years)	50.8 (12.6)	45.8 (9.2)	48.0 (14.1)	51.7 (7.4)
Number of women	15 (94%)	10 (91%)	7 (88%)	18 (100%)
Ethnicity (# white)	16 (100%)	10 (91%)	8 (100%)	14 (78%)
Marital status (# married)	8 (50%)	9 (82%)	5 (63%)	12 (71%)
Education (# some college or more)	13 (81%)	11 (100%)	8 (100%)	14 (78%)
Right-handed (#)	15 (94%)	8 (73%)	7 (88%)	17 (94%)
Duration of fibromyalgia (years)	8.6 (7.2)	15.5 (15.2)	18.9 (19.7)	13.8 (12.4)
Meet chronic fatigue syndrome diagnostic criteria (# with CFS)	13 (81%)	10 (91%)	6 (75%)	15 (83%)
Bell Chemical Intolerance Score	6.9 (2.7)	6.6 (3.7)	7.1 (2.9)	7.6 (2.6)
Severity of illness—Baseline Clinical Global Impression (0–7) (Rheumatologist)[a]	2.6 (0.63)	3.0 (0.45)	2.9 (0.99)	2.6 (0.70)
Severity of illness—Baseline Clinical Global Impression (0–7) (Homeopaths Avg.)[a]	4.0 (0.65)	4.1 (0.76)	4.1 (0.99)	4.0 (0.54)
Patient expectation of benefit from Tx (0–10)	8.3 (2.1)	8.5 (1.9)	7.3 (1.4)	8.5 (1.8)
Rheumatologist expectation of benefit from Tx (0–10)	3.4 (0.84)	4.4 (1.5)	2.8 (0.5)	3.9 (1.4)
Avg. Homeopath Expectation of benefit from Tx (0–10)	6.7 (0.86)	7.1 (1.1)	6.9 (1.4)	6.6 (1.5)
Non-narcotic pain medications	6 (38%)	6 (55%)	3 (38%)	13 (72%)
Serotonin reuptake inhibitor drugs	1 (6%)	2 (18%)	2 (25%)	4 (22%)
Muscle relaxant drugs	1 (6%)	3 (27%)	2 (13%)	2 (11%)
Antihistamine or expectorant use[b]	0	0	3 (38%)	5 (28%)
Individualization ratio of Initial Homeopathic Remedies = [different # chosen/# patients]	14 (88%)	10 (91%)	8 (100%)	15 (83%)

[a]Severity of illness rating: 1 = normal; 2 = borderline ill; 3 = mildly ill; 4 = moderately ill; 5 = markedly ill; 6 = severely ill; 7 = among the most extremely ill patients.

[b]χ^2 (3) = 10.2, $p = 0.017$ overall, with P-Stay < V-Switch, V-Stay by Fisher's exact test ($p < 0.05$).

CFS, Chronic fatigue syndrome.

40%–50% of the other three subgroups fell into the poor responder category, as opposed to only 18% of the verum-stay subgroup.

Figure 4 demonstrates that the proportions of the optional crossover subgroups containing exceptional and poor responders was similar at the 6 month follow-up ($\chi^2(6) = 19.0, p = 0.004$) to those seen at 3 months. Forty-four percent (44%) of the verum-stay versus only 7% of the placebo-stay subgroups fell into the exceptional responder category at 6 months. As noted above, homeopathic emphasis on change in the person as a whole (Vithoulkas, 1980) leads to the prediction that self-actualization should increase in verum responders over time (Hyland and Lewith, 2002). Figure 5 reveals a steady improvement pattern in the verum-stay subgroup's JAREL self-actualization scores, whereas the other subgroups fluctuated over time. Subgroups did not differ on follow-ups for rates of utilization of conventional or other CAM health care services. Ratings on the patient satisfaction scale for the homeopaths as clinical providers did not differ significantly between subgroups at 3 months ($F(3,46) = 2.1$, ns) or 6 months ($F(3,44) = 2.1$, ns).

Stay versus switch optional crossover decision

When the combined subgroups who chose to stay with their randomly assigned group were compared to those who chose to switch, we found that the combined switch decision patients were significantly lower in baseline trait absorption and higher in early life emotional and physical neglect ratings than were the combined stay patients (Absorption—switch, 16.3 SD 8.0; stay, 21.0 SD 6.1, $p = 0.024$; emotional neglect—switch, 24.1 SD 12.0; stay, 14.4 SD 11.1, $p = 0.005$; physical neglect—switch, 2.67 SD 3.73; stay, 1.18 SD 1.45, $p = 0.04$). Controlling for absorption and the two neglect variables, the combined stay groups rated the treatment at 4 months prior to the optional crossover as significantly more helpful than did the combined switch groups (stay, 7.3 SE 0.5; switch, 4.8 SE 0.7; $F(1,40) = 8.0$, $p = 0.007$). Backwards logistic regression confirmed that lower levels of perceived helpfulness of the treatment (odds ratio [OR] 0.58 confidence interval [CI] 0.38–0.89), lower trait absorption (OR 0.85 CI 0.73–0.99), and higher childhood emotional neglect (OR 1.1 CI 1.0–1.2) were significant predictors of the decision to switch assign-

Table 2. List of Individualized Homeopathic Remedies Chosen at Baseline for Study: Patients who Subsequently Reached the Optional Crossover Decision Point at Four Months (n = 53)

Remedy	*Placebo-stay (P-P)* (n = *16*)	*Placebo-switch (P-V)* (n = *11*)	*Verum-switch (V-P)* (n = *8*)	*Verum-stay (V-V)* (n = *18*)
Aethusa	2			
Arsenicum Album	1	1		
Bamboo			1	
Baryta Muriatica		1		
Belladonna	1			
Calcarea Carbonica	1		1	2
Calcarea Phosphorica				1
Calcarea Sulphurica				1
Causticum		1		2
Cimicifuga				1
Conium				1
Cyclamen				1
Helleborus	1			
Ignatia			1	
Iodum	1			
Kali Carbonicum	1		1	
Kali Phosphoricum	1		1	
Lac Defloratum			1	
Lycopodium		1		
Magnesia Muriaticum		1		
Magnesium Sulphuricum			1	
Mercurius Vivus				1
Natrum Muriaticum				1
Nitric Acidum	1			
Papaver	1			1
Phosphorus	2			
Platina		1		1
Pulsatilla		2		
Rhododendron	1			
Rhus Toxicondendron	1	1		2
Ruta Graveolens				1
Silica	1	1		
Staphysagria			1	1
Thuja				1
Zincum		1		

Patients initially randomized to placebo group did not receive a verum remedy unless they elected to switch groups after 4 months.

ments (final model predicting stay-switch group membership was accurate at 83% overall). Patient Satisfaction Scale scores with the homeopaths and mood variables (anger-hostility, depression) were not significant predictors.

DISCUSSION

Patients who elected to stay on placebo or to stay on verum under double-blinded conditions scored higher in trait absorption scores than did patients who chose to switch from placebo to verum after 4 months in the study. In addition, the patients who chose to switch from placebo to verum treatment reported higher levels of childhood neglect in comparison with those who stayed with their originally assigned randomized group. Interestingly, the small subgroup of patients originally assigned to verum treatment who decided to switch to placebo after 4 months scored highest on the POMS anger-hostility and depression scales at baseline.

Absorption by treatment interaction in verum-stay subgroup

The present findings suggest that high absorbers are drawn not only to use more CAM, as Owens et al. (1999) previously showed, but also to stay with and respond better than low absorbers to both the specific (active/verum remedy) and nonspecific (placebo) components of a leading CAM therapy (i.e., constitutional, classic homeopathy). At the same time, in terms of differential clinical outcomes, the verum-stay subgroup in this study showed the highest proportion of exceptional and the lowest proportion of poor

TABLE 3. BASELINE TRAIT/STATE CHARACTERISTICS (UNADJUSTED MEANS, SD) OF SUBGROUPS GENERATED BY PATIENTS' ORIGINAL RANDOM ASSIGNMENTS AND SUBSEQUENT OPTIONAL CROSSOVER DECISIONS AFTER FOUR MONTHS OF TREATMENT

	Placebo-stay (P-P) (n = 16)	*Placebo-switch (P-V) (n = 11)*	*Verum-switch (V-P) (n = 7)*	*Verum-stay (V-V) (n = 18)*
POMS Depression[a]	3.9 (5.1)	5.6 (6.2)	15.8 (14.9)	7.0 (10.8)
POMS Anger-Hostility[b]	2.5 (4.1)	1.5 (2.4)	9.8 (9.0)	2.9 (5.7)
Emotional neglect[c]	14.4 (13.9)	26.9 (12.3)	19.7 (10.8)	14.4 (8.4)
Physical neglect[d]	1.0 (1.5)	3.5 (4.5)	1.4 (1.4)	1.3 (1.5)
Physical abuse	3.5 (4.0)	5.5 (5.8)	5.0 (3.7)	3.8 (4.6)
Sexual abuse	1.6 (3.4)	2.5 (3.4)	2.6 (3.2)	2.0 (3.3)
Absorption[e]	20.4 (6.3)	15.1 (8.3)	18.3 (7.8)	21.4 (6.1)
Somatic amplification	12.1 (3.9)	12.3 (3.5)	13.4 (1.6)	11.3 (2.4)
Marlowe-Crowne Social Desirability	8.3 (2.4)	7.1 (3.1)	7.8 (0.9)	7.7 (3.0)
Self-efficacy managing FM	38.5 (7.2)	33.7 (7.7)	36.4 (9.9)	33.9 (7.3)
Active coping	13.2 (1.8)	12.0 (4.2)	11.6 (1.7)	11.6 (3.5)
Passive coping	11.3 (3.2)	13.3 (4.6)	12.3 (4.2)	12.3 (4.1)
Internal locus of control	25.3 (6.2)	27.1 (4.5)	25.9 (4.6)	26.0 (4.0)
Chance locus of control	16.3 (4.6)	15.6 (4.4)	18.6 (3.3)	16.3 (3.7)
Powerful other locus of control	14.1 (5.4)	14.8 (4.0)	17.0 (4.7)	17.1 (4.1)
JAREL[f] Faith	34.4 (5.7)	36.8 (5.5)	31.0 (8.3)	36.2 (5.6)
JAREL[f] Self-Responsibility	34.1 (5.8)	33.6 (5.7)	29.5 (7.1)	33.0 (5.5)
JAREL[f] Self-Actualization	33.2 (4.6)	30.3 (6.0)	31.4 (5.0)	31.6 (4.8)
Quality of Social Support	45.8 (6.9)	44.3 (7.8)	44.4 (5.2)	44.7 (6.6)

[a] $F(3,49) = 3.0$, $p = 0.04$; V-switch > P-stay ($p < 0.05$).
[b] $F(3,49) = 4.4$, $p = 0.009$; V-switch > P-stay, P-switch, V-stay ($p < 0.05$).
[c] $F(3,48) = 3.4$, $p = 0.03$; P-switch > P-stay, V-stay ($p < 0.05$).
[d] $F(3,48) = 2.5$, $p = 0.07$; P-stay < P-switch ($p = 0.01$), V-stay < P-switch ($p = 0.03$).
[e] $F(3,48) = 2.1$, $p = 0.108$; P-stay > P-switch ($p = 0.051$), V-stay > P-switch ($p = 0.02$).
[f] JAREL scale named for developers, Jo-Ann-Ruth-Eileen-Loretta.
POMS, Profile of Mood State scale; FM, fibromyalgia; SD, standard deviation.

clinical responders. As seen in the verum-stay subgroup, homeopaths claim that the expected pattern of favorable clinical response to LMs, as opposed to other potency dose series of remedies, would be progressive, steady improvement with fewer temporary worsenings or extreme shifts in state (De Schepper, 1999). The clinical outcomes, notably the self-actualization score patterns of the verum-stay subgroup over time, are consistent with the latter prediction. Patients in the verum-stay subgroup apparently recognized the benefit of their assigned treatment and remained on it for the duration of the protocol. Thus, the data indicate a form of aptitude (patient trait: higher vs. low trait absorption) by treatment (group assignment: verum homeopathy versus placebo) interaction in the study patients, perhaps parallel to that originally described in the psychotherapy literature (Smith and Sechrest, 1991).

Dysphoria and limited responsiveness in verum-switch subgroup

In addition, psychologic disturbances were greater in the switch subgroups compared to the stay subgroups. The POMS data in the verum-switch subgroup raise the possibility that dysphoric emotional states play a role in lack of adherence and/or limited responses to homeopathic treatment. Such CAM findings are consistent with the larger body of literature on the role of traumatic life events and negative affect in poor compliance and adverse clinical outcomes during conventional medical care for various chronic conditions (Boscarino, 1997; Ciechanowski et al., 2000; Felitti et al., 1998; Katon, 2003; Russek and Schwartz, 1997; Starace et al., 2002; Unutzer et al., 2002; Wang et al., 2002). On the other hand, homeopaths have also asserted that some patients on active treatment in double-blinded RCTs could have received a homeopathically active but incorrect remedy, thereby inducing the oscillatory or bidirectional dynamic in a subset of patients and compromising the potential for the "active" treatment group to show a difference from placebo (Hyland and Lewith, 2002). Reportedly, daily dosing with even the correct remedy in LM potency can worsen certain patients, who may need less frequent treatment (De Schepper, 1999). The present data do not permit distinguishing between competing hypotheses (affective disturbance versus incorrect remedy or dosing) that might account for the verum-switch outcomes.

Placebo responsivity in placebo-stay subgroup

The findings for each of the placebo subgroups raise other important issues for further investigation. In view of the relatively marginal clinical improvements of the placebo-stay subgroup, their decision to remain on placebo for 6 months

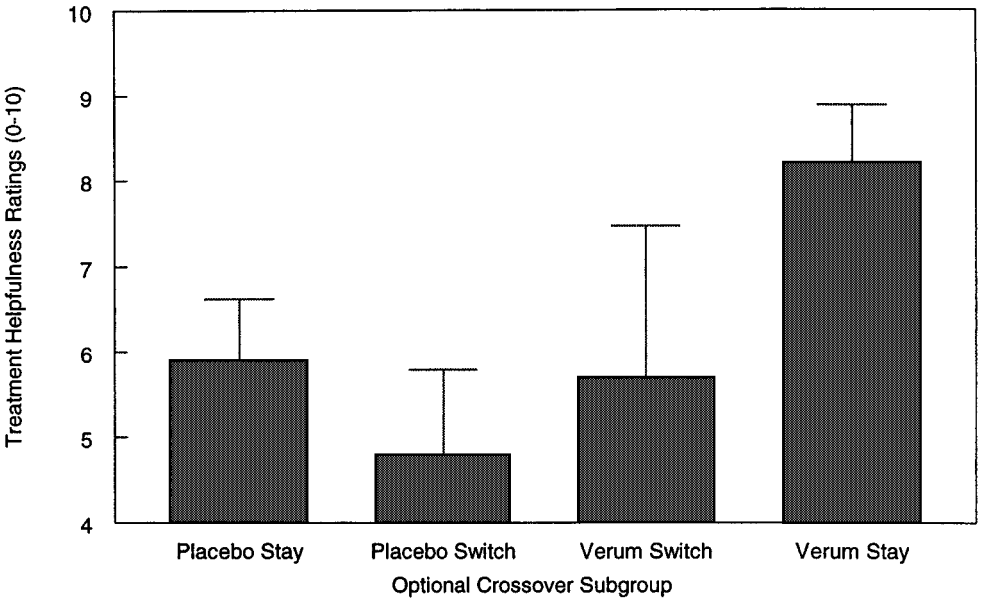


FIG. 2. Mean patient-rated helpfulness of the study treatment at 4- (precrossover) and 6-month (postcrossover) follow-up visits (with standard errors), adjusted for baseline covariates of profile of mood states (POMS) depression, POMS anger-hostility, childhood emotional neglect, medication use (Hotelling's Trace, $F(3,30) = 3.4$, $p = 0.029$; *post hocs:* V-stay > P-switch, V-switch, $p < 0.05$). Subgroups did not differ in findings as a function of visit. P-stay: $n = 13$; P-switch: $n = 8$; V-switch: $n = 3$; V-stay: $n = 14$.

is remarkable. The data suggest that the placebo-stay patients were satisfied with their perceived progress. Prior research on subjective shifts in perceived retrospective baseline status over time during conventional care offers a conceptual understanding of why some people might elect to stay with a biologically "inactive" treatment (placebo).

Studies on response shift processes have shown that an individual's internalized standards for evaluating the same

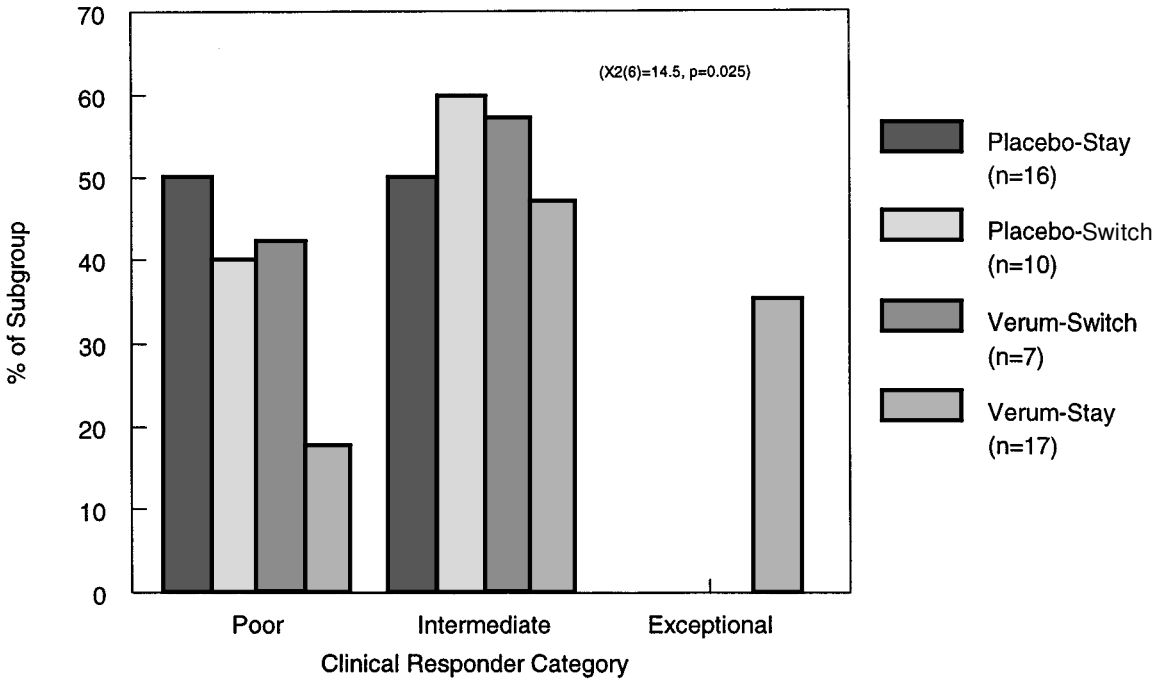


FIG. 3. Percentage of each optional crossover subgroup falling into exceptional, intermediate, and poor responder categories at the 3-month follow-up visit, before implementation of crossover decision ($\chi^2(6) = 14.5$, $p = 0.025$). V-stay versus P-stay subgroup comparison, $\chi^2(2) = 8.3$, $p = 0.016$. Based on top one third of patients with improvement (change scores from baseline) in mean tender-point pain and/or Global Health Rating Scale scores at 3 months (see text).

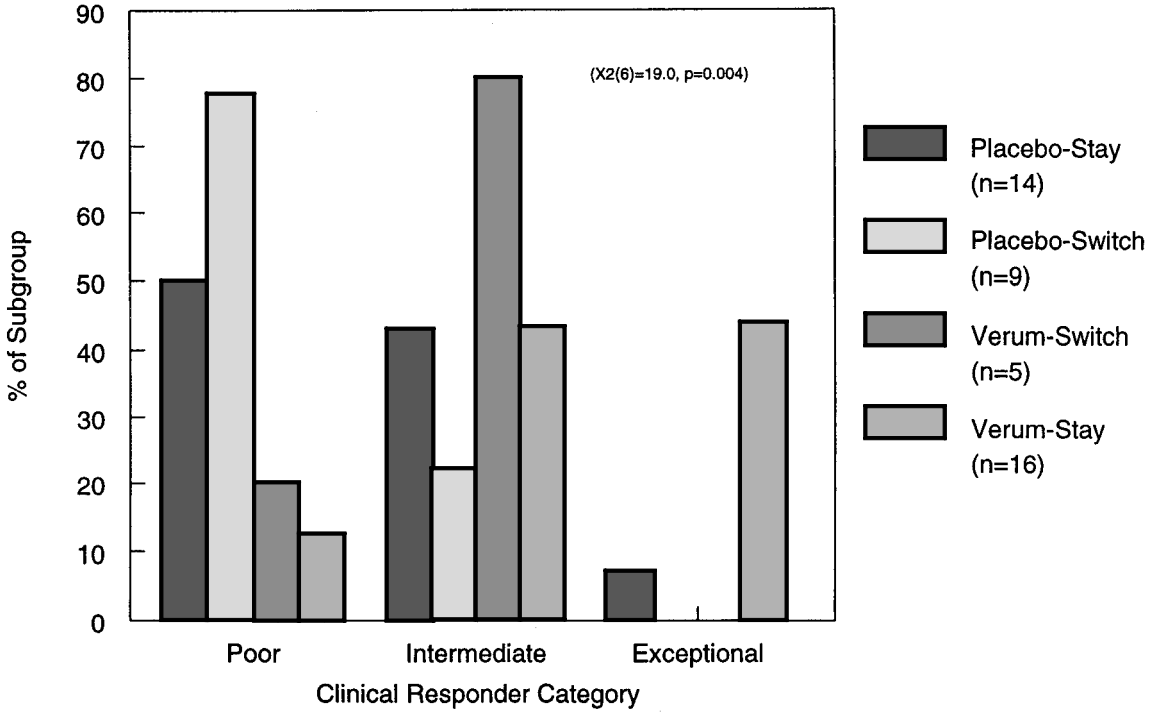


FIG. 4. Percentage of each optional crossover subgroup falling into exceptional, intermediate, and poor responder categories at the final 6-month follow-up visit, 2 months after implementation of crossover decision ($\chi^2(6) = 19.0, p = 0.004$). V-Stay versus P-stay subgroup comparison, $\chi^2(2) = 7.3, p = 0.027$; V-stay versus P-switch subgroup comparison, $\chi^2(2) = 11.5, p = 0.003$. Based on top one third of patients for improvement (change scores from baseline) in mean tender-point pain and/or Global Health Rating Scale scores at 6 months (see text).

symptom or condition may change or recalibrate over time. Comparative recall of baseline status may drift and cause patients to reconceptualize a target construct such as overall current health in a more positive light than objective observations would otherwise support (Golembiewski et al., 1976; Sprangers et al., 1999; Terborg et al., 1982). The finding of higher treatment helpfulness ratings in the stay versus switch subgroups, even after controlling for absorption and neglect, might suggest a contribution of a response shift factor in the perception of improved outcomes.

The data do not rule out some entanglement between verum and placebo, leading to simultaneous improvements in both groups (Walach, 2003). However, an entanglement hypothesis would have predicted improvements to a comparable degree in both verum and placebo groups. On the contrary, the verum group, including the verum-stay subgroup, improved the most on verum treatment, thereby demonstrating some degree of treatment-specific response. Electrophysiologic responses of verum patients during sniffs of treatment solutions also distinguished them from the placebo patients. That is, patients on verum remedy had EEG relative alpha changes that progressively differed over time from those of patients on placebo (Bell et al., this issue, pp. 285–299). Furthermore, the exceptional verum responders, who scored extremely high in trait absorption, exhibited EEG alpha cordance patterns on initial exposure to verum that differed from those of all other patients in the active or placebo groups (Bell et al., 2004c). Consequently, a response shift explanation for the placebo-stay subgroup's choice to stay on placebo would appear more plausible than entanglement between verum and placebo for the present study.

Poor responsivity in placebo-switch subgroup

At face value, the placebo-switch subgroup's decision makes sense. These patients apparently perceived a poor outcome on placebo after 4 months and elected to try the other group (verum). This subgroup would be predicted to have a turnaround in their deteriorating course, if only from positive expectations, knowing they had switched groups (Caspi and Bootzin, 2002). Nonetheless, the placebo-switch subgroup's medical and self-actualization outcomes at 6 months were still poor.

One possible explanation for the continued deterioration of the placebo-switch patients would be a treatment resistant condition from persistent psychobiologic effects of early life neglect. It is possible that the placebo-switch subgroup, with their history of more emotional neglect and possible failure to engage in a therapeutic alliance (Eltz et al., 1995), would not respond well to either placebo or active homeopathic treatment. The observation that the homeopaths recommended significantly more and different individual remedies during the study for the placebo-switch patients suggests that

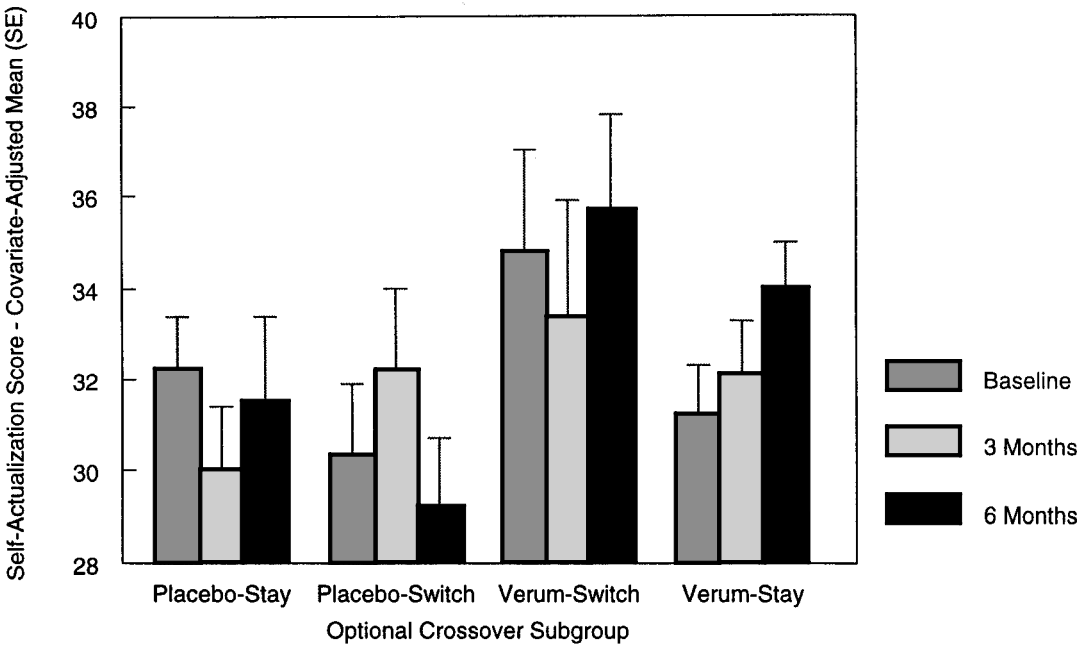


FIG. 5. Changes in JAREL Self-Actualization Score by Subgroup over Time Hotelling's Trace, $F(6,68) = 2.4$, $p = 0.035$. Patterns of change in JAREL self-actualization patterns (means with standard errors, adjusted for baseline covariates of profile of mood states (POMS) depression, POMS anger-hostility, childhood emotional neglect, medication use). (P-stay: $n = 14$; P-switch: $n = 9$; V-switch: $n = 5$; V-stay: $n = 16$.) JAREL scale is named for developers, JoAnn-Ruth-Eileen-Loretta.

the homeopaths may have been recognizing a failure of their initial remedy choice to "act" as expected or intended and assumed their original selection had been incorrect.

The placebo-switch subgroup correctly perceived themselves as doing poorly over time (i.e., these were truly placebo nonresponders). In terms of individual differences in clinical status, the placebo-switch subgroup appears to be those individuals who have impoverished early psychosocial histories. Past research has shown that FM patients in general have increased rates of abuse and neglect compared with controls (Walker et al., 1997). Prior trauma and poor parental caring are each a predictor of adverse medical outcomes many years later (Boscarino 1997; Russek and Schwartz, 1997). Prior neglect may increase certain patients' clinical needs for support and emotional nurturance. Providing an enriched therapeutic setting might improve the likelihood of their adherence to a given treatment for the length of time required to make progress with the presenting complaint. A question for future studies is the extent to which nature (high versus low trait absorption) and nurture (nurturing versus neglectful early environment) elements would interact with specific individualized homeopathic treatment to mobilize or not mobilize healing responses.

Alternatively, the placebo-switch subgroup could have undergone unrecognized adverse effects of early treatment with the verum remedy between months 4–6. Homeopaths claim that a proportion of patients with chronic illnesses experience a transient exacerbation or aggravation of symptoms on initiation of treatment, prior to undergoing improvement (Vithoulkas, 1980). The postcrossover treatment period lasted only 2 months and could have encompassed this type of worsening. The use of the LM potencies and the option for dosage regimen adjustments were intended to minimize the risk of any aggravations occurring, but it is not possible to rule out such events with the available data.

Implications for reproducibility of findings in homeopathy studies

Taken together, the current findings summarized above raise the possibility that some of the difficulties in reproducibility of previous homeopathic clinical studies (Bell, 2003; Ernst and Hahn, 1998) derive from unmeasured influences of variables such as trait absorption, early life trauma, and/or affective state. Especially in small sample studies from the homeopathic literature, a testable hypothesis is that assignment of low absorbers or highly dysphoric individuals to the active remedy and/or of high absorbers to the placebo, whether by failure of randomization or deliberate stratification, would reduce the probability of finding significant differences between groups, whereas the reverse would favor a positive outcome in a study. Recruitment of patients with histories of marked early neglect might lead to poorer responses in both active and placebo groups.

In the present study, variables that prior clinical outcomes research indicates could have been relevant did not differ

between the stay and switch groups (e.g., baseline levels of social support, spirituality, self-efficacy, health locus of control, social desirability scores, expectation ratings for benefit from the homeopathic treatment by patients, homeopaths, and rheumatologist, or patient satisfaction ratings with the homeopaths as clinical providers). Interestingly, the subgroups did not differ significantly for patient, rheumatologist, or homeopath expectations of benefit from treatment. However, the professionals' expectation ratings correlated overall with one another but not with those of the patients. In previous conventional research areas, observer and self-ratings diverge in a similar fashion (Lasalvia et al., 2002). For predicting mortality and health care utilization outcomes, patient self-ratings of global health are more accurate than are physician assessments or laboratory tests (Bath, 1999; Idler and Benyamini, 1997). Thus, the present expectation findings are compatible with those from earlier studies in conventional medicine.

Study limitations

The relatively small sample size, risk of Type I error with examination of multiple individual difference variables (but see Rothman, 1986), and missing data are potential limitations of this study. Nonetheless, the present findings highlight the need for innovative experimental designs (Aiken, 2003) and interdisciplinary collaborations in clinical homeopathy research that address the complex biopsychosocial features of this leading CAM system of medicine (Bell, 2003; Bell et al., 2002). The implications of the current individual difference findings on absorption, childhood emotional neglect, and negative mood states for differential patient outcomes and patient decision-making during treatment with homeopathy and other types of CAM deserve further examination.

SUMMARY

The goal of clinical medicine is to facilitate the healing of patients without doing harm, presumably by evoking robustly both treatment-specific and treatment-nonspecific responses (Walach, 2001). However, not all treatments are equally effective at mobilizing healing in a given person. Past research on individual differences in the placebo response suggests that there are no universal placebo responders (Caspi and Bootzin, 2002). Ernst and Resch (1995) originally suggested the optional crossover procedure as a straightforward outcome measure (i.e., how many patients ended up with active versus placebo treatment when given a choice to stay with or switch from their randomized assignment). If clinical outcomes depended only on activity or lack of activity of the treatment *per se* (Kirsch et al., 2002), this strategy could provide another measure of treatment specificity. In contrast, the present data, while suggesting an advantage for active homeopathic remedies over placebo treatment in FM, indicate that characteristics of the patients themselves also influence their capacity to respond to nonspecific elements of care and to stay with or switch from their original group.

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