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Osteopathic medicine for fibromyalgia: a sham-controlled randomized clinical trial

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Abstract

Background: Patients with fibromyalgia (FM) frequently resort to osteopathic or chiropractic treatment, despite very weak supporting evidence. We aimed to assess the efficacy of osteopathic manipulation in FM in a properly controlled and powered randomized clinical trial.

Methods: Patients were randomized to osteopathic or sham treatment. Treatment was administered by experienced physical medicine physicians, and consisted of six sessions per patient, over 6 weeks. Treatment credibility and expectancy were repeatedly evaluated. Patients completed standardized questionnaires at baseline, during treatment, and at 6, 12, 24, and 52 weeks after randomization. The primary outcome was pain intensity (100-mm visual analog scale) during the treatment period. Secondary outcomes included fatigue, functioning, and health-related quality of life. We performed primarily intention-to-treat analyses adjusted for credibility, using multiple imputation for missing data.

Results: In total, 101 patients (94% women) were included. Osteopathic treatment did not significantly decrease pain relative to sham treatment (mean difference during treatment: −2.2 mm; 95% confidence interval, −9.1 to 4.6 mm). No significant differences were observed for secondary outcomes. No serious adverse events were observed, despite a likely rebound in pain and altered functioning at week 12 in patients treated by osteopathy. Patient expectancy was predictive of pain during treatment, with a decrease of 12.9 mm (4.4–21.5 mm) per 10 points on the 0–30 scale. Treatment credibility and expectancy were also predictive of several secondary outcomes.

Conclusion: Osteopathy conferred no benefit over sham treatment for pain, fatigue, functioning, and quality of life in patients with FM. These findings do not support the use of osteopathy to treat these patients. More attention should be paid to the expectancy of patients in FM management.

Keywords: expectancy, fibromyalgia, osteopathic treatment, randomized clinical trial, sham control, treatment credibility

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Introduction

Fibromyalgia (FM) is a common chronic pain disorder, affecting between 1.5% and 2% of the general population.[1] However, its pathophysiology remains unclear and there is no gold standard treatment for patients with this condition. Pharmacological treatments, principally antidepressants and analgesics, are of limited benefit and adverse effects are frequently experienced by patients.[2,3] Opioids are particularly unsuitable for FM treatment.[4] Exercise, cognitive behavior therapies, and patient education appear to be most beneficial approaches, but may be insufficient or unavailable.[5] Patients with FM, therefore, often seek complementary or alternative therapies,[6,7] and frequently resort to chiropractic and osteopathic treatments. These treatments have been proposed for patients with FM since the mid-1990s,[8] but their efficacy has seldom been investigated, particularly in robust studies with high

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evidence levels, such as randomized clinical trials (RCTs). Reviewing four trials of low methodological quality in 2017, Perry *et al.*[9] concluded that "the current trial evidence is insufficient to conclude that chiropractic treatment is an effective treatment for FM". Furthermore, protocols for chiropractic or osteopathic manipulation are often heterogeneous and poorly reported.[9–11]

The increasing use of osteopathy by patients with FM (about half of the patients questioned in France in 2014 reported having used osteopathy in the last year[12]) prompted us to design a new RCT to obtain more conclusive evidence on the efficacy of this treatment in these patients. Given the fundamental importance of correctly controlling for placebo effects and for the expectations of patients from complementary and alternative medicine,[13] particular care was taken to ensure the credibility of the control procedure (a sham osteopathic treatment) and in the assessments of patient expectations of improvement (expectancy). The primary objective of this trial was to evaluate the analgesic effects of 6 weeks of osteopathic treatment in patients with FM. The secondary objectives were: (a) to assess the effect of osteopathic treatment on functioning, fatigue, and quality of life; (b) to evaluate the safety profile of this treatment, that is, the induction of pain or more serious traumatic events.

Materials and methods

Protocol, design, randomization, and assessment of treatment credibility

The FIBROPATHIC trial (ClinicalTrials.gov identifier: NCT02343237) was a randomized, controlled, multicenter trial comparing osteopathic with sham osteopathic treatment. A blind interim assessment of treatment credibility and expectancies of improvement was conducted on the first 30 patients (2×15) included in the trial. It was decided that a large, statistically significant difference between treatments (osteopathic *versus* sham), as implemented, would lead to discontinuation of the trial.

Patients were randomized in a 1:1 (osteopathic–sham osteopathic) ratio, with a centralized randomization procedure and permuted blocks, with various numbers per block, stratified by participating pain clinic, derived from a computer-generated random number program independently of the study staff. The therapists were necessarily unblinded to study group assignment given their role in delivering the assigned treatment, but they were not aware of block size and variation. Patients were blind to treatment assignment. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by the local Institutional Review Board (the CPP Ile de France III approved the study protocol on 16 December 2014). All study participants gave written informed consent.

Participants

Participants were recruited at two tertiary care university hospital pain clinics in Paris, France (the Cochin and Saint-Antoine hospitals). The criteria for patient eligibility were: aged over 18 years; FM according to the American College of Rheumatology 1990 criteria for more than 1 year; an average pain intensity of at least 50 on a 100-mm visual analog scale for pain intensity (VAS-PI); stable pharmacological and nonpharmacological treatment for more than 1 month; no history of severe psychiatric conditions (major depression, psychosis); no pregnancy or breast feeding; no physical treatment (physiotherapy, osteopathic, or chiropractic manipulation, manual medicine) during the last 3 months; no concomitant participation in another clinical trial; able to attend all six treatment sessions and to attend follow-up visits for at least 12 months (52 weeks) after the end of the treatment sessions; covered by health insurance.

Interventions

Subjects underwent osteopathic or sham manipulations over a 6-week period (total of six sessions, once per week, over 6 consecutive weeks). The first session occurred within 1 month of randomization and baseline assessment. Within 2 days after the first, third, and sixth sessions, patients completed the French-language version[14] of the credibility/expectancy questionnaire (CEQ).[15] This instrument includes six items assessing a cognition-based credibility dimension (three items, giving a score of 0–30), and an affect-based expectancy dimension (three items, giving a score of 0–30).

The treatments were delivered by four medical doctors with diplomas in Manual Medicine – Osteopathy (the official title of the French university diploma), after a training period in which

practices were harmonized according to the following protocol.

Patients with FM are usually normally mobile or even hypermobile, with diffuse muscle tenderness and a low pain threshold, and these features had to be taken into account in the treatment. The basic maneuvers used were therefore gentle, painless techniques involving repetitive mobilization and stretching, with the aim of relieving muscle tension or spasm and relaxing the patient. Thrust manipulation was permitted in the 'real' treatment group only, in situations in which a localized painful area was identified.

The 'real' treatment consisted of the following maneuvers. The patient was first placed in a prone position. Each vertebra from C7 to L5 was mobilized in a dorsoventral direction by progressive pressure on the spinous process (SP), and in rotation by applying pressure on the lateral surface of the SP (bilaterally). The sacral bone was repeatedly mobilized in nutation–counternutation (5–10 times). The piriformis muscles were progressively stretched. The hip joint was then progressively mobilized in extension combined with abduction and adduction to stretch the adductor, abductor, and flexor muscles (10 times). The shoulders were progressively mobilized, one by one, with a repeated circumduction movement of the glenohumeral joint (10 times). The patient was then placed in a supine position, for the following maneuvers. At the neck, bimanual traction was performed, followed by repeated mobilization in lateral flexion and in rotation (both sides, five times, 3–5 times each). At the shoulders, we first performed a cranial traction of both arms and then a repeated caudal traction of one arm and then the other, by blocking the clavicle, thereby opening the acromioclavicular and glenohumeral joints (three times). At the hips, repeated tractions were performed on the legs (three times) and the hip joint was mobilized by circumduction movements. Finally, the patient was placed in the lateral decubitus position for mobilization of the lumbar and thoracolumbar spine. Thrust manipulations were allowed at any level, according to the patient's complaint.

The sham treatment followed the same order, but the maneuvers were stopped halfway through to prevent joint mobilization at the spine. At the hips and shoulders, the stretching techniques were also stopped halfway. The joint techniques were simulated, with no significant mobilization. Thrust manipulation was forbidden.

Treatment duration (15–20 min) and the comments made by the physicians were the same in both groups.

Outcome measures

Participants completed questionnaires at baseline and at the 6-, 12-, 24-, and 52-week follow-up visits. Baseline questionnaires included a form for demographic data, a VAS-PI, the hospital anxiety and depression scale,[16] the fear-avoidance beliefs questionnaire,[17] the pain catastrophizing scale,[18] the 20-item multidimensional fatigue inventory (MFI-20),[19] the fibromyalgia impact questionnaire (FIQ)[20] a 10-item instrument measuring the impact of FM on activities of daily living and quality of life,[21] and the short form health survey (SF-36) of the Medical Outcomes Study.[22–24] The VAS-PI, MFI-20, FIQ, and SF-36 questionnaires were completed at each follow-up visit, along with the patient global impression of change (PGIC), a seven-point ordinal scale ranging from 'much worse' to 'much better'. During the 6-week treatment period, the participants were also asked to assess their average overall pain intensity weekly on the VAS-PI (0–100) (six assessments). The trial physicians recorded medical history and examination results at baseline, and at the 6-, 12-24-, and 52-week follow-up visits, together with any serious adverse events.

The primary outcome was average pain intensity during the treatment period, quantified as the area under the curve[25] of the six VAS-PI assessments. Secondary outcomes included VAS-PI, FIQ total score, MFI-20 total score, and three subscales of the SF-36 (physical functioning, general health, and mental health) standardized scores, and PGIC scores at each follow-up visit. For the safety assessment, the most common anticipated adverse effect was pain, which was evaluated through the VAS-PI assessments.

Statistical analysis

The primary analysis of primary and secondary outcomes described above was performed on the full intention-to-treat (ITT) population of randomized subjects,[26] with missing data imputed by multiple imputation.[27] Multiple imputation was

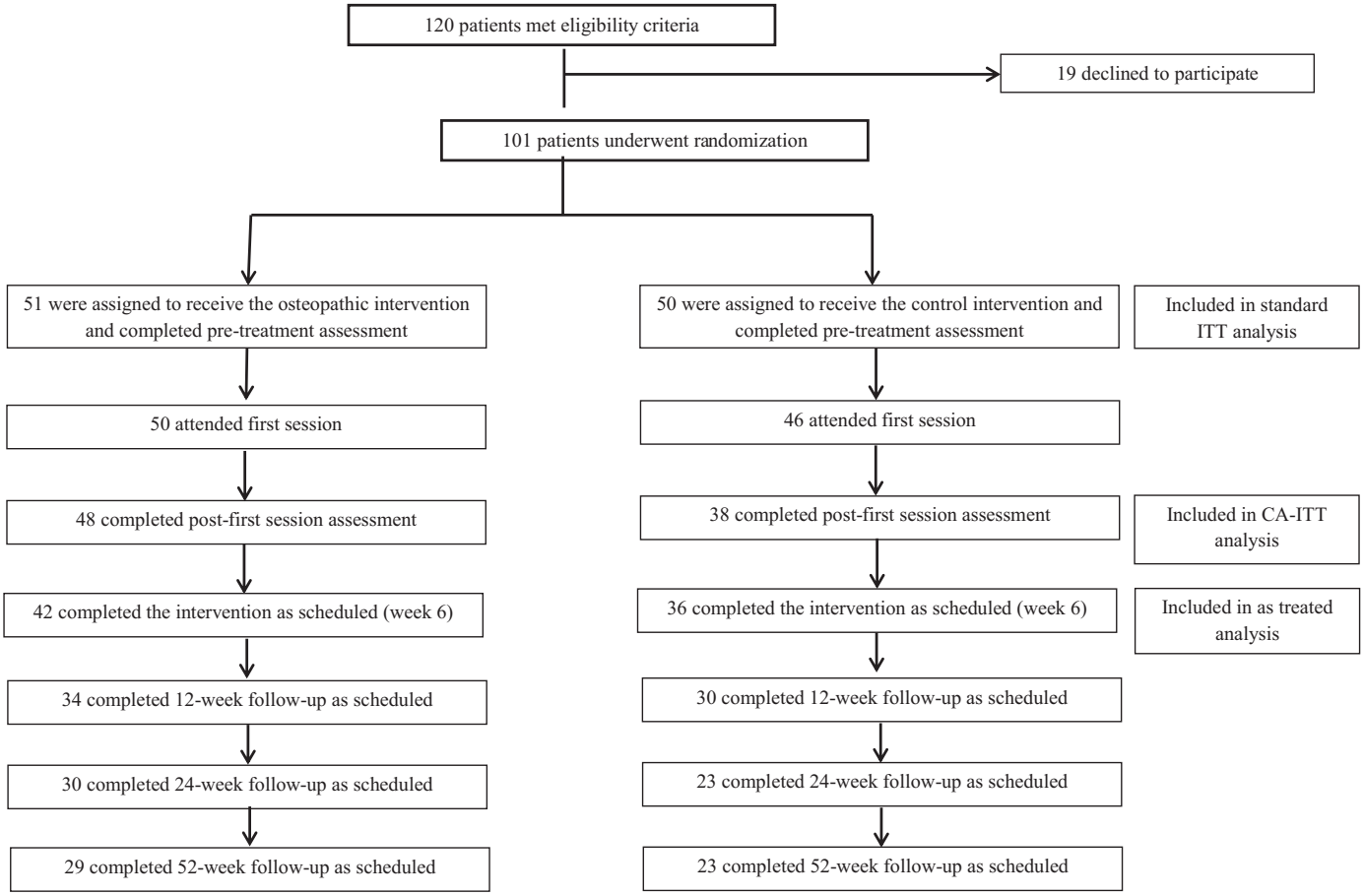

Figure 1. The flow of participants through each stage of the study.
CA-ITT, credibility assessed intention-to-treat; ITT, intention-to-treat.

performed with chained equations and 20 data sets to derive estimates of missing values or scores at each time point using all available baseline (prerandomization) variables and the variable at the previous time point to take into account any trend observed for the variable concerned. Given the considerable importance of credibility and expectation in this study, a second analysis was performed, considering the population of subjects for whom treatment credibility/expectancy was assessed at least once: the 'credibility assessed' intention to treat (CA-ITT) analysis. This population corresponds to the classical 'modified ITT' of all randomized patients undergoing at least one post-treatment assessment. A third 'as treated analysis' (in the population of subjects completing the six scheduled treatment sessions) and a fourth complete case analysis (including all available data, without imputation) were also performed as sensitivity analyses. All p values were obtained in two-tailed tests and p values less than 0.05 were considered statistically significant.

A power analysis indicated that a sample size of 130 would be sufficient to detect a group difference of 10 mm in the main outcome measure with 80% power, assuming a standard deviation of 20 mm for the primary outcome in both groups and a significance threshold of 5% in two-tailed tests.

Results

Between December 2015 and May 2017, 120 patients met eligibility criteria at the two participating centers; 101 of these patients agreed to participate, gave written consent, and were randomized. This restriction to 101 patients, 78% of the sample size initially planned, was imposed by the burden of follow up, which was very time-consuming for the clinical research staff. The flow diagram in Figure 1 describes the flow of participants through each stage of the study.[28] Dropouts (due to patient dissatisfaction or non-adherence in 82% of cases) were observed at each stage of the study, but the dropout rate was particularly high before and during the first

session. Moreover, dropout rates differed between the groups: 12/50 in the sham group *versus* 3/51 in the osteopathic group left the study early ($p = 0.02$, Fisher's exact test). However, for subjects attending and completing the first session, there was no difference between groups in terms of credibility and expectancy, in either the scheduled interim assessment on the first 30 patients (2×15) performed in October 2016, or in the final samples (Supplemental Table 1). Treatment credibility and expectancy remained stable and similar across groups over the six sessions. At 6 weeks (the end of the sessions) and 52 weeks, 23 (23%) and 49 (49%) participants, respectively, were lost to follow up. The participants lost to follow up did not differ from the other patients in terms of the principal baseline characteristics (Supplemental Table 2).

The baseline characteristics of the two treatment groups were similar (Table 1). The patients were mostly single (64%) and not actively working (67%), and 94% were women. Pain scores and the impact on daily activities (FIQ) and quality of life (SF-36) were high.

Supplemental Table 3 summarizes the outcome measures (primary and secondary) and their variations over time. Most indicators followed a trend towards improvement, with the exception of a worsening observed at week 12 in the osteopathy group. VAS-PI scores did not differ significantly between the osteopathic and sham osteopathic treatments during the sessions (primary outcome), or at 6, 12, 26, or 52 weeks (secondary outcome), in the full ITT analysis (Table 2), CA-ITT analysis (Tables 3 and 4), 'as treated analysis' (Supplemental Table 4), and 'case complete analysis' (Supplemental Table 5). There was also no significant difference in odds ratios for improvement between the two groups (Supplemental Table 6). Most other secondary outcomes were similar in the two groups, except for the FIQ score at 12 weeks, which was significantly higher (worse) in the osteopathy group than in the sham group in the full ITT analysis ($p = 0.04$). For most outcomes and most analyses, scores tended to be worse in the osteopathy group at 12 weeks, suggesting a possible rebound effect after treatment discontinuation. No other major safety issues were reported.

Expectancy of improvement was highly predictive of pain during treatment, the primary outcome, with a decrease of 12.9 mm (4.4–21.5 mm) in VAS-PI score per 10 points of the 0–30 scale ($p = 0.003$). No such predictive value was observed for credibility. The effects of expectancy on pain appeared to decrease over time, and a reversal was even observed for fatigue and mental health at week 12. Credibility had a milder but consistent positive effect on daily activities during follow up (Supplemental Table 7).

Discussion

This properly controlled and powered randomized clinical trial indicated that osteopathic treatment has no significant positive effect on FM. Whatever the outcomes considered (pain, fatigue, functioning, and quality of life) and the type of analysis performed (ITT, CA-ITT, as treated, or complete case), the differences between osteopathic and sham treatment were extremely small and far from statistical and clinical significance. These results are consistent with those of previous published studies ($N = 4$) and reviews ($N = 3$) concluding that there is no evidence that chiropractic or osteopathic treatment is effective in FM. However, these previous studies were of limited sample size (21–60 subjects), poorly reported, and, above all, did not include adequate control for placebo effects with a waiting list,[8] training,[29] electrotherapy stimulation,[30] ultrasound, or no treatment[31] controls. No difference between groups was observed in two of these studies[8,29] and no statistics at all were available for the other two.

The rebound of pain and the impact observed in the osteopathy group but not the sham treatment group, reaching statistical (but not clinical) significance for the FIQ, has not been reported before. These findings may indicate some sort of habituation, or may be related to evoked pain due to central sensitization, which would merit further exploration. Apart from this rebound, the safety profile of the treatment was good, as the manual therapists were all experienced physicians.

The most significant and, perhaps, also the most striking finding of this study was the effect of patient expectancy on pain reduction during treatment. In particular, a 10-point difference on the expectancy subscale of the CEQ (maximum score of 30) elicited an effect greater than the target change of 10 mm on the VAS-PI considered

Table 1. Characteristics of patients at baseline.

Characteristic	Osteopathic intervention group (*N* = 51)	Control intervention group (*N* = 50)
Age, mean (SD), years	51.0 (10.3)	50.2 (13.9)
Female, *n*, (%)	48 (94)	47 (94)
Body mass index, mean (SD)	25.9 (5.7)	25.3 (5.8)
Marital status		
Married/living with a partner, *n*, (%)	21 (41)	15 (30)
Separated/divorced/widowed, *n*, (%)	9 (18)	11 (22)
Single, *n*, (%)	21 (41)	24 (48)
With children, *n*, (%)	39 (76)	33 (66)
Occupation		
Manager, professional, *n*, (%)	9 (18)	6 (12)
Middle manager, teacher, *n*, (%)	16 (31)	12 (24)
Other employee, manual worker, *n*, (%)	25 (49)	27 (54)
No occupation or studying, *n*, (%)	1 (2)	5 (10)
Employment status		
Paid employment, *n*, (%)	16 (31)	17 (34)
Paid employment but on sick leave, *n*, (%)	9 (18)	10 (20)
Unemployed, *n*, (%)	4 (7)	4 (8)
Homemaker, *n*, (%)	3 (6)	2 (4)
Retired, *n*, (%)	10 (20)	14 (28)
Permanent disability, *n*, (%)	9 (18)	3 (6)
Concomitant medication use, *n*, (%)	50 (98)	44 (88)
Pain catastrophizing scale (0–52), mean (SD)	30.6 (12.3)	26.5 (12.8)
FABQ, work subscale (0–42), mean (SD)	19.4 (11.8)	22.3 (11.4)
FABQ, physical activity subscale (0–24), mean (SD)	13.4 (7.3)	13.8 (6.8)
HAD, anxiety scale (0–21), mean (SD)	11.3 (3.8)	11.4 (3.2)
HAD, depression scale (0–21), mean (SD)	9.7 (4.1)	9.3 (4.6)
Pain VAS-PI (0–100), mean (SD)	71.0 (14.0)	67.0 (20.6)
FIQ, total score (0–100), mean (SD)	58.9 (10.9)	58.6 (12.3)
FIQ, physical function score (0–10), mean (SD)	5.8 (2.2)	5.8 (2.1)
FIQ, feel-good score (0–10), mean (SD)	7.8 (2.5)	7.6 (2.6)
FIQ, pain score (0–10), mean (SD)	7.9 (1.5)	7.7 (1.9)

(Continued)

Table 1. (Continued)

Characteristic	Osteopathic intervention group (*N* = 51)	Control intervention group (*N* = 50)
FIQ, fatigue score (0–10), mean (SD)	8.5 (1.4)	8.3 (2.0)
FIQ, sleep score (0–10), mean (SD)	8.4 (1.7)	7.9 (2.4)
FIQ, stiffness score (0–10), mean (SD)	7.8 (2.1)	7.8 (2.0)
FIQ, anxiety score (0–10), mean (SD)	7.1 (2.4)	6.9 (2.4)
FIQ, depression score (0–10), mean (SD)	5.3 (3.2)	5.4 (3.0)
MFI, total score (20–100), mean (SD)	60.7 (6.3)	60.7 (5.2)
SF-36, physical functioning, standardized score, mean (SD)	−2.6 (1.7)	−2.7 (1.7)
SF-36, general health, standardized score, mean (SD)	−1.9 (1.0)	−1.9 (1.1)
SF-36, mental health, standardized score, mean (SD)	−1.4 (1.3)	−1.3 (1.1)

FABQ, fear-avoidance beliefs questionnaire; FIQ, fibromyalgia impact questionnaire; HAD, hospital anxiety and depression scale; MFI, multidimensional fatigue inventory; SD, standard deviation; SF-36, MOS 36-item short form health survey; VAS-PI, visual analog scale for pain intensity.

to constitute a significant effect in this study, and corresponds to the threshold (13 mm) often considered to indicate clinical significance in pain studies.[30] This effect on pain tended to decrease over time, but expectancy and, to a lesser extent, credibility remained associated with several secondary outcomes during the follow-up period.

Therapy credibility and expectancy for improvement are increasingly recognized as major determinants of both the response and adherence to therapy.[32] Therapy credibility is defined as the extent to which a treatment makes sense, is believable, convincing, and logical, whereas expectancy is the improvements that patients believe will occur on the basis of this particular treatment.[33] These components of every therapeutic procedure underlie so-called 'placebo effects'[34,35] and must therefore be carefully taken into account in both clinical practice and research, particularly when assessing the efficacy of psychotherapies[36] and alternative or complementary medicine procedures.[37] In these fields, where sham interventions are not easily disguised and blinding may be difficult, therapy credibility and patient expectancy of improvement may vary across groups. It is therefore important to take these factors into account as they may partly explain differences in response to treatment across groups. Note that although outcome expectancy for a given treatment may develop, at least in part, from how credible it seems, credibility is viewed as a separate construct.[15,38] Indeed, credibility develops from knowledge gained through direct experience or observation of a treatment, whereas outcome expectancy can exist without any contact with the medical treatment.[39] The importance of expectancy and its influence on outcomes have been demonstrated in diverse mental disorders, including mood and anxiety disorders,[40] and in medical conditions, such as Parkinson's disease treated by deep brain stimulation.[41,42] A role of expectancy has also been demonstrated in the management of pain conditions by complementary approaches, such as the use of acupuncture to treat chronic low back pain.[43]

This study has many strengths relative to earlier reports (appropriate control group, validated indicators, reasonable statistical power, assessment of treatment credibility), but it also has several limitations. First, difficulties in participant follow up were encountered (such difficulties are, unfortunately, common in studies of FM[44]), and attrition rates were, therefore, relatively high in this study; between 23% and 49%, according to the outcome considered (23% for the primary outcome). This attrition inevitably weakens the

Table 2. Estimated mean differences between groups during treatment at 6, 12, 24, and 52 weeks, adjusted for baseline value with multiple imputation for missing data. Full ITT analysis ($N = 101$).

	During treatment*		Week 6		Week 12		Week 24		Week 52	
	Estimate	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**	**Estimate**	***p* value**
Pain VAS-PI[$] (0–100)	−2.2 (−9.1 to 4.6)	0.52	−2.7 (−11.0 to 5.6)	0.53	0.6 (−10.9 to 12.1)	0.92	−5.6 (−22.1 to 10.8)	0.50	−5.0 (−24.8 to 14.7)	0.62
FIQ, total score[$] (0–100)	–	–	0.8 (−4.8 to 6.4)	0.77	5.1 (0.2 to 9.9)	0.04	1.2 (−4.9 to 7.3)	0.70	−1.1 (−7.9 to 5.6)	0.74
MFI, total score[$] (20–100)	–	–	0.4 (−1.9 to 2.7)	0.73	−0.1 (−2.3 to 2.1)	0.92	0.2 (−2.4 to 2.7)	0.90	−0.3 (−3.1 to 2.4)	0.82
SF-36, physical functioning, standardized score	–	–	0.0 (−0.4 to 0.5)	0.91	0.0 (−0.3 to 0.3)	1.00	0.1 (−0.4 to 0.5)	0.80	0.1 (−0.4 to 0.7)	0.63
SF-36, general health, standardized score	–	–	0.0 (−0.3 to 0.3)	0.98	−0.1 (−0.4 to 0.2)	0.51	0.0 (−0.4 to 0.3)	0.87	0.1 (−0.3 to 0.4)	0.75
SF-36, mental health, standardized score	–	–	0.1 (−0.3 to 0.5)	0.53	0.1 (−0.3 to 0.5)	0.69	−0.2 (−0.7 to 0.2)	0.33	0.1 (−0.4 to 0.6)	0.65

*Pain quantified by the area under the curve of the post-session assessment scores (primary outcome) (see text).
[$]Negative values indicate a better mean in the osteopathy group than in the control (sham osteopathic treatment) group.
FIQ, fibromyalgia impact questionnaire; ITT, intention to treat; MFI, multidimensional fatigue inventory; SF-36, MOS 36-item short form health survey; VAS-PI, visual analog scale for pain intensity.

Table 3. Estimated mean differences between groups during treatment at 6, 12, 24, and 52 weeks, adjusted for the baseline value with multiple imputation for missing data. CA-ITT analysis ($N = 86$).

	During treatment*		Week 6		Week 12		Week 24		Week 52	
	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value
Pain VAS-PI[$] (0–100)	−2.3 (−9.8 to 5.2)	0.55	−3.1 (−11.4 to 5.3)	0.48	0.6 (−11.6 to 12.8)	0.92	−2.6 (−22.3 to 17.0)	0.79	−8.5 (−29.0 to 12.0)	0.41
FIQ, total score[$] (0–100)	–	–	−1.1 (−6.8 to 4.6)	0.71	2.8 (−2.3 to 8.0)	0.28	−0.4 (−7.4 to 6.6)	0.91	−1.7 (−8.5 to 5.1)	0.63
MFI, total score[$] (20–100)	–	–	−0.4 (−2.7 to 1.9)	0.73	0.0 (−2.3 to 2.2)	0.97	0.2 (−2.5 to 3.0)	0.87	−0.1 (−2.9 to 2.7)	0.96
SF-36, physical functioning, standardized score	–	–	0.2 (−0.3 to 0.6)	0.40	0.0 (−0.4 to 0.4)	0.92	0.0 (−0.4 to 0.5)	0.86	0.0 (−0.5 to 0.6)	0.89
SF-36, general health, standardized score	–	–	0.0 (−0.3 to 0.4)	0.85	0.0 (−0.4 to 0.3)	0.91	0.0 (−0.3 to 0.3)	0.98	0.1 (−0.3 to 0.5)	0.77
SF-36, mental health, standardized score	–	–	0.2 (−0.2 to 0.6)	0.29	0.3 (−0.1 to 0.7)	0.17	−0.3 (−0.7 to 0.2)	0.26	0.0 (−0.5 to 0.5)	0.91

*Pain quantified by the area under the curve of the post-session assessment scores (primary outcome) (see text).
[$]Negative values indicate a better score in the osteopathy group than in the control group (sham osteopathic treatment).
CA-ITT, credibility assessed intention to treat; FIQ, fibromyalgia impact questionnaire; MFI, multidimensional fatigue inventory; SF-36: MOS 36-item short form health survey; VAS-PI, visual analog scale for pain intensity.

Table 4. Estimated mean differences between groups during treatment at 6, 12, 24, and 52 weeks, adjusted for the baseline value and for mean credibility and expectancy during treatment, with multiple imputation for missing data. CA-ITT analysis ($N = 86$).

	During treatment*		Week 6		Week 12		Week 24		Week 52	
	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value	Estimate	*p* value
Pain VAS-PI[$] (0–100)	−1.6 (−8.4 to 5.2)	0.64	−2.0 (−9.9 to 5.9)	0.61	−0.2 (−12.6 to 12.2)	0.97	−6.8 (−21.6 to 8.1)	0.37	−12.6 (−34.6 to 9.4)	0.26
FIQ, total score[$] (0–100)	–	–	−0.7 (−6.2 to 4.8)	0.80	4.4 (−1.3 to 10.1)	0.13	1.1 (−5.0 to 7.2)	0.72	−2.0 (−8.7 to 4.6)	0.55
MFI, total score[$] (20–100)	–	–	−0.5 (−2.8 to 1.8)	0.65	−0.2 (−2.4 to 1.9)	0.82	0.5 (−2.6 to 3.7)	0.75	−0.2 (−2.9 to 2.4)	0.86
SF-36, physical functioning, standardized score	–	–	0.2 (−0.2 to 0.6)	0.43	−0.1 (−0.4 to 0.3)	0.81	0.1 (−0.4 to 0.5)	0.78	0.1 (−0.4 to 0.6)	0.73
SF-36, general health, standardized score	–	–	0.0 (−0.3 to 0.3)	0.94	0.0 (−0.4 to 0.4)	0.88	0.1 (−0.3 to 0.4)	0.77	0.1 (−0.3 to 0.5)	0.57
SF-36, mental health, standardized score	–	–	0.2 (−0.2 to 0.6)	0.30	0.3 (−0.1 to 0.7)	0.17	−0.3 (−0.8 to 0.2)	0.20	0.0 (−0.5 to 0.5)	0.97

*Pain quantified by the area under the curve of the post-session assessment scores (primary outcome) (see text).
[$]Negative values indicate better score in the osteopathy group than in the control group (sham osteopathic treatment).
CA-ITT, credibility assessed intention to treat; FIQ, fibromyalgia impact questionnaire; MFI, multidimensional fatigue inventory; SF-36, MOS 36-item short form health survey; VAS-PI, visual analog scale for pain intensity.

analysis of long-term results. However, the actual statistical power of the primary outcome analysis decreased only slightly, to 75%, rather than the prespecified 80%, because the variance was lower than hypothesized. Moreover, the participants lost to follow up did not differ from those who completed the study in terms of the principal baseline characteristics. Second, the differential dropout rate before the end of the first treatment session, resulting in missing-not-at-random data, suggests that blinding was not successful for some of the included subjects. However, the credibility and expectancy of subjects who completed the assessment after the first session were similar in the groups compared, and the consistency of results across analyses (full ITT, CA-ITT, as treated, and complete case) are reassuring, making it possible to draw conclusions. Third, the osteopathic treatment lasted only 6 weeks in this study (a duration commonly used in RCTs on FM) and we cannot, therefore, rule out possible beneficial effects of longer treatment durations. However, we think it is unlikely that patients with FM would commit themselves to longer periods of treatment in the absence of a substantial effect during the initial 6-week period.

Conclusion

Among patients with poorly controlled FM, osteopathic treatment provided no benefit over sham treatment for pain, fatigue, functioning, and quality of life. These findings do not support the recommendation of osteopathic treatment for FM. Expectancy of improvement was found to have a large positive effect and should be taken into account to a greater extent in FM management.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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Supplemental material

Supplemental material for this article is available online.

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