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Original article

Clinical response and relapse in patients with chronic low back pain following osteopathic manual treatment: Results from the OSTEOPATHIC Trial

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ABSTRACT

Clinical response and relapse following a regimen of osteopathic manual treatment (OMT) were assessed in patients with chronic low back pain (LBP) within the OSTEOPATHIC Trial, a randomized, double-blind, sham-controlled study. Initial clinical response and subsequent stability of response, including final response and relapse status at week 12, were determined in 186 patients with high baseline pain severity (≥50 mm on a 100-mm visual analogue scale). Substantial improvement in LBP, defined as 50% or greater pain reduction relative to baseline, was used to assess clinical response at weeks 1, 2, 4, 6, 8, and 12. Sixty-two (65%) patients in the OMT group attained an initial clinical response vs. 41 (45%) patients in the sham OMT group (risk ratio [RR], 1.45; 95% confidence interval [CI], 1.11−1.90). The median time to initial clinical response to OMT in these patients was 4 weeks. Among patients with an initial clinical response prior to week 12, 13 (24%) patients in the OMT group vs. 18 (51%) patients in the sham OMT group relapsed (RR, 0.47; 95% CI, 0.26−0.83). Overall, 49 (52%) patients in the OMT group attained or maintained a clinical response at week 12 vs. 23 (25%) patients in the sham OMT group (RR, 2.04; 95% CI, 1.36−3.05). The large effect size for short-term efficacy of OMT was driven by stable responders who did not relapse.

1. Introduction

Manual therapies are often provided by practitioners within the fields of osteopathy, chiropractic, and physical therapy for patients with low back pain (LBP). Nevertheless, it is commonly believed that manual therapies are no better than standard medical care (Assendelft et al., 2003) or other recommended interventions for LBP (Rubinstein et al., 2011, 2012). Despite the artificial dichotomy propagated by such beliefs, the use of conventional medical treatments and manual therapies need not be mutually exclusive in managing patients with LBP (Licciardone, 2004). For example, osteopathic physicians in the United States are trained and licensed to provide both standard medical care and osteopathic manual treatment (OMT). Their ability to bridge the chasm between "conventional medicine" and "complementary and alternative medicine" may explain the disproportionately high levels of ambulatory medical care provided by osteopathic physicians for patients with LBP, particularly those with chronic LBP (Licciardone, 2008).

The OSTEOPAThic Health outcomes In Chronic low back pain (OSTEOPATHIC) Trial was conducted to assess the short-term efficacy of OMT as a complement to usual medical care in patients with chronic LBP (Licciardone et al., 2008). The results of this trial demonstrated that OMT provided statistically significant and clinically relevant improvements in LBP (Licciardone et al., 2013b). Subgroup analyses subsequently found large treatment effects with OMT, accompanied by significant improvements in back-specific functioning, in patients with high baseline pain severity (Licciardone et al., 2013a). Such improvements in LBP and related functioning were not observed in patients with low baseline pain severity.

The contemporary view of LBP is that it resembles a long-term condition such as asthma rather than a self-limiting condition such as the common cold and, therefore, should be treated and managed as a lifelong process (Axen and Leboeuf-Yde, 2013).

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Deficits in musculoskeletal and psychosocial functioning represent common sequela of chronic LBP. Thus, an important consideration in assessing manual therapies in patients with chronic LBP is to learn more about clinical response and relapse following such treatment and to identify factors associated with these outcomes. Consequently, to begin exploring these phenomena, we used data from the subgroup of patients with high baseline pain severity in the OSTEOPATHIC Trial to study clinical response to OMT and relapse within the short-term endpoint of 12 weeks.

2. Methods

2.1. Overview of the OSTEOPATHIC Trial design, implementation, and previous findings

The OSTEOPATHIC Trial used a randomized, double-blind, sham-controlled, 2 × 2 factorial design to study the short-term efficacy of OMT and ultrasound therapy in 455 adult patients with chronic LBP within the Dallas-Fort Worth metroplex from 2006 through 2011. The protocol has been previously described (Licciardone et al., 2008), and the study was approved by the Institutional Review Board at the University of North Texas Health Science Center and registered with ClinicalTrials.gov (NCT00315120) prior to inception. Herein, we do not further report on ultrasound therapy because it was not efficacious in providing moderate or substantial LBP improvement and there was no significant statistical interaction with OMT, thereby suggesting that ultrasound therapy made little to no contribution to OMT outcomes (Licciardone et al., 2013b).

Essentially, study criteria were established to recruit and randomize patients with nonspecific chronic LBP as determined by the presence of LBP on most days in the previous three months and absence of "red flag" conditions (Bigos et al., 1994). We further restricted our study to patients who were either OMT-naïve or who had infrequently used manual therapies in the previous 12 months, and who lacked motives for secondary gain from their LBP. The study protocol consisted of six treatment sessions provided at weeks 0, 1, 2, 4, 6, and 8, and an exit visit at week 12 to ascertain overall short-term outcomes (i.e., efficacy). Patients were randomized to either an active or sham OMT protocol that was delivered within 15-minute treatment sessions. The OMT protocol consisted of high-velocity, low-amplitude thrusts; moderate-velocity, moderate-amplitude thrusts; soft tissue stretching, kneading, and pressure; myofascial stretching and release; positional treatment of myofascial tender points; and muscle energy techniques. The sham OMT protocol simulated these techniques, but with improper patient positioning, purposely misdirected movements, and diminished treatment provider force. It also provided active and passive range of motion. Treatment fidelity methods (Bellg et al., 2004) were used to train providers to deliver the study protocols. These methods included standardized provider training using structured practice and role playing with pilot participants and regular booster sessions to minimize drift in provider skills over time.

Aside from the assigned active or sham OMT intervention (and acquiescence to avoid any other forms of manual therapy), patients could use any LBP self-care modalities and receive any other LBP co-treatments from practitioners of their choice. This OMT protocol was found to be safe, well accepted by patients, and associated with significant and clinically relevant LBP improvement (Licciardone et al., 2013b). Reduction in LBP was further corroborated by decreased use of prescription rescue medication for LBP in patients who received OMT vs. those who received sham OMT. In subgroup analyses of patients with high baseline pain severity (≥50 mm on a 100-mm visual analogue scale [VAS]), there was a large treatment effect with OMT in attaining substantial LBP improvement in concert with clinically relevant improvement in back-specific functioning (Licciardone et al., 2013a).

2.2. Measures of clinical response and relapse

Low back pain was measured immediately prior to each treatment session and at the week 12 exit visit with a 100-mm VAS. The VAS pain score for any missed treatment session or exit visit was imputed using the last-observation-carried-forward method. The threshold of ≥50% pain reduction relative to baseline was used to indicate substantial LBP improvement based upon recommendations from the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (Dworkin et al., 2008). This threshold, which is most commonly used to define responders in randomized controlled trials involving patients with chronic LBP (Henschke et al., 2014), was used to assess clinical response at weeks 1, 2, 4, 6, 8, and 12. Consequently, an initial clinical response to treatment may have been recorded at any of these time points. Stable clinical response was defined as the attainment of an initial clinical response without subsequently dropping below the 50% pain reduction threshold for substantial LBP improvement. Never-response was defined as never attaining an initial clinical response during the 12-week trial period. Relapse occurred if a patient dropped below the 50% pain reduction threshold for substantial LBP improvement at the week 12 exit visit after having previously attained an initial clinical response to treatment. Patients whose initial clinical response occurred at the week 12 exit visit were considered stable responders and were not at risk of relapse. Clinical response status at the week 12 exit visit was used to measure the overall short-term efficacy of OMT, regardless of whether or not an initial clinical response previously occurred.

2.3. Statistical analyses and interpretation of results

Differences between treatment groups in baseline patient characteristics and flow through the trial were analyzed using non-parametric statistical methods for continuous variables and the χ^2 test for 2 × 2 contingency tables. Clinical response and relapse profiles were plotted over time for each patient. The proportion of time over 12 weeks that each patient experienced substantial LBP improvement was measured and weighted means and 95% confidence intervals (CIs) were computed for each treatment group. Clinical response status at weeks 1, 2, 4, 6, and 8 was used to predict clinical response at the week 12 exit visit by adapting statistical measures and 95% CIs for diagnostic tests, including sensitivity, specificity, positive predictive value (PPV), negative predictive value, and likelihood ratios for presence or absence of a clinical response (Centre for Evidence-Based Medicine, 2014). Kaplan–Meier analysis and response curves were used to assess differences between treatment groups, using time to initial clinical response as the endpoint. Risk ratios (RRs) and 95% CIs were used to summarize contingency table results for OMT vs. sham OMT for the following primary outcome measures: initial clinical response, stable clinical response (vs. never-response), relapse, and clinical response at the week 12 exit visit. Subgroup analyses based on patient characteristics and use of non-prescription and prescription medication for LBP during the trial were conducted for each primary outcome. A *P*-value for interaction was computed to assess the statistical significance of differences between subgroups (Altman and Bland, 2003).

The Cochrane Back Review Group criteria were used to interpret the magnitude of treatment effects (i.e., effect sizes) for OMT based on the relevant RR. For statistically significant results pertaining to clinical response, treatment effects were classified as large (RR > 2), medium (1.25 ≤ RR ≤ 2), or small (RR < 1.25). Correspondingly, for

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relapse, treatment effects were classified as large (RR < 0.5), medium (0.5 ≤ RR ≤ 0.8), or small (RR > 0.8) (Furlan et al., 2009). Analyses were primarily performed using intention-to-treat methods with per-protocol analyses available for further assessment of study findings. Hypotheses were tested using a 0.05 level of statistical significance with the SPSS Statistics version 21 software package (IBM Corporation, Armonk, NY).

3. Results

3.1. Patient flow and baseline characteristics

The flow of patients through the trial is illustrated in the CONSORT diagram (Fig. 1). A total of 186 patients with high baseline pain severity were randomized, including 95 patients assigned to OMT and 91 patients assigned to sham OMT. Overall, the median age of patients was 43 years (IQR, 22 years) and 115 (62%) patients were women. The median baseline VAS pain score was 63 mm (IQR, 16 mm). A total of 103 (55%) patients reported LBP for more than one year, although relatively few patients had ever been hospitalized or had surgery for LBP. Co-morbid depression was reported by 46 (25%) patients. There was no significant difference between treatment groups in any baseline patient characteristic (Table 1). Patients in the OMT group were more likely to be treated by faculty physicians than fellows or residents ($P = 0.04$) and more frequently developed a contraindication to continued trial participation ($P = 0.03$) than patients in the sham OMT group. There was no significant difference between treatment groups in any other measure of patient follow-up or treatment adherence.

3.2. Clinical response and relapse profiles

Clinical response and relapse profiles over time for each patient revealed important differences between the OMT and sham OMT groups (Fig. 2). The weighted proportion of time wherein patients experienced substantial LBP improvement was 0.39 (95% CI, 0.32–0.47) for patients who received OMT vs. 0.20 (95% CI, 0.14–0.26) for patients who received sham OMT ($P < 0.001$). There were 11 (12%) patients in the OMT group who responded after the first scheduled treatment session. Such rapid response was strongly predictive of a clinical response to OMT at the week 12 exit visit (PPV, 0.82; 95% CI, 0.52–0.95) (Table 2). Clinical response at week 12 was maintained in 27 (90%) of the 30 patients who attained an initial clinical response to OMT after four or more scheduled

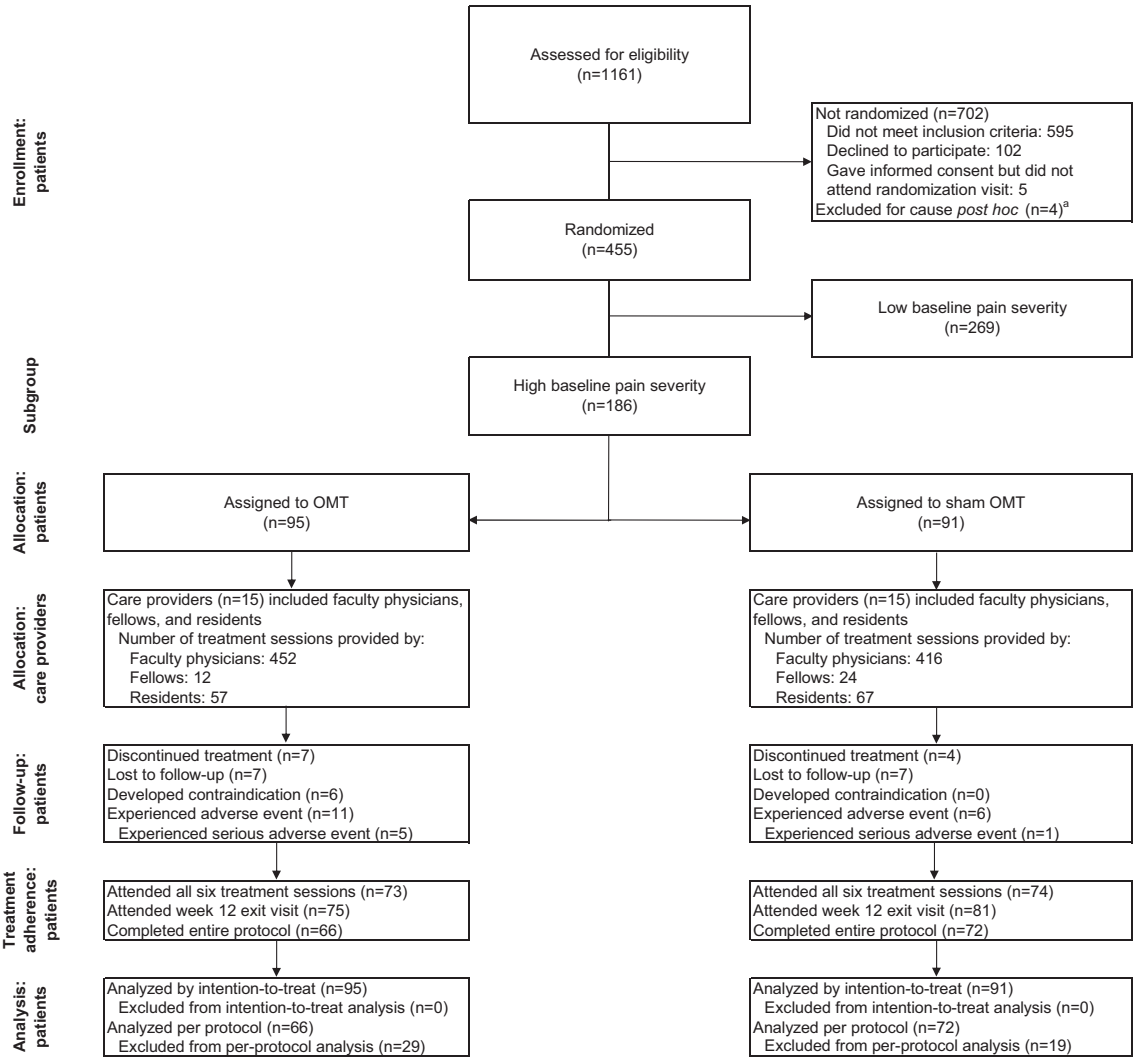

Fig. 1. Flow of patients through the OSTEOPATHIC Trial. The ultrasound therapy main effects groups are not displayed. OMT = osteopathic manual treatment. [a]Four patients were excluded for cause *post hoc* because it was subsequently discovered that they did not meet the inclusion criteria. Two of these patients provided false information to initially qualify for the study.

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Table 1
Baseline patient characteristics.

Characteristic	Intention-to-treat			Per-protocol		
	OMT ($n = 95$)	Sham OMT ($n = 91$)	P	OMT ($n = 66$)	Sham OMT ($n = 72$)	P
Median age (yrs) (IQR)	43 (23)	42 (22)	0.88[d]	45 (21)	44 (17)	0.72[d]
No. (%) of women	62 (65)	53 (58)	0.32	45 (68)	40 (56)	0.13
No. (%) completed college education	40 (42)	30 (33)	0.20	27 (41)	20 (28)	0.10
No. (%) employed full-time	40 (42)	38 (42)	0.96	28 (42)	29 (40)	0.80
No. (%) medically uninsured	41 (43)	36 (40)	0.62	26 (39)	28 (39)	0.95
No. (%) of current smokers	30 (32)	30 (33)	0.84	22 (33)	25 (35)	0.86
No. (%) with co-morbid conditions						
Hypertension	20 (21)	13 (14)	0.23	18 (27)	12 (17)	0.13
Diabetes mellitus	14 (15)	7 (8)	0.13	11 (17)	7 (10)	0.23
Osteoarthritis	8 (8)	8 (9)	0.93	6 (9)	7 (10)	0.90
Depression	26 (27)	20 (22)	0.39	20 (30)	14 (19)	0.14
No. (%) with duration of chronic LBP greater than one year	52 (55)	51 (56)	0.86	36 (55)	40 (56)	0.91
No. (%) previously hospitalized for LBP	9 (9)	6 (7)	0.47	4 (6)	6 (8)	0.75
No. (%) previously had surgery for LBP	2 (2)	3 (3)	0.68	1 (2)	3 (4)	0.62
Median VAS score for LBP (mm) (IQR)[a]	63 (16)	61 (15)	0.56[d]	63 (14)	61 (16)	0.56[d]
Median Roland–Morris disability score (IQR)[b]	7 (9)	7 (9)	0.94[d]	7 (9)	7 (9)	0.83[d]
Median SF-36 general health score (IQR)[c]	63 (30)	67 (37)	0.75[d]	67 (26)	67 (39)	0.91[d]
No. (%) used medication for LBP during previous four weeks						
Non-prescription	46 (48)	44 (48)	0.99	30 (45)	35 (49)	0.71
Prescription	16 (17)	19 (21)	0.48	9 (14)	16 (22)	0.19

IQR denotes interquartile range; LBP, low back pain; OMT, osteopathic manual treatment; SF-36, Medical Outcomes Study Short Form-36 Health Survey; VAS, visual analogue scale.

[a] A 100 mm VAS was used to measure LBP severity, with higher scores indicating more pain.

[b] The Roland–Morris Disability Questionnaire (0–24 points) was used to measure back-specific functioning, with higher scores indicating greater disability.

[c] The SF-36 general health scale (0–100 points) was used to measure generic health, with higher scores indicating better health.

[d] Based on the Mann–Whitney U test, as the baseline values were not normally distributed.

treatment sessions (i.e., at week 6 or later). Forty-two (86%) of the 49 responders to OMT at the week 12 exit visit were stable responders who never dropped below the 50% pain reduction threshold for substantial LBP improvement following their initial clinical response.

3.3. Primary outcomes

Sixty-two (65%) patients in the OMT group attained an initial clinical response at weeks 1, 2, 4, 6, 8, or 12; however, only 41 (45%) patients in the sham OMT group similarly responded (RR, 1.45; 95% CI, 1.11–1.90) (Table 3). There was a shorter time to attainment of initial clinical response in patients who received OMT vs. those who received sham OMT (log-rank $P = 0.003$) (Fig. 3). Among all 95 patients who received OMT, the median time to initial clinical response was 8 weeks. However, among the 62 initial responders to OMT, the median time to initial clinical response was 4 weeks. The median time to initial clinical response to sham OMT was in excess of 12 weeks, as only 41 (45%) patients attained an initial clinical response by week 12. There were 42 (56%) stable responders to OMT vs. 18 (26%) stable responders to sham OMT (RR, 2.12; 95% CI, 1.36–3.30). Among the 54 patients with an initial clinical response to OMT prior to week 12, 13 (24%) relapsed at the week 12 exit visit. By comparison, 18 (51%) of 35 patients who had initially responded to sham OMT relapsed at week 12 (RR, 0.47; 95% CI, 0.26–0.83). Overall, 49 (52%) patients in the OMT group either initially attained or maintained a clinical response at the week 12 exit visit vs. 23 (25%) patients in the sham OMT group (RR, 2.04; 95% CI, 1.36–3.05).

3.4. Subgroup analyses

There were several notable findings within subgroups; however, none of the subgroup differences relating to clinical response or relapse achieved statistical significance based on P-values for interaction (Table 4). Co-morbid depression was the only factor associated with a large OMT effect in attaining an initial clinical response and was also prevalent among stable clinical responders to OMT, although the statistical significance of the latter finding was obviated by the small number of observations. Several subgroups also exhibited large OMT effects in attaining a stable clinical response. The largest, significant OMT effects in preventing relapse were observed in patients without co-morbid depression and in patients whose LBP had endured for more than one year. Patients with co-morbid depression exhibited the largest, significant OMT effect with respect to overall efficacy at the week 12 exit visit.

3.5. Per-protocol analyses

A total of 138 (74%) patients completed the study per protocol (Fig. 1). Among these patients, there was no significant difference in any baseline patient characteristic between patients in the OMT group and those in the sham OMT group (Table 1). Per-protocol analyses for primary outcomes corroborated the statistical significance and clinical relevance of the intention-to-treat results (Table 3), including time to initial clinical response (Fig. 3). The remaining per-protocol results were generally comparable to the observed intention-to-treat results and, therefore, are not reported herein.

4. Discussion

The clinical response and relapse profiles of these patients with moderate to severe chronic LBP provide a unique perspective on the short-term outcomes of OMT. Patients who received OMT experienced about twice as much substantial LBP improvement over time as those who received sham OMT. A large majority of rapid responders who were identifiable after one scheduled OMT session maintained a clinical response to OMT at the week 12 exit visit. Typically, in patients who were clinical responders to OMT at week 12, three scheduled treatment sessions within four weeks were sufficient to cross the 50% pain reduction threshold for substantial LBP improvement. Thus, it appears that relatively few treatment

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Fig. 2. Patient profiles according to treatment group and clinical response status at week 12. There are 49, 46, 23, and 68 patients, respectively, represented in plots A, B, C, and D. Each horizontal bar represents the longitudinal experience of an individual patient for the six time intervals following each scheduled treatment session. Green shading indicates that the patient's low back pain was reduced by $\geq$ 50% relative to baseline, thereby representing a clinical response during the relevant time interval. OMT = osteopathic manual treatment.

Table 2
Characteristics of clinical response status over time as a predictor of overall response at the week 12 exit visit.

Week	Cumulative no. of treatments previously scheduled[a]	Group	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
1	1	OMT	0.18 (0.10–0.31)	0.96 (0.86–0.99)	0.82 (0.52–0.95)	0.52 (0.42–0.63)	4.22 (0.96–18.53)	0.85 (0.74–0.99)
		Sham OMT	0.22 (0.10–0.42)	0.99 (0.92–1.00)	0.83 (0.44–0.97)	0.79 (0.69–0.86)	14.78 (1.82–120.04)	0.79 (0.64–0.99)
2	2	OMT	0.33 (0.21–0.47)	0.87 (0.74–0.94)	0.73 (0.52–0.87)	0.55 (0.43–0.66)	2.50 (1.07–5.84)	0.77 (0.62–0.97)
		Sham OMT	0.35 (0.19–0.55)	0.94 (0.86–0.98)	0.67 (0.39–0.86)	0.81 (0.71–0.88)	5.91 (1.96–17.82)	0.69 (0.51–0.94)
4	3	OMT	0.45 (0.32–0.59)	0.76 (0.62–0.86)	0.67 (0.50–0.80)	0.56 (0.44–0.68)	1.88 (1.03–3.43)	0.72 (0.54–0.98)
		Sham OMT	0.48 (0.29–0.67)	0.91 (0.82–0.96)	0.65 (0.41–0.83)	0.84 (0.74–0.91)	5.42 (2.26–13.01)	0.57 (0.38–0.85)
6	4	OMT	0.71 (0.58–0.82)	0.72 (0.58–0.83)	0.73 (0.59–0.83)	0.70 (0.56–0.81)	2.53 (1.54–4.14)	0.40 (0.25–0.64)
		Sham OMT	0.61 (0.41–0.78)	0.84 (0.73–0.91)	0.56 (0.37–0.73)	0.86 (0.76–0.93)	3.76 (1.99–7.08)	0.47 (0.28–0.79)
8	5	OMT	0.84 (0.71–0.92)	0.70 (0.55–0.81)	0.75 (0.62–0.84)	0.80 (0.65–0.90)	2.75 (1.75–4.33)	0.23 (0.12–0.46)
		Sham OMT	0.74 (0.54–0.88)	0.74 (0.62–0.83)	0.49 (0.33–0.64)	0.89 (0.79–0.95)	2.79 (1.76–4.44)	0.35 (0.18–0.72)

CI denotes confidence interval; LR+, likelihood ratio for attainment of a clinical response; LR−, likelihood ratio for failure to attain a clinical response; NPV, negative predictive value; OMT, osteopathic manual treatment; PPV, positive predictive value.

[a] The reported characteristics reflect attainment of a clinical response based on visual analogue scale scores for low back pain immediately prior to receiving the assigned treatment at a given session. Thus, the week 1 results are based on one scheduled treatment session at week 0, the week 2 results are based on two scheduled treatment sessions at weeks 0 and 1, and so forth. Thus, there are no reported results for the sixth and final treatment session because there was no other scheduled visit to determine these results prior to the week 12 exit visit.

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Table 3
Clinical response and relapse outcomes.[a]

Outcome	Intention-to-treat analyses						Per-protocol analyses					
	OMT	Sham OMT	RR	(95% CI)	*P*	CBRG effect size	OMT	Sham OMT	RR	(95% CI)	*P*	CBRG effect size
Initial clinical response	62/95 (65)	41/91 (45)	1.45	(1.11–1.90)	0.006	Medium	53/66 (80)	37/72 (51)	1.56	(1.21–2.02)	<0.001	Medium
Stable clinical response[b]	42/75 (56)	18/68 (26)	2.12	(1.36–3.30)	<0.001	Large	35/48 (73)	16/51 (31)	2.32	(1.50–3.61)	<0.001	Large
Relapse[c]	13/54 (24)	18/35 (51)	0.47	(0.26–0.83)	0.008	Large	11/47 (23)	16/32 (50)	0.47	(0.25–0.87)	0.01	Large
Clinical response at the week 12 exit visit	49/95 (52)	23/91 (25)	2.04	(1.36–3.05)	<0.001	Large	42/66 (64)	21/72 (29)	2.18	(1.46–3.27)	<0.001	Large

CBRG denotes Cochrane Back Review Group; CI, confidence interval; LBP, low back pain; OMT, osteopathic manual treatment; RR, risk ratio.

[a] The RRs are for OMT vs. sham OMT, using ≥50% LBP reduction relative to baseline (substantial LBP improvement) as the threshold for a clinical response and failure to maintain a clinical response at week 12 as the criterion for a relapse. The CBRG treatment effect is based on the *P* value and RR (Furlan et al., 2009). The effect size for an RR that is statistically significant is classified as small (RR < 1.25), medium (1.25 ≤ RR ≤ 2.0), or large (RR > 2) for the clinical response outcomes, and as small (>0.8), medium (0.5 ≤ RR ≤ 0.8), or large (RR < 0.5) for relapse.

[b] Stable clinical responders never dropped below the 50% pain reduction threshold for substantial LBP improvement after their initial clinical response. The reference group in these analyses consisted of patients who never attained an initial clinical response (i.e., never-responders).

[c] Fourteen and 11 patients, respectively, in the intention-to-treat and per-protocol analyses were excluded because they achieved their initial clinical response at week 12 and, therefore, were not at risk of relapse.

sessions may be needed to attain and predict short-term response to OMT.

The large effect size for overall short-term efficacy of OMT was driven by stable responders who never dropped below the 50% pain reduction threshold for substantial LBP improvement throughout the study. With the caveats of limited sample size and statistical power, and originally unplanned analyses, our subgroup analyses yielded findings that may help guide future studies in this field. There were very large RRs for stable clinical response and clinical response at the week 12 exit visit in the subgroup of patients with co-morbid depression vs. those without depression, although patients with depression were more likely to relapse. Other subgroups that consistently exhibited large RRs for stable clinical response and clinical response at the week 12 exit visit, coupled with small RRs for relapse, included those in the 21–39 year age category; current cigarette smokers; and patients with LBP duration greater than one year, greater deficits in back-specific functioning, and poorer general health. Although OMT was associated with decreased need of prescription rescue mediation (RR, 0.66; 95% CI, 0.43–1.00) in the originally reported outcomes of the OSTEOPATHIC Trial (Licciardone et al., 2013b), our present findings suggest that patients who concurrently use non-prescription medication for LBP may experience an enhanced response to OMT and decreased likelihood of relapse.

It is interesting to review potential mechanisms by which OMT may exert its treatment effects in light of our subgroup findings. Previous analyses of OSTEOPATHIC Trial data have found reductions in serum tumor necrosis factor (TNF)-α concentration (Licciardone et al., 2012) and remission of psoas syndrome (Licciardone et al., 2014) to be associated with clinical response to OMT. Cytokines facilitate pain via a pathway that leads to release of neurotransmitters or neuromodulators that activate spinal cord glia and enhance pain (Watkins and Maier, 2005). Although the TNF-α inhibitors infliximab (Karppinen et al., 2003) and etanercept (Genevay et al., 2004) had each shown encouraging results in open-label studies involving disk-related sciatica prior to inception of the OSTEOPATHIC Trial, few patients in our study involving nonspecific chronic LBP were likely to be using such agents. Thus, it is possible that OMT may have reduced serum TNF-α concentration, thereby enhancing the analgesic effects of prescription and non-prescription medications that were mediated via different mechanisms. It also has been shown that healthy cigarette smokers have higher serum TNF-α concentrations than comparable non-smokers (Petrescu et al., 2010). Consequently, it is reasonable to speculate that any TNF-α reducing effects of OMT may inhibit pathways that maintain or enhance pain in cigarette smokers.

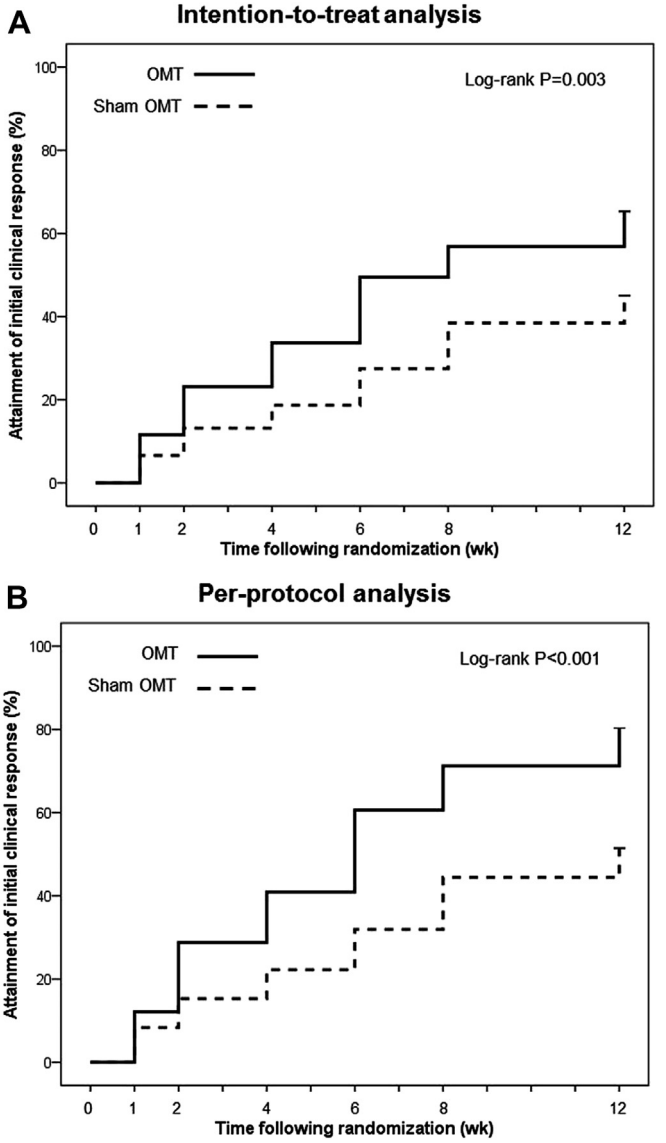

Fig. 3. Attainment of an initial clinical response over time according to treatment group. OMT = osteopathic manual treatment.

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Table 4
Clinical response and relapse outcomes according to subgroup.[a]

	Initial clinical response				Stable clinical response[b]				Relapse[c]				Clinical response at the week 12 exit visit			
	OMT ($n = 95$) no. (%)	Sham OMT ($n = 91$) no. (%)	RR	(95% CI)	OMT ($n = 75$) no. (%)	Sham OMT ($n = 68$) no. (%)	RR	(95% CI)	OMT ($n = 54$) no. (%)	Sham OMT ($n = 35$) no. (%)	RR	(95% CI)	OMT ($n = 95$) no. (%)	Sham OMT ($n = 91$) no. (%)	RR	(95% CI)
Overall	62 (65)	41 (45)	1.45	(1.11–1.90)	42 (56)	18 (26)	2.12	(1.36–3.30)	13 (24)	18 (51)	0.47	(0.26–0.83)	49 (52)	23 (25)	2.04	(1.36–3.05)
Subgroup variables																
Baseline characteristics																
Age (yrs)																
21–39	27 (66)	14 (37)	1.79	(1.12–2.86)	18 (56)	5 (17)	3.26	(1.39–7.66)	6 (25)	7 (54)	0.46	(0.20–1.09)	21 (51)	7 (18)	2.78	(1.34–5.79)
40–69	35 (65)	27 (51)	1.27	(0.92–1.77)	24 (56)	13 (33)	1.67	(1.00–2.81)	7 (23)	11 (50)	0.47	(0.22–1.01)	28 (52)	16 (30)	1.72	(1.06–2.79)
Sex																
Male	19 (58)	15 (39)	1.46	(0.89–2.38)	16 (53)	7 (23)	2.29	(1.10–4.74)	2 (12)	5 (45)	0.26	(0.06–1.11)	17 (52)	10 (26)	1.96	(1.05–3.66)
Female	43 (69)	26 (49)	1.41	(1.03–1.95)	26 (58)	11 (29)	2.00	(1.14–3.48)	11 (30)	13 (54)	0.55	(0.30–1.02)	32 (52)	13 (25)	2.10	(1.24–3.58)
Educational level attained																
<College degree	34 (62)	26 (43)	1.45	(1.01–2.07)	23 (52)	11 (24)	2.19	(1.21–3.93)	8 (26)	11 (52)	0.49	(0.24–1.02)	26 (47)	15 (25)	1.92	(1.14–3.24)
≥College degree	28 (70)	15 (50)	1.40	(0.93–2.11)	19 (61)	7 (32)	1.93	(0.98–3.77)	5 (22)	7 (50)	0.43	(0.17–1.11)	23 (58)	8 (27)	2.16	(1.13–4.13)
Current cigarette smoker																
No	44 (68)	30 (49)	1.38	(1.01–1.87)	30 (59)	15 (33)	1.80	(1.12–2.90)	9 (24)	12 (48)	0.49	(0.24–1.00)	35 (54)	18 (30)	1.82	(1.17–2.86)
Yes	18 (60)	11 (37)	1.64	(0.94–2.85)	12 (50)	3 (14)	3.67	(1.19–11.30)	4 (25)	6 (60)	0.42	(0.16–1.12)	14 (47)	5 (17)	2.80	(1.15–6.80)
Co-morbid depression																
Absent	46 (67)	36 (51)	1.31	(0.99–1.75)	35 (60)	17 (33)	1.85	(1.19–2.87)	7 (17)	14 (47)	0.37	(0.17–0.79)	39 (57)	22 (31)	1.82	(1.22–2.73)
Present	16 (62)	5 (25)	2.46	(1.09–5.58)	7 (41)	1 (6)	6.59	(0.91–47.76)	6 (46)	4 (80)	0.58	(0.28–1.20)	10 (38)	1 (5)	7.69	(1.07–55.23)
Duration of LBP																
≤1 yr	30 (70)	18 (45)	1.55	(1.04–2.30)	23 (64)	11 (33)	1.92	(1.12–3.29)	6 (24)	5 (33)	0.72	(0.27–1.96)	24 (56)	13 (33)	1.72	(1.02–2.89)
>1 yr	32 (62)	23 (45)	1.36	(0.94–1.98)	19 (49)	7 (20)	2.44	(1.17–5.09)	7 (24)	13 (65)	0.37	(0.18–0.76)	25 (48)	10 (20)	2.45	(1.31–4.57)
RMDQ score																
<8	35 (69)	24 (51)	1.34	(0.96–1.88)	22 (58)	9 (28)	2.06	(1.11–3.81)	8 (25)	11 (50)	0.50	(0.24–1.04)	27 (53)	13 (28)	1.91	(1.13–3.25)
≥8	27 (61)	17 (39)	1.59	(1.02–2.47)	20 (54)	9 (25)	2.16	(1.14–4.10)	5 (23)	7 (54)	0.42	(0.17–1.06)	22 (50)	10 (23)	2.20	(1.18–4.09)
SF-36-GH score																
<70	34 (61)	20 (39)	1.55	(1.04–2.31)	23 (51)	8 (21)	2.49	(1.26–4.92)	8 (27)	11 (65)	0.41	(0.21–0.82)	26 (46)	9 (18)	2.63	(1.36–5.07)
≥70	28 (72)	21 (53)	1.37	(0.96–1.95)	19 (63)	10 (34)	1.84	(1.04–3.25)	5 (21)	7 (39)	0.54	(0.20–1.42)	23 (59)	14 (35)	1.68	(1.03–2.77)
Co-treatments during trial																
Non-prescription medication																
Not used	36 (62)	21 (43)	1.45	(0.99–2.12)	26 (54)	11 (28)	1.92	(1.09–3.38)	7 (21)	7 (37)	0.58	(0.24–1.39)	29 (50)	14 (29)	1.71	(1.03–2.86)
Used	26 (70)	20 (48)	1.48	(1.01–2.16)	16 (59)	7 (24)	2.46	(1.20–5.03)	6 (29)	11 (69)	0.42	(0.20–0.88)	20 (54)	9 (21)	2.58	(1.35–4.96)
Prescription medication																
Not used	52 (65)	30 (43)	1.52	(1.11–2.08)	38 (58)	16 (29)	2.02	(1.27–3.20)	9 (19)	10 (40)	0.48	(0.22–1.02)	43 (54)	20 (29)	1.88	(1.23–2.87)
Used	10 (67)	11 (52)	1.27	(0.74–2.19)	4 (44)	2 (17)	2.67	(0.62–11.49)	4 (57)	8 (80)	0.71	(0.35–1.46)	6 (40)	3 (14)	2.80	(0.83–9.46)

CI denotes confidence interval; LBP, low back pain; OMT, osteopathic manual treatment; RMDQ, Roland–Morris Disability Questionnaire; RR, risk ratio; SF-36-GH, Medical Outcomes Study Short Form-36 Health Survey general health scale.

[a] The RRs are for OMT vs. sham OMT, using 50% LBP reduction relative to baseline as the cutpoint for clinical response and relapse. For subgroup variables, the numbers and percentages refer to patients with the relevant outcomes within each subgroup category. None of the differences between the categories within a subgroup variable achieved a statistically significant *P*-value for interaction. The reported results are all based on intention-to-treat analysis.

[b] Stable responders never dropped below the 50% pain reduction threshold for substantial LBP improvement after their initial clinical response. The reference group in these analyses consisted of patients who never attained a clinical response (i.e., never-responders).

[c] Eight patients in the OMT group and 6 patients in the sham OMT group were not at risk of relapse because their initial clinical response occurred at week 12.

Psoas syndrome is a muscular imbalance that may be frequently missed in patients with LBP (Tufo et al., 2012). Muscle functional magnetic resonance imaging has demonstrated greater transverse relaxation time asymmetry of the psoas muscle in patients with LBP vs. controls, and OMT significantly reduced this asymmetry while also providing LBP improvement (Clark et al., 2009). Because psoas syndrome is often found in patients with longstanding and disabling LBP (Greenman, 1996), remission of psoas syndrome is a feasible mechanism of action underlying clinical response to OMT in subgroups of patients with LBP duration greater than one year, greater deficits in back-specific functioning, and poorer general health. Indeed, we found psoas syndrome to be present at baseline in 117 (51%) of the 230 patients allocated to receive OMT in the OSTEOPATHIC Trial, and remission of psoas syndrome at the final scheduled treatment session at week 8 was strongly predictive of a clinical response at the week 12 exit visit (Licciardone et al., 2014).

There are several limitations of the present study. The assessment of clinical response to OMT was performed only at six study visits and there were no data on possible response at other intervening time points. The inclusion of only those patients with high baseline pain severity wherein OMT was most efficacious limited the sample size and statistical power of the subgroup analyses and their generalizability. These subgroup analyses were not originally planned and the absence of blocked randomization within any subgroup raises the possibility that unknown confounders may have biased the subgroup results. No attempt was made to identify such potential confounders, nor to use multivariate techniques to control for available covariates because of the relatively small sample size.

In summary, the large effect size for overall short-term efficacy of OMT in patients with high baseline pain severity was driven by patients who experienced a stable clinical response to OMT without subsequently relapsing at the week 12 exit visit. Typically, initial clinical response was seen with three scheduled treatment sessions delivered within four weeks of randomization in patients who were determined to be clinical responders to OMT at the week 12 exit visit. Clinical response and relapse findings in several patient subgroups were consistent with hypothesized actions of OMT; however, additional mechanistic research is needed to further address the latter findings.

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