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Original article

Outcomes of osteopathic manual treatment for chronic low back pain according to baseline pain severity: Results from the OSTEOPATHIC Trial

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ABSTRACT

Purpose: To assess response to osteopathic manual treatment (OMT) according to baseline severity of chronic low back pain (LBP).
Methods: The OSTEOPATHIC Trial used a randomized, double-blind, sham-controlled, 2 × 2 factorial design to study OMT for chronic LBP. A total of 269 (59%) patients reported low baseline pain severity (LBPS) (<50 mm/100 mm), whereas 186 (41%) patients reported high baseline pain severity (HBPS) (≥50 mm/100 mm). Six OMT sessions were provided over eight weeks and outcomes were assessed at week 12. The primary outcome was substantial LBP improvement (≥50% pain reduction). The Roland–Morris Disability Questionnaire (RMDQ) and eight other secondary outcomes were also studied. Response ratios (RRs) and 95% confidence intervals (CIs) were used in conjunction with Cochrane Back Review Group criteria to determine OMT effects.
Results: There was a large effect size for OMT in providing substantial LBP improvement in patients with HBPS (RR, 2.04; 95% CI, 1.36–3.05; $P < 0.001$). This was accompanied by clinically important improvement in back-specific functioning on the RMDQ (RR, 1.80; 95% CI, 1.08–3.01; $P = 0.02$). Both RRs were significantly greater than those observed in patients with LBPS. Osteopathic manual treatment was consistently associated with benefits in all other secondary outcomes in patients with HBPS, although the statistical significance and clinical relevance of results varied.
Conclusions: The large effect size for OMT in providing substantial pain reduction in patients with chronic LBP of high severity was associated with clinically important improvement in back-specific functioning. Thus, OMT may be an attractive option in such patients before proceeding to more invasive and costly treatments.

1. Introduction

The Global Burden of Disease Study 2010 reported a low back pain (LBP) prevalence of 632 million persons, making it the leading cause of years lived with disability (Vos et al., 2013). In the United States, LBP is the most common reason for adults to use complementary and alternative medicine (CAM) (Barnes et al., 2008), including utilization of manual therapy practitioners. Practice guidelines have recommended spinal manipulation for chronic or persistent LBP (Chou et al., 2007, National Institute for Health and Clinical Excellence, 2009) and, specifically, osteopathic manual treatment (OMT) (Clinical Guideline Subcommittee on Low Back Pain, 2010). Nevertheless, a Cochrane Collaboration review subsequently concluded that spinal manipulation is not more effective than sham interventions for short-term relief of chronic LBP (Rubinstein et al., 2011). Recently, however, the OSTEOPAThic Health outcomes In Chronic low back pain (OSTEOPATHIC) Trial demonstrated statistically significant and clinically relevant LBP improvement over 12 weeks with OMT when compared with sham OMT (Licciardone et al., 2013). Notably, OMT was associated with substantial LBP improvement, decreased use of prescription medication for LBP, and greater patient satisfaction with back care in the OSTEOPATHIC Trial. The present study now aims to determine if response to OMT differs significantly according to baseline

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severity of chronic low back pain by comparing patient subgroups within the OSTEOPATHIC Trial.

2. Methods

2.1. Study overview

The OSTEOPATHIC Trial was approved by the Institutional Review Board at the University of North Texas Health Science Center and registered with ClinicalTrials.gov (NCT00315120). Its methodology has been previously described (Licciardone et al., 2008; Licciardone et al., 2013). The trial used a randomized, double-blind, sham-controlled, 2 × 2 factorial design (Fig. 1) to study OMT (factor 1) and ultrasound therapy (factor 2) over 12 weeks in patients with nonspecific chronic LBP. Therein, OMT was shown to be safe, well accepted by patients, and associated with statistically significant and clinically relevant reduction in LBP (Licciardone et al., 2013). Consequently, the present study focused on comparing OMT vs. sham OMT in patient subgroups with low baseline pain severity (LBPS) and high baseline pain severity (HBPS). Ultrasound therapy was not studied herein because the OSTEOPATHIC Trial failed to demonstrate its efficacy.

2.2. Enrollment and randomization

Patients were recruited throughout Dallas–Fort Worth from August 2006 to September 2010 through newspaper advertisements, community agencies, and medical clinics, including those affiliated with the group practice of the University of North Texas Health Science Center, exclusive of clinics that provided OMT specialty services. The eligibility criteria were developed to include patients with nonspecific chronic LBP and to exclude patients who recently used manual therapy for LBP. Essentially, patients were those 21–69 years of age who self-reported low back pain on most days during the past three months, but who were without any of the following: "red flag" conditions; history of recent low back surgery, receipt of worker's compensation benefits, or ongoing litigation involving back problems; medical conditions that might impede OMT (or ultrasound therapy) protocol implementation; corticosteroid use in the past month; or clinical evidence of lumbar radiculopathy, as determined by the presence of ankle dorsiflexion weakness, great toe extensor weakness, impaired ankle reflexes, loss of light touch sensation in the medial, dorsal, and lateral aspects of the foot, or shooting posterior leg pain or foot pain upon ipsilateral or contralateral straight leg raising (Bigos et al., 1994). Patients who had received manual therapy in the past three months, or more than three times in the past year, were also excluded. Patients were randomly allocated to either OMT or sham OMT by a computer-based process. These assignments were conveyed to treatment providers via opaque sealed envelopes. Randomization was not stratified according to baseline pain severity. Patients and outcome assessors were not informed of treatment group assignments.

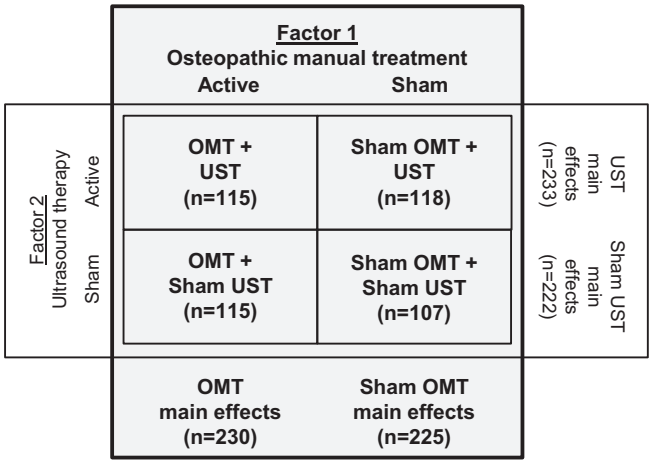

Fig. 1. Overview of the OSTEOPATHIC Trial's 2 × 2 factorial design. OMT denotes osteopathic manual treatment; UST, ultrasound therapy. As indicated by the shaded box, the present study focuses on OMT (factor 1) because it was found to be efficacious in reducing low back pain in the OSTEOPATHIC Trial, whereas UST (factor 2) was not efficacious.

2.3. Patient subgroups

Low back pain was measured with a 100-mm visual analog scale (VAS) at baseline, before each treatment session, and at week 12. We dichotomized patients into two subgroups defined as having LBPS (VAS < 50 mm/100 mm) or HBPS (VAS ≥ 50 mm/100 mm) for three reasons. First, dichotomization yielded relatively larger subgroups than would have been obtained with other polychotomous categorizations (e.g., trichotomization as "mild", "moderate", or "severe"). Second, it was intuitively appealing to simply bisect the 100-mm VAS. Third, the 50-mm cutpoint would facilitate extrapolation of our LBP results to numerical and other rating scales used in research settings or clinical practice.

2.4. Treatment protocols

Treatment fidelity methods (Bellg et al., 2004) were used to train 15 treatment providers to deliver the OMT and sham OMT protocols. Both protocols consisted of 15-min treatment sessions at weeks 0–2, 4, 6, and 8, delivered by the same provider to a given patient unless there was a scheduling conflict. Osteopathic manual treatment included 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. These techniques were aimed primarily at the lumbosacral, iliac, and pubic regions. Other osteopathic techniques were allowed only if the treatment provider judged a designated technique to be contraindicated or ineffective for a given patient. The sham OMT protocol was based on that developed in the North Texas Clinical Trial (Licciardone et al., 2003) and subsequently determined to provide a robust response in comparison with other placebo treatments for pain (Hrobjartsson and Gotzsche, 2001). The sham methods included hand contact, active and passive range of motion, and techniques that simulated OMT, but that utilized such maneuvers as light touch, improper patient positioning, purposely misdirected movements, and diminished treatment provider force. Patients were allowed to receive their usual LBP care and other co-treatments during the study with the exception of manual therapies.

2.5. Outcomes

2.5.1. Substantial low back pain improvement

Substantial LBP improvement was based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement recommendations (Dworkin et al., 2008). We used the relative threshold of ≥50% pain reduction to determine substantial improvement at week 12, rather than the absolute threshold of ≥40 mm pain reduction, to minimize floor effects in assessing OMT efficacy in patients with LBPS. This threshold is highly sensitive and specific in predicting global

impression of change in chronic pain patients (Emshoff et al., 2011) and provides readily interpretable evidence for clinical applications and recommendations (Farrar et al., 2000).

2.5.2. Secondary outcomes and safety

Patient-based secondary outcomes were also assessed at week 12 (Bombardier, 2000). The Roland and Morris (1983) Disability Questionnaire (RMDQ) was used to measure back-specific functioning. A RMDQ score reduction ≥5 points represents a minimally important change in a patient (Ostelo et al., 2008). The Medical Outcomes Study Short Form-36 Health Survey general health (SF-36 GH) scale was used to measure generic health. Correspondingly, a SF-36 GH score increase of ≥6 points represents a minimally important change on this scale (Yarlas et al., 2013). Work disability was measured by the number of lost work days because of LBP during the study in patients who worked full-time at baseline. Satisfaction with back care was measured with a five-point Likert scale ("very satisfied", "satisfied", "neither satisfied nor dissatisfied", "dissatisfied", "very dissatisfied"). We also measured use of exercise programming, non-prescription medication, prescription medication, physical therapy, and other CAM therapies for LBP. Work disability and LBP co-treatment data were collected at four-week intervals and aggregated over 12 weeks. There was no severity threshold for self-reported adverse events. Serious adverse events were defined as deaths, life-threatening situations, hospitalizations, severe or permanent disability, or other important medical events. The safety officer assessed causality of serious adverse events in relation to study interventions.

2.6. Statistical analysis

Responder analysis was used to assess substantial LBP improvement at week 12. Response ratios (RRs) and 95% confidence intervals (CIs) for OMT vs. sham OMT were used to estimate population effect size. Statistically significant results for substantial LBP improvement (as well as for back-specific functioning, general health, and satisfaction with back care) were considered clinically relevant if they met the Cochrane Back Review Group criteria for medium ($1.25 \leq RR \leq 2$) or large ($RR > 2$) effect sizes (Furlan et al., 2009). Our multidimensional approach for assessing OMT efficacy is illustrated by a $3 \times 3 \times 2$ matrix based on three levels of patient improvement (minimal, moderate, substantial), three levels of population effect size (small, medium, large), and two subgroups of baseline pain severity (LBPS, HBPS) (Fig. 2). We focused on the six cells (Fig. 2, cells 311, 312, 321, 322, 331, 332) that potentially characterize OMT efficacy in providing substantial LBP improvement. We took this highly specific analytical approach of assessing substantial improvement at the patient level as opposed to more sensitive assessments of minimal or moderate patient improvement to ensure that any positive study findings would have clinical significance. Previous reviews have attributed only "small and not apparently clinically relevant" effects (Rubinstein et al., 2011) or, at best, "moderate" efficacy (Chou and Huffman, 2007) to spinal manipulative therapy.

Responder analysis was also used to assess secondary outcomes. Satisfaction with back care was dichotomized by combining "very satisfied" and "satisfied" responses vs. all others. For work disability and use of LBP co-treatments, the Cochrane Back Review Group criteria are reversed such that medium and large effect sizes are represented by $0.5 \leq RR \leq 0.8$ and $RR < 0.5$, respectively. Patient flow, treatment provider assignment, treatment adherence, and safety were assessed by contingency table methods.

Hypothesis testing was by intention-to-treat with a two-sided $\alpha = 0.05$. Rothman's T statistic (Hogan et al., 1978) was used to test for statistical interaction between OMT and ultrasound therapy

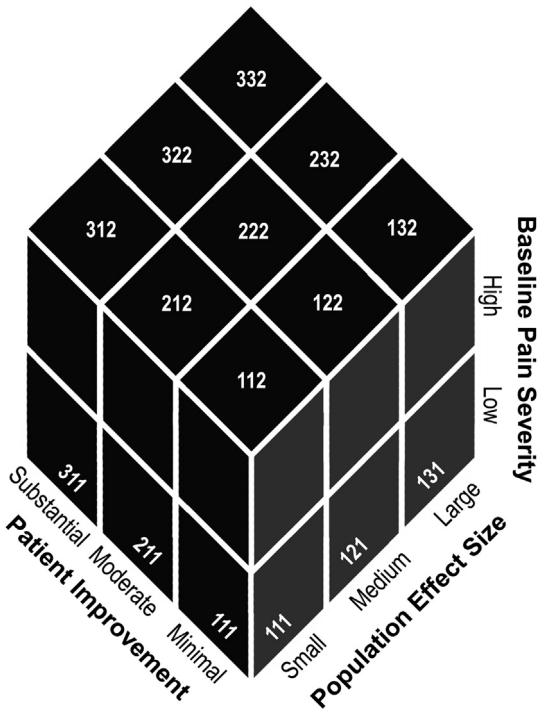

Fig. 2. Schematic representation of the multidimensional approach for assessing the efficacy of osteopathic manual treatment in patients with chronic low back pain. Patient improvement in low back pain is based on the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) consensus statement recommendations (Dworkin, et al., 2008). The relevant thresholds are ≥50% pain reduction for substantial improvement; ≥30% pain reduction for moderate improvement; and ≥10% pain reduction for minimal improvement. For simplicity, however, any treatment effect that fails to reach the thresholds for moderate or substantial improvement may be considered minimal. Population effect size is estimated using the Cochrane Back Review Group criteria (Furlan, et al., 2009). The relevant criteria are response ratio (RR) > 2 for a large effect size; $1.25 \leq RR \leq 2$ for a medium effect size; and $RR < 1.25$ for a small effect size. The cells within the $3 \times 3 \times 2$ matrix are uniquely identified by a three-digit code sequentially based on patient improvement (1, minimal; 2, moderate; 3, substantial), population effect size (1, small; 2, medium; 3, large), and baseline pain severity (1, low; 2, high). This study focused on assessing the efficacy of osteopathic manual treatment in providing substantial low back pain improvement in patients with low baseline pain severity (<50 mm/100 mm) and high baseline pain severity (≥50 mm/100 mm), as depicted by cells 311, 312, 321, 322, 331, and 332.

in assessing substantial LBP improvement. Missing data generally were imputed using the last observation carried forward. However, because relevant baseline data were not available for work disability and were not feasible for satisfaction with back care, we used multivariate regression to impute missing data for these variables. Work disability was regressed on age, sex, and baseline work status, whereas satisfaction with back care was regressed exclusively on age and sex. Per-protocol analyses were conducted to assess the impact of treatment non-adherence and robustness of our data imputation methods.

There were 269 (59%) patients in the LBPS subgroup and 186 (41%) patients in the HBPS subgroup. *Post-hoc* subgroup-specific estimates of statistical power in detecting medium and large effect sizes (Furlan et al., 2009) were computed under the assumption of a common sham OMT response across subgroups (Table 1). Statistical power in detecting large effect sizes exceeded 0.80 for the primary outcome and four secondary outcome measures in both subgroups. Statistical power in detecting medium effect sizes was low in both subgroups with the exception of satisfaction with back care. We used the P for interaction (Altman and Bland, 2003) to compare subgroup treatment effects for each outcome to minimize the likelihood of spurious results and invalid conclusions

Table 1
Post-hoc statistical power in detecting medium and large effect sizes for primary and secondary outcomes according to baseline pain severity.[a]

Outcome measure	LBPS (<50 mm) ($n = 269$)		HBPS (≥50 mm) ($n = 186$)	
	Medium effect size	Large effect size	Medium effect size	Large effect size
Primary outcome				
Visual analog scale score for LBP	0.31	>0.99	0.23	>0.99
Secondary outcomes				
Roland–Morris disability score	0.16	0.95	0.13	0.84
SF-36 general health score	0.20	0.99	0.15	0.94
Work disability[b]	0.11	0.50	0.09	0.31
Satisfaction with back care	0.93	>0.99	0.82	>0.99
Use of co-treatments for LBP during the trial				
Exercise programming	0.13	0.62	0.11	0.47
Non-prescription medication	0.33	0.98	0.24	0.91
Prescription medication	0.14	0.64	0.11	0.49
Physical therapy	0.08	0.27	0.07	0.20
CAM therapies	0.12	0.55	0.10	0.41

CAM denotes complementary and alternative medicine; HBPS, high baseline pain severity; LBPS, low baseline pain severity; SF-36, Medical Outcomes Study Short Form-36 Health Survey.

[a] Statistical power was computed under the assumption of a common sham OMT response across both subgroups. The thresholds for medium and large effect sizes were based on the Cochrane Back Review Group criteria (Furlan, et al., 2009).

[b] Work disability analyses included only patients who were employed full-time at baseline.

(Brookes et al., 2004). Statistical analyses were performed with the SPSS Statistics version 20 software (IBM Corporation, Armonk, NY).

3. Results

3.1. Patient flow and characteristics

The CONSORT diagram illustrates patient flow (Fig. 3). It demonstrates similar allocation to treatment providers, treatment adherence, and follow-up in the OMT and sham OMT groups within both subgroups. Patients in the HBPS subgroup reported significantly poorer back-specific functioning and general health than patients in the LBPS subgroup (Table 2). Patients in the HBPS subgroup were also more likely to have been taking prescription medicine for LBP prior to randomization and were more often hospitalized for LBP than patients in the LBPS subgroup. Co-morbid diabetes mellitus and depression were also more common in the HBPS subgroup. Patient characteristics in the OMT and sham OMT groups were comparable within each subgroup (Table 3).

3.2. Substantial low back pain improvement

There was no statistical interaction between OMT and ultrasound therapy in assessing substantial LBP improvement (T, −0.05; 95% CI, −0.23 to 0.13; $P = 0.61$). In the LBPS subgroup, 65 (48%) patients who received OMT vs. 56 (42%) patients who received

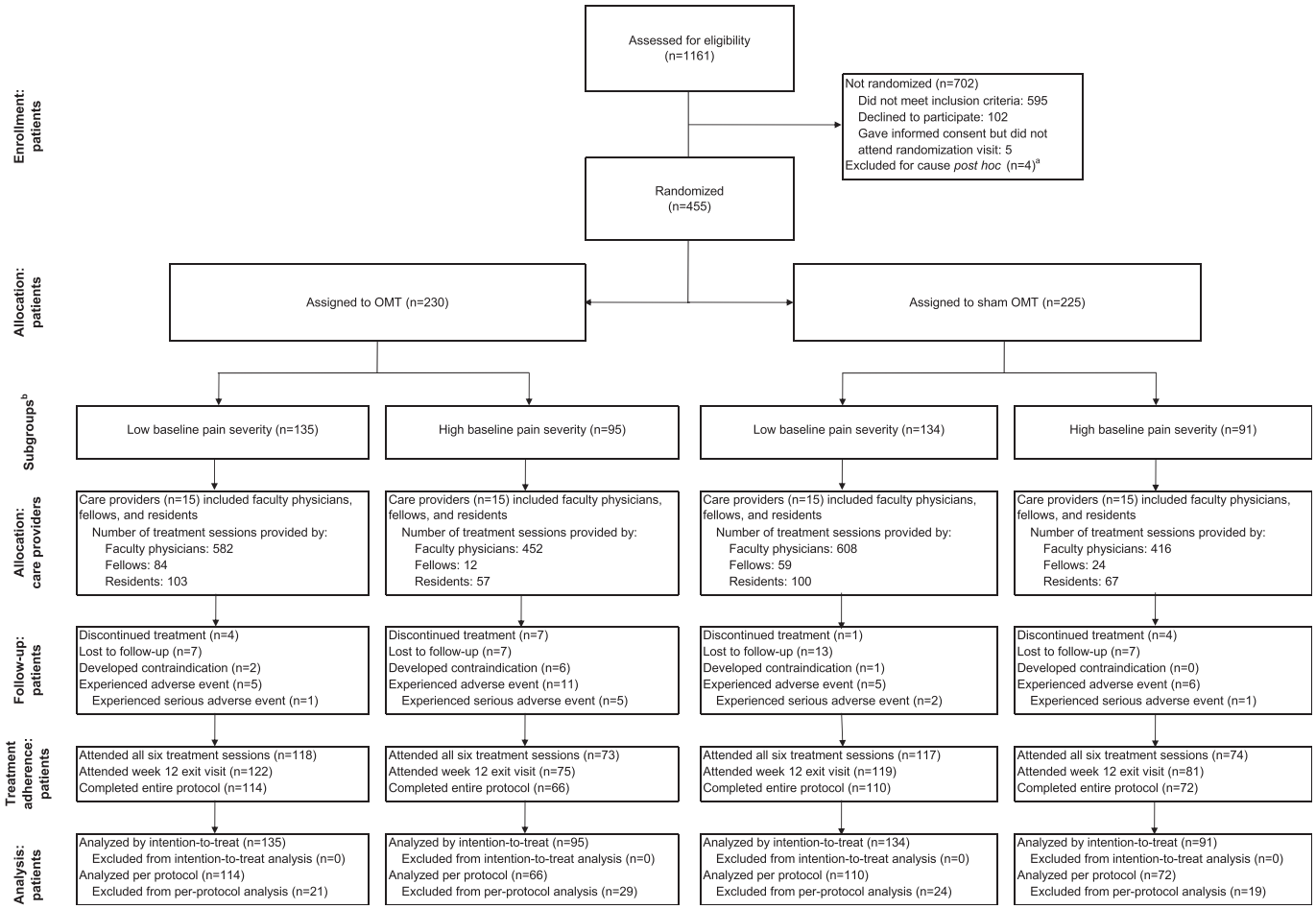

Fig. 3. CONSORT diagram. OMT denotes osteopathic manual treatment. [a]Four patients were excluded for cause *post-hoc* because it was subsequently discovered that they did not meet the inclusion criteria. Two of these patients provided false information to initially qualify for the study. [b]Randomization was not stratified according to baseline pain severity.

Table 2
Patient characteristics according to baseline pain severity.

Characteristic	Total ($n = 455$)	LBPS (<50 mm) ($n = 269$)	HBPS (≥50 mm) ($n = 186$)	*P*
Median age (yrs) (IQR)	41 (22)	40 (22)	43 (22)	0.18[d]
No. (%) of women	284 (62)	169 (63)	115 (62)	0.83
No. (%) completed college education	200 (44)	130 (48)	70 (38)	0.02
No. (%) employed full-time	215 (47)	137 (51)	78 (42)	0.06
No. (%) medically uninsured	163 (36)	86 (32)	77 (41)	0.04
No. (%) current smoker	119 (26)	59 (22)	60 (32)	0.01
No. (%) with co-morbid conditions				
Hypertension	71 (16)	38 (14)	33 (18)	0.30
Diabetes mellitus	34 (7)	13 (5)	21 (11)	0.01
Osteoarthritis	33 (7)	17 (6)	16 (9)	0.36
Depression	90 (20)	44 (16)	46 (25)	0.03
No. (%) with duration of chronic LBP greater than one year	228 (50)	125 (46)	103 (55)	0.06
No. (%) previously hospitalized for LBP	21 (5)	6 (2)	15 (8)	0.004
No. (%) previously had surgery for LBP	10 (2)	5 (2)	5 (3)	0.75[e]
Median VAS score for LBP (mm) (IQR)[a]	44 (34)	30 (22)	63 (16)	<.001[d]
Median Roland–Morris disability score (IQR)[b]	5 (6)	4 (5)	7 (9)	<.001[d]
Median SF-36 general health score (IQR)[c]	72 (30)	72 (25)	65 (32)	<.001[d]
No. (%) used medication for LBP during past four weeks				
Non-prescription	222 (49)	132 (49)	90 (48)	0.89
Prescription	59 (13)	24 (9)	35 (19)	0.002

HBPS denotes high baseline pain severity; IQR, interquartile range; LBP, low back pain; LBPS, low baseline pain severity; OMT, osteopathic manual treatment; SF-36, Medical Outcomes Study Short Form-36 Health Survey; VAS, visual analog scale.
[a] A 100-mm VAS was used to measure LBP severity, with higher scores indicating greater 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 data were not normally distributed.
[e] Based on Fisher's exact test.

sham OMT reported substantial LBP improvement (RR, 1.15; 95% CI, 0.88–1.50; $P = 0.29$) (Table 4). By contrast, in the HBPS subgroup, 49 (52%) patients who received OMT vs. 23 (25%) patients who received sham OMT reported substantial LBP improvement (RR, 2.04; 95% CI, 1.36–3.05; $P < 0.001$). The between-subgroup difference in RRs was significant (P for interaction = 0.02). The treatment effect for substantial LBP improvement with OMT in the HBPS subgroup exceeded the Cochrane Back Review Group criterion for a large effect size. In per-protocol analysis for the HBPS subgroup, 42 (64%) patients in the OMT group vs. 21 (29%) patients

Table 3
Patient characteristics according to baseline pain severity and treatment group.

Characteristic	LBPS (<50 mm)			HBPS (≥50 mm)		
	OMT ($n = 135$)	Sham OMT ($n = 134$)	*P*	OMT ($n = 95$)	Sham OMT ($n = 91$)	*P*
Median age (yrs) (IQR)	40 (22)	39 (20)	0.33[d]	43 (23)	42 (22)	0.88[d]
No. (%) of women	82 (61)	87 (65)	0.48	62 (65)	53 (58)	0.32
No. (%) completed college education	67 (50)	63 (47)	0.67	40 (42)	30 (33)	0.20
No. (%) employed full-time	70 (52)	67 (50)	0.76	40 (42)	38 (42)	0.96
No. (%) medically uninsured	45 (33)	41 (31)	0.63	41 (43)	36 (40)	0.62
No. (%) of current smokers	31 (23)	28 (21)	0.68	30 (32)	30 (33)	0.84
No. (%) with co-morbid conditions						
Hypertension	22 (16)	16 (12)	0.31	20 (21)	13 (14)	0.23
Diabetes mellitus	5 (4)	8 (6)	0.39	14 (15)	7 (8)	0.13
Osteoarthritis	9 (7)	8 (6)	0.81	8 (8)	8 (9)	0.93
Depression	18 (13)	26 (19)	0.18	26 (27)	20 (22)	0.39
No. (%) with duration of chronic LBP greater than one year	66 (49)	59 (44)	0.42	52 (55)	51 (56)	0.86
No. (%) previously hospitalized for LBP	4 (3)	2 (1)	0.68[e]	9 (9)	6 (7)	0.47
No. (%) previously had surgery for LBP	3 (2)	2 (1)	>0.99[e]	2 (2)	3 (3)	0.68[e]
Median VAS score for LBP (mm) (IQR)[a]	28 (21)	32 (22)	0.34[d]	63 (16)	61 (15)	0.56[d]
Median Roland–Morris disability score (IQR)[b]	4 (4)	4 (5)	0.23[d]	7 (9)	7 (9)	0.94[d]
Median SF-36 general health score (IQR)[c]	72 (20)	77 (30)	0.41[d]	63 (30)	67 (37)	0.75[d]
No. (%) used medication for LBP during previous four weeks						
Non-prescription	69 (51)	63 (47)	0.50	46 (48)	44 (48)	0.99
Prescription	11 (8)	13 (10)	0.65	16 (17)	19 (21)	0.48

HBPS denotes high baseline pain severity; IQR, interquartile range; LBP, low back pain; LBPS, low baseline pain severity; OMT, osteopathic manual treatment; SF-36, Medical Outcomes Study Short Form-36 Health Survey; VAS, visual analog scale.
[a] A 100 mm VAS was used to measure LBP severity, with higher scores indicating greater 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 data were not normally distributed.
[e] Based on Fisher's exact test.

Table 4
Outcomes of osteopathic manual treatment at week 12 according to baseline pain severity.[a]

Outcomes	LBPS (<50 mm)					HBPS (≥50 mm)					*P* for interaction
	OMT (*n* = 135) No. (%)	Sham OMT (*n* = 134) No. (%)	RR	(95% CI)	*P*	OMT (*n* = 95) No. (%)	Sham OMT (*n* = 91) No. (%)	RR	(95% CI)	*P*	
Primary outcome											
Substantial LBP improvement (≥50% reduction in VAS score)	65 (48)	56 (42)	1.15	(0.88–1.50)	0.29	49 (52)	23 (25)	2.04	(1.36–3.05)	<0.001	0.02
Secondary outcomes											
Back-specific functioning											
Clinically important change (≥5 point reduction in RMDQ score)	21 (16)	27 (20)	0.77	(0.46–1.30)	0.33	32 (34)	17 (19)	1.80	(1.08–3.01)	0.02	0.02
General health											
Clinically important change (≥6 point increase in SF-36 GH score)	34 (25)	30 (22)	1.12	(0.73–1.73)	0.59	37 (39)	25 (27)	1.42	(0.93–2.15)	0.10	0.44
Work disability[b]											
≥1 lost work day because of LBP during the trial	14 (20)	15 (22)	0.89	(0.47–1.71)	0.73	8 (20)	13 (34)	0.58	(0.27–1.25)	0.16	0.40
Satisfaction with back care											
Satisfied or very satisfied	126 (93)	91 (68)	1.37	(1.21–1.56)	<0.001	88 (93)	65 (71)	1.30	(1.13–1.49)	<0.001	0.58
Use of co-treatments for LBP during the trial											
Exercise programming	27 (20)	25 (19)	1.07	(0.66–1.75)	0.78	16 (17)	19 (21)	0.81	(0.44–1.47)	0.48	0.48
Non-prescription medication	68 (50)	60 (45)	1.12	(0.87–1.45)	0.36	37 (39)	42 (46)	0.84	(0.60–1.18)	0.32	0.18
Prescription medication	16 (12)	25 (19)	0.64	(0.36–1.13)	0.12	15 (16)	21 (23)	0.68	(0.38–1.24)	0.21	0.89
Physical therapy	16 (12)	6 (4)	2.65	(1.07–6.56)	0.03	10 (11)	11 (12)	0.87	(0.39–1.95)	0.74	0.07
CAM therapies	20 (15)	16 (12)	1.24	(0.67–2.29)	0.49	15 (16)	22 (24)	0.65	(0.36–1.18)	0.15	0.14

CAM denotes complementary and alternative medicine; CI, confidence interval; HBPS, high baseline pain severity; LBP, low back pain; LBPS, low baseline pain severity; RMDQ, Roland–Morris Disability Questionnaire; RR, response ratio; SF-36 GH, Medical Outcomes Study Short Form-36 Health Survey general health scale.

[a] The RRs are for OMT vs. sham OMT. The treatment effect in each baseline pain severity subgroup is based on the *P* value and RR (Furlan et al., 2009). For substantial LBP improvement, back-specific functioning, general health, and satisfaction with back care, the effect size for a RR that is statistically significant is classified as small (RR < 1.25), medium (1.25 ≤ RR ≤ 2.0), or large (RR > 2). For work disability and co-treatments for LBP, the corresponding criteria for effect sizes are small (RR > 0.8), medium (0.5 ≤ RR ≤ 0.8), or large (RR < 0.5).

[b] Based on patients who were employed full-time at baseline (LBPS, OMT, *n* = 70; LBPS, sham OMT, *n* = 67; HBPS, OMT, *n* = 40; HBPS, sham OMT, *n* = 38).

in the sham OMT group reported substantial LBP improvement (RR, 2.18; 95% CI, 1.46–3.27; $P < 0.001$). This RR was also significantly greater than the corresponding RR in the LBPS subgroup (*P* for interaction = 0.02). We were also unable to detect a statistically significant effect size for OMT at the IMMPACT thresholds for moderate (≥30% pain reduction) (RR, 1.19; 95% CI, 0.95–1.48; $P = 0.13$) or minimal (≥10% pain reduction) (RR, 1.04; 95% CI, 0.86–1.26; $P = 0.67$) LBP improvement in the LBPS subgroup.

3.3. Secondary outcomes

The secondary outcomes are summarized in Table 4. In the HBPS subgroup, 32 (34%) patients who received OMT vs. 17 (19%) patients who received sham OMT reported clinically important improvement in back-specific functioning on the RMDQ (RR, 1.80; 95% CI, 1.08–3.01; $P = 0.02$). The latter RR was significantly greater than the corresponding RR in the LBPS subgroup (*P* for interaction = 0.02) and met the threshold for clinical relevance. In the per-protocol analysis for the HBPS subgroup, 28 (42%) patients who received OMT vs. 16 (22%) patients who received sham OMT reported clinically important improvement in back-specific functioning (RR, 1.91; 95% CI, 1.14–3.20; $P = 0.01$). Again, this RR was significantly greater than the corresponding RR in the LBPS subgroup (*P* for interaction = 0.02). Patients who received OMT reported significantly greater and clinically relevant levels of satisfaction with their back care than patients who received sham OMT in both subgroups.

Medium effect sizes were observed for OMT in improving general health and in decreasing work disability, use of prescription medication, and use of CAM therapies for LBP in the HBPS subgroup. However, none of these results achieved statistical significance. There was no significant medium or large effect size observed for OMT in the LBPS subgroup except for increased satisfaction with back care.

3.4. Safety profile

Adverse events were reported in 27 (6%) patients (Fig. 2). Nine (2%) patients had a serious adverse event, none of which was adjudicated by the safety officer as definitely or probably related to OMT. There were no significant differences in the frequency of adverse events or serious adverse events between the OMT and sham OMT groups in either subgroup. In the HBPS subgroup, six (6%) patients who received OMT vs. no patients who received sham OMT developed a contraindication to continued study participation ($P = 0.03$). However, OMT was adjudicated to be possibly related to development of the contraindication in only one of these patients.

4. Discussion

Osteopathic manual treatment was associated with a large effect size in substantially reducing pain in patients with chronic LBP of high severity (Fig. 2, cell 332). Moreover, OMT was further associated with another clinically relevant effect by providing important improvement in back-specific functioning in this subgroup. Chronic LBP is often managed with costly or invasive interventions of questionable benefit and safety, including diagnostic imaging, opioid analgesics, epidural corticosteroid injections, and spinal surgery (Deyo et al., 2009). High pain severity, corresponding to our ≥50 mm cutpoint and associated with deficits in back-specific functioning (Von Korff et al., 1992), is the most important predictor of health care costs for LBP and lost productivity (Becker et al., 2010). Patients with high pain severity are also more likely to accept risks of complication and symptom persistence after lumbar spinal fusion (Bono et al., 2013). Thus, cost reduction strategies for chronic LBP should focus on patients with high pain severity.

A priority for primary care research is to better tailor treatment and management strategies to subgroups of patients with LBP

(Costa et al., 2013). Our dichotomization strategy may be easily applied in clinical practice to target patients with chronic LBP of high severity for a short course of OMT to reduce pain and improve back-specific functioning, as demonstrated herein. Our OMT regimen involving six treatment sessions was parsimonious, being well within the recommended guideline of nine treatment sessions over 12 weeks for persistent LBP (National Institute for Health and Clinical Excellence, 2009). By contrast, a typical initial trial of chiropractic care would have entailed six to 12 treatment sessions over two–four weeks, with potentially up to 36 treatment sessions over 12 weeks depending on patient progress and prognosis (Globe et al., 2008).

An unanswered question is why OMT yielded a large effect size in our HBPS subgroup while a Cochrane Collaboration review found spinal manipulative therapy to be no more effective than sham spinal manipulative therapy in providing short-term pain relief or improvement in functional status (Rubinstein et al., 2011). One possible explanation is that our *a-posteriori* HBPS subgroup analysis was biased by confounders that were no longer distributed at random in this subgroup (Hennekens and Demets, 2009). However, patients appeared to be adequately balanced on sociodemographic, clinical, and baseline outcome characteristics in each subgroup (Table 3). Another possibility is that previous studies (Waagen et al., 1986; Licciardone et al., 2003; Ghroubi et al., 2007) suffered from high risk of bias (Rubinstein et al., 2011), thereby reducing their likelihood of detecting significant treatment effects. A third possible explanation involves the high prevalence of dysfunction in the lumbar, sacral, pelvic, and innominate regions of patients with chronic LBP (Licciardone and Kearns, 2012). Our multimodal OMT regimen included six techniques in a comprehensive approach for treating the dysfunctions underlying LBP severity and associated with deficits in back-specific functioning. Previous trials involving unimodal approaches (e.g., high-velocity, low-amplitude thrusting in the lumbar region) may not have adequately addressed multifocal dysfunction in patients with chronic LBP. The association of lumbar dysfunction with higher baseline pain severity in our patients (Licciardone and Kearns, 2012) also helps to explain the greater response to OMT within the HBPS subgroup. A fourth possible explanation for our results is that the majority of treatments was provided by osteopathic physicians who received fidelity training in implementing the study protocol. Nevertheless, we believe that our results may be generalizable to other manual therapy practitioners because several OMT techniques in our protocol were accepted for LBP treatment by professional associations representing chiropractors and physiotherapists (Harvey et al., 2003).

The overarching strengths and limitations of the OSTEOPATHIC Trial have been previously described (Licciardone et al., 2008, 2013). Essentially, strengths included allocation concealment, blinding of outcome assessors, high levels of treatment adherence and outcomes reporting, and intention-to-treat analysis. We also pragmatically assessed OMT as practiced in real-life settings to complement usual care and self-care for chronic LBP. Limitations included patient self-reporting of co-morbid conditions, work disability, and LBP co-treatments. Additionally, despite our efforts to maintain patient blinding during the study, it is possible that some degree of unblinding may have occurred.

To our knowledge, the OSTEOPATHIC Trial is the largest OMT trial to date. Consequently, its sample size facilitated the performance of selected subgroup analyses. Statistical power exceeded 0.80 for analyses aimed at detecting large effect sizes in both LBPS and HBPS subgroups for the primary outcome variable. Both subgroup analyses were also adequately powered for detecting large effect sizes for clinically relevant improvements in back-specific functioning and general health, and for satisfaction with back care and use of non-prescription medication as a LBP co-treatment. Thus, our analyses were powered to detect the most important and clinically relevant treatment effects of OMT, such as those observed for substantial LBP improvement on the VAS (Fig. 2, cell 332) and change in back-specific functioning on the RMDQ. In the HBPS subgroup, and to a lesser degree in the LBPS subgroup, other potentially important benefits of OMT could not be ruled out because of low statistical power. We were also unable to definitively classify OMT effects in reducing LBP in the LBPS subgroup because of inadequate statistical power. However, based on the RRs and 95% CIs for patients with LBPS, OMT effects in this subgroup lie in one of six possible cells (Fig. 2, cells 111, 121, 211, 221, 311, 321).

5. Conclusions

The large effect size for OMT in providing substantial LBP improvement in patients with HBPS was associated with clinically important improvement in back-specific functioning. Based on these results, and on safety and satisfaction with back care, OMT appears to be an attractive option in patients with chronic LBP of high severity before proceeding to more invasive and costly treatments. Our results and conclusions should be interpreted in light of the usual caveats that accompany subgroup analyses, including statistical power limitations and the potential for unknown confounding.

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