Targeting Patient Subgroups With Chronic Low Back Pain for Osteopathic Manipulative Treatment: Responder Analyses From a Randomized Controlled Trial

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Context: Osteopathic manipulative treatment (OMT) is often used to treat patients with low back pain (LBP).

Objective: To identify subgroups of patients with chronic LBP who achieve medium to large treatment effects with OMT based on responder analyses involving pain and functioning outcomes from the OSTEOPAThic Health outcomes In Chronic low back pain (OSTEOPATHIC) Trial.

Methods: This randomized, double-blind, sham-controlled trial involving 455 patients in Dallas-Fort Worth was conducted from 2006 to 2011. A 100-mm visual analog scale (VAS) for LBP intensity and the Roland-Morris Disability Questionnaire (RMDQ) for back-specific functioning were used to assess primary and secondary outcomes, respectively. Substantial improvement was defined as 50% or greater reduction at week 12 compared with baseline. Cumulative distribution functions for the RR and number-needed-to-treat (NNT) were used to assess response.

Results: Medium treatment effects for LBP intensity were observed overall (RR, 1.41; 95% CI, 1.13-1.76; P=.002; NNT, 6.9; 95% CI, 4.3-18.6). However, large treatment effects were observed in patients with baseline VAS scores of 35 mm or greater. Although OMT was not associated with overall substantial improvement in back-specific functioning, patients with baseline RMDQ scores of 7 or greater experienced medium effects, and patients with baseline scores 16 or greater experienced large effects that were significant. The OMT effects for LBP intensity and back-specific functioning were independent of baseline patient demographic characteristics, comorbid medical conditions, and medication use for LBP during the trial.

Conclusions: Subgrouping according to baseline levels of chronic LBP intensity and back-specific functioning appears to be a simple strategy for identifying sizeable numbers of patients who achieve substantial improvement with OMT and may thereby be less likely to use more costly and invasive interventions. (ClinicalTrials.gov number NCT00315120)

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Low back pain (LBP) is a worldwide problem and the leading cause of disability.[1] International clinical guidelines differ on the usefulness of spinal manipulation in managing LBP in primary care.[2] The early management pathway of the National Institute for Health and Care Excellence[3] and the joint clinical practice guidelines of the American College of Physicians and American Pain Society[4] both recommend spinal manipulation for persistent or chronic LBP. Nevertheless, a Cochrane Review[5] concluded that spinal manipulation is no more effective than sham

spinal manipulation in providing short-term LBP relief. However, the latter was based on very low-quality evidence, including small sample sizes, high risk of bias, and heterogeneity of research design in many included studies.[5]

There has been growing interest in targeting subgroups of patients with LBP to identify those most likely to improve with intervention. A clinical prediction rule for spinal manipulation that included 5 patient-reported or practitioner-based measurements showed promising results over 4 weeks in patients with LBP of varying duration.[6] The Keele University Subgroups for Targeted Treatment (STarT) Back Screening Tool was subsequently validated as a brief instrument for assessing risk of persistence and disability to be used in a stratified approach to managing LBP in primary care.[7] There are no corresponding strategies, however, for exclusively targeting patients with chronic LBP for spinal manipulation. Moreover, responder analyses that may inform such strategies have been infrequently and inconsistently reported in randomized controlled trials.[8] The National Institutes of Health Task Force on Research Standards for Chronic Low Back Pain has identified the reporting of cumulative distribution functions of responses for treatment and control groups as an attractive aspect of responder analysis because of the lack of consensus and data on response thresholds.[9]

The OSTEOPAThic Health outcomes In Chronic low back pain (OSTEOPATHIC) Trial was conducted in the United States to assess the short-term efficacy of osteopathic manipulative treatment (OMT) in patients with chronic LBP. Its findings of clinically relevant LBP improvement with OMT[10-12] bring into question previous Cochrane Review conclusions.[5] Herein, to further guide the use of OMT in subgroups of patients with chronic LBP, we report the results of responder analyses from the OSTEOPATHIC Trial that describe the effects of OMT on patients' LBP intensity and back-specific functioning.

Methods

Study Design

The design and results of the OSTEOPATHIC Trial have been previously published.[10-12] This double-blind, sham-controlled trial of OMT for nonspecific chronic LBP was conducted at The Osteopathic Research Center at the University of North Texas Health Science Center in the Dallas-Fort Worth metroplex from August 2006 through January 2011. A total of 455 men and women aged 21 to 69 years were recruited from primary care settings and randomly allocated to OMT or sham OMT within a 2×2 factorial design. Ultrasound therapy, which was the second factor studied, was found to be nonefficacious and to have no statistical interaction with OMT. Six treatment sessions were provided at weeks 0, 1, 2, 4, 6, and 8. The OMT package was delivered during 15-minute treatment sessions and included soft tissue, articulatory, and high-velocity, low-amplitude techniques. These 3 techniques were agreed to by the osteopathy, chiropractic, and physiotherapy professional associations in the UK Back pain Exercise And Manipulation (UK BEAM) trial.[13] Additionally, our protocol included myofascial release, counterstrain, and muscle energy techniques, as well as other optional techniques if time permitted.[10] Sham OMT involved hand contact, active and passive range of motion, and techniques that simulated OMT but used such maneuvers as light touch, improper patient positioning, purposely misdirected movements, and diminished provider force.[10] This approach has achieved a robust placebo response[14] compared with other placebo treatments for pain[15] and has been adopted elsewhere.[16] The study protocol was approved by the Institutional Review Board at the University of North Texas Health Science Center, and all patients provided written informed consent. The trial was registered with ClinicalTrials.gov (NCT00315120).

Outcome Measures

The primary outcome measure in the OSTEOPATHIC Trial was a 100-mm visual analog scale (VAS) for LBP intensity. Substantial LBP improvement at week 12 (≥50% pain reduction vs baseline)[10-12] was assessed based on recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[17] Back-specific functioning was measured with the Roland-Morris Disability Questionnaire (RMDQ),[18] a legacy measure of limitations in physical functioning attributable to LBP.[9]

Analysis for Cumulative Percentage of Responders to Treatment

We used cumulative percentage of responders analysis[19] to measure and plot treatment response to OMT and sham OMT over the range of outcomes from 0-mm to 100-mm reductions on the VAS and from 0- to 24-point reductions on the RMDQ at week 12. Corresponding analyses were performed and plots constructed for treatment response based on percentage reductions in VAS and RMDQ scores ranging from 0% to 100%. Presenting outcomes in these 4 responder analyses in this manner, without a priori criteria for therapeutic success, has the advantage of comparing treatment groups at responder levels that may be most valid for—and applicable to—differing patient care populations.[19]

Estimation of Cumulative Distribution Functions for Substantial Response to Treatment

We estimated cumulative distribution functions in another 4 responder analyses for the efficacy of OMT based on RRs and numbers-needed-to-treat (NNTs) for substantial improvement in LBP intensity and back-specific functioning. Herein, 2 strategies for targeting patient subgroups for OMT according to baseline VAS and RMDQ scores were compared. The lowest-to-highest (LTH) strategy was assessed by computing and plotting RRs and NNTs according to cumulative baseline VAS scores ranging from 0 mm to 100 mm. This approach was reversed in the highest-to-lowest (HTL) strategy wherein outcomes were determined by cumulative baseline scores ranging from 100 mm to 0 mm. For back-specific functioning, the analyses and plots were based on cumulative baseline RMDQ scores ranging from 0 to 24 (LTH strategy) and from 24 to 0 (HTL strategy). Substantial improvement in back-specific functioning was also defined as a 50% or greater reduction in the RMDQ score vs baseline because this response threshold has been used in multiple trials[8] and was consistent with our threshold for LBP intensity. Using both relative (RR) and absolute (NNT) outcome metrics provided a robust assessment of OMT response. Additionally, the current study focused both on improvements in LBP and related functioning that are important to individual patients and on treatment effects at the population level that are important to policy makers and stakeholders.

Statistical Analysis

Data were summarized as median (interquartile range [IQR]) for continuous variables and as number (%) for categorical variables. Risk ratios and 95% CIs were computed using contingency table methods. The NNTs were computed as the reciprocal of the absolute difference in proportion of substantial improvement with OMT relative to sham OMT and 95% CIs were computed using the Wilson score method.[20] Areas under the curve (down to 0 for percentage of responders and RR, and down to 1 for NNT) and 95% CIs were computed in all analyses. Undefined values of RR or NNT (attributable to small cell sizes and division by 0) were assigned RR=1 (no effect) or NNT=100 (minimal effect). Number-needed-to-treat outcomes greater than 100 or less than 0 were also assigned a score of 100 in computing areas under the curve. The RR and NNT plots comparing the LTH and HTL strategies excluded patients with baseline scores of 10 mm or less or greater than 90 mm on the VAS and with 2 or

less or greater than 21 on the RMDQ to avoid extreme or undefined summary measures attributable to small sample size. These plots were smoothed by using the moving average of cumulative response over successive 10-mm intervals of baseline VAS scores and 3-point intervals of baseline RMDQ scores. In each graph, a treatment or patient subgrouping strategy was considered to dominate the alternative if superior outcomes were observed for all plotted data points. The number at risk of substantial improvement was determined for patient subgroups that demonstrated medium or large treatment effects.

The clinical relevance of RR outcomes was assessed using guidelines established by the Cochrane Back Review Group[21]: RR<1, negative effect or harm; 1≤RR<1.25, small effect; 1.25≤RR≤2, medium effect; and RR>2, large effect. There are no commonly accepted guidelines for interpreting clinical relevance of NNT outcomes because they are sensitive to the level of efficacy of the control group and depend on various study design features, including the outcome measure and how it is dichotomized.[22] Consequently, assessment of the clinical relevance of NNTs was guided by a systematic review of clinical trials wherein oral analgesics were compared with placebo controls using 50% or greater pain reduction as the measure of short-term treatment success.[23] The following guidelines were thus established: NNT≥10, small effect; 5≤NNT<10, medium effect; and 1≤NNT<5, large effect (NNT<0 represents a negative effect or harm). This NNT classification scheme is compatible with the interpretation of RMDQ outcomes in the UK BEAM trial.[24]

Finally, multiple logistic regression was used to compute ORs and 95% CIs for substantial improvements in LBP intensity and back-specific functioning with OMT while simultaneously controlling for patient demographic characteristics, comorbid medical conditions, LBP co-treatments during the trial, and reported adverse events. All analyses were based on intention-to-treat, with missing data imputed using the last-observation-carried-forward method. A sensitivity analysis was performed by repeating all analyses using moderate improvement in LBP intensity and back-specific functioning (≥30% reduction in VAS and RMDQ scores vs baseline) as the threshold for a minimally important change.[25] Hypotheses were tested at the .05 level of statistical significance. Data were managed and analyzed with SPSS software (version 21; IBM), and Microsoft Excel 2010 (Microsoft Corporation) was used to plot cumulative distribution functions.

Results

Patient Characteristics and Overall Study Results

The baseline patient characteristics of the treatment groups were comparable (*Table 1*). The overall study outcomes demonstrated that OMT was efficacious in yielding moderate and substantial improvements in LBP intensity but not in back-specific functioning. Patients who received OMT also reported marginally less frequent use of prescription medications for LBP during the trial.

Cumulative Percentage of Responders

The cumulative percentage of responders analysis demonstrated that OMT dominated sham OMT in achieving percentage improvements in VAS scores for LBP intensity (*Figure 1*). This was further corroborated by significant differences between treatment groups in the corresponding areas under the curve (0.46, 95% CI, 0.42-0.50 for OMT vs 0.34, 95% CI, 0.31-0.38 for sham OMT; $P<.001$). There were also statistical trends favoring OMT for absolute improvement in LBP intensity and percentage improvement in back-specific functioning. These were manifested by greater probability of response with OMT at all VAS absolute reduction thresholds less than 70 mm and at all RMDQ percentage reduction thresholds greater than 22%. Response to OMT was virtually indistinguishable from sham OMT for absolute improvement in back-specific functioning.

Table 1.
Baseline Characteristics of Patients With Chronic Low Back Pain and Study End Outcomes[a] (N=455)

Variables	OMT (n=230)	Sham OMT (n=225)
Baseline Patient Characteristics		
Age, y, median (IQR)	41 (22)	40 (21)
Women	144 (62.6)	140 (62.2)
Current smoker	61 (26.5)	58 (25.8)
Duration of LBP >1 y	118 (51.3)	110 (48.9)
Previous hospitalization or surgery for LBP	16 (7.0)	10 (4.4)
LBP intensity,[b] median (IQR)	44 (36)	45 (33)
Back-specific dysfunction,[c] median (IQR)	5 (6)	5 (7)
Comorbid Medical Conditions		
Hypertension	42 (18.3)	29 (12.9)
Diabetes mellitus	19 (8.3)	15 (6.7)
Osteoarthritis	17 (7.4)	16 (7.1)
Depression	44 (19.1)	46 (20.4)
Co-treatments for LBP During Trial		
Prescription medication[d]	31 (13.5)	46 (20.4)
Nonprescription medication	105 (45.7)	102 (45.3)
Adverse Event Reported During Trial	16 (7.0)	11 (4.9)
Study End		
Moderate improvement in LBP intensity (30% reduction on VAS score)[e]	145 (63.0)	103 (45.8)
Substantial improvement in LBP intensity (50% reduction on VAS score)[f]	114 (49.6)	79 (35.1)
Moderate improvement in back-specific dysfunction (30% reduction on RMDQ score)	129 (56.1)	121 (53.8)
Substantial improvement in back-specific dysfunction (50% reduction on RMDQ score)	115 (50.0)	100 (44.4)

[a] Data are given as No. (%) unless otherwise noted.
[b] The visual analog scale (VAS) is 100 mm, with 0 mm indicating no pain and 100 mm indicating worst possible pain.
[c] The Roland-Morris Disability Questionnaire (RMDQ) is a 24-point scale, with 0 indicating no disability and 24 indicating maximum disability.
[d] $P=.048$
[e] $P<.001$
[f] $P=.002$

Abbreviations: LBP, low back pain; OMT, osteopathic manipulative treatment.

Cumulative Distribution Functions

The cumulative distribution function for RR demonstrated that the HTL strategy for patient subgrouping yielded significantly better OMT outcomes than the LTH strategy in improving LBP intensity and back-specific functioning, including dominance in both plots (*Figure 2*). Medium effect sizes for LBP intensity were observed with the HTL strategy in the overall group of

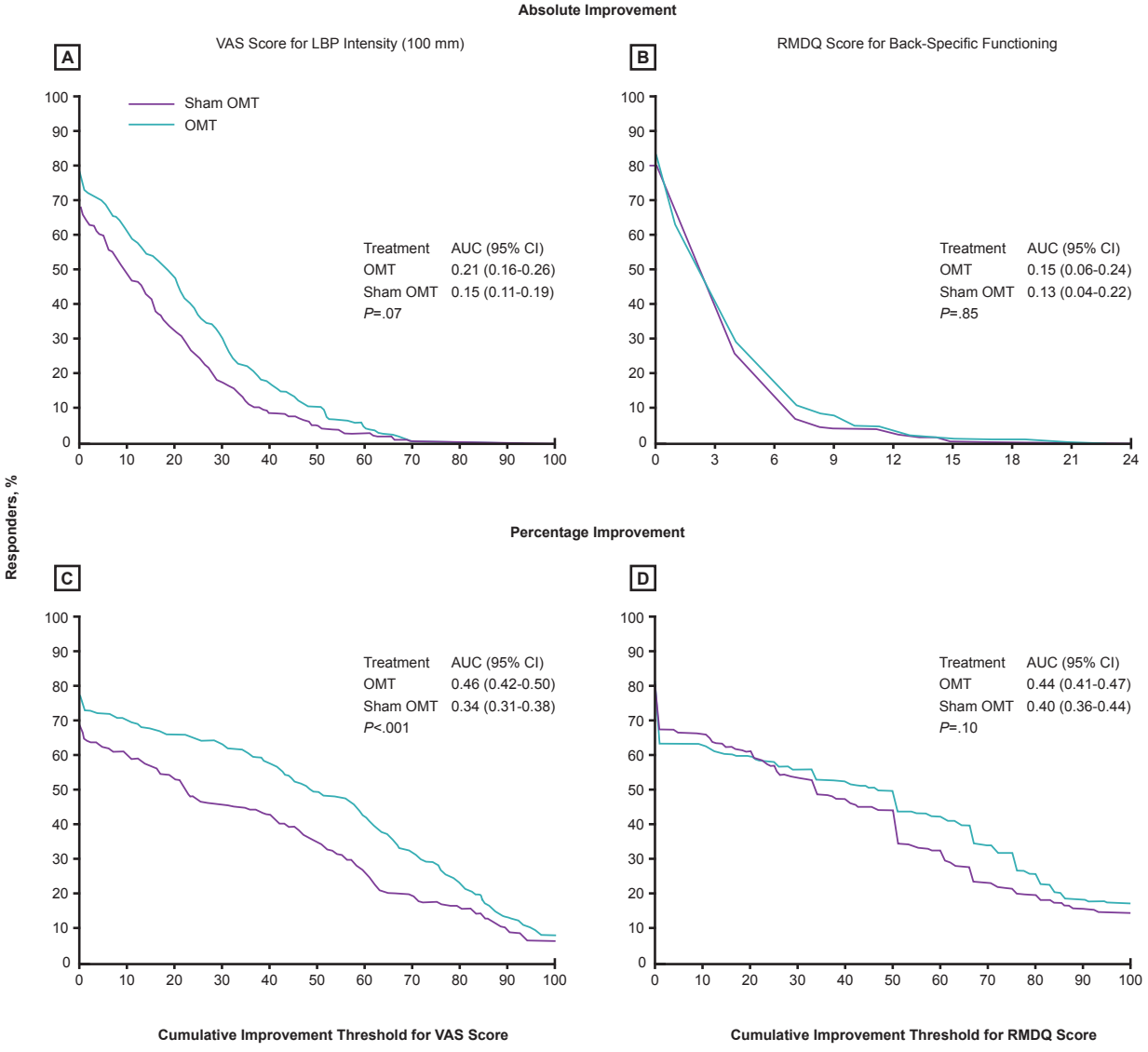
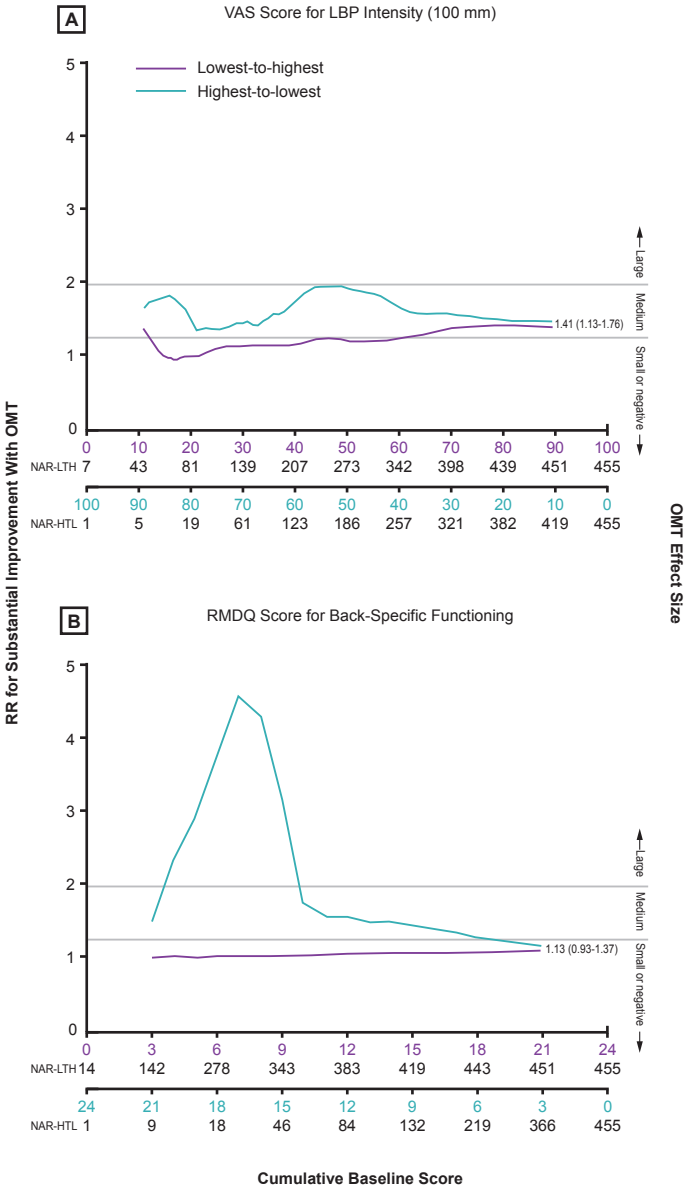


Figure 1.
Cumulative percentage of responders. The data are plotted as the percentage of responders to each treatment for 101 discrete points representing response at cumulative improvement thresholds from 0 mm to 100 mm on the visual analog scale (VAS), and for 25 discrete points representing response at cumulative improvement thresholds from 0 to 24 on the Roland-Morris Disability Questionnaire (RMDQ). Similarly, the percentage of responders is plotted for 101 discrete points representing response at cumulative improvement thresholds from 0% to 100% on the VAS and RMDQ. *Abbreviations*: AUC, area under the curve; LBP, low back pain; OMT, osteopathic manipulative treatment.



455 patients (RR, 1.41; 95% CI, 1.13-1.76; *P*=.002). A large effect size was seen in 186 patients (41%) with VAS scores of 50 mm or greater. The LTH strategy yielded RRs near the threshold for small to medium treatment effects in reducing VAS scores for LBP intensity. Medium effect sizes for back-specific functioning were observed with the HTL strategy in the subgroup of 177 patients (39%) with cumulative baseline RMDQ scores of 7 or greater; however, large OMT effect sizes were observed in 24 patients (5%) with cumulative baseline RMDQ scores of 17 or greater. The LTH strategy yielded RRs near the threshold for very small or negative OMT effect sizes over the entire spectrum of cumulative RMDQ scores.

Similar outcomes for patient subgrouping were observed in the cumulative distribution functions for NNT (*Figure 3*). The HTL strategy yielded substantially better OMT outcomes for LBP intensity and back-specific functioning, including dominance in both plots. Medium effect sizes for LBP intensity were observed in the overall group of 455 patients (NNT, 6.9; 95% CI, 4.3-18.6). Large effect sizes were seen in 294 patients (65%) with cumulative VAS scores of 35 or greater. The LTH strategy yielded OMT effect sizes in the small to moderate range. Medium effect sizes for back-specific functioning were observed with the HTL strategy in 177 patients (39%) with RMDQ scores of 7 or greater. Large OMT effect sizes were seen in 36 patients (8%) with RMDQ scores of 16 or greater. The LTH strategy consis-

Figure 2.
Cumulative distribution functions for the RR for substantial improvement with osteopathic manipulative treatment (OMT). The data are plotted as the RR for alternate strategies for targeting subgroups of patients for treatment according to cumulative baseline severity of symptoms (lowest-to-highest [LTH] vs highest-to-lowest [HTL]). The LTH strategy involved computing and plotting the RR for 101 discrete points representing cumulative baseline visual analog scale (VAS) scores from 0 mm to 100 mm, whereas the HTL strategy was based on scores from 100 mm to 0 mm. For back-specific functioning, the analyses and plots were based on 25 discrete points representing cumulative baseline Roland-Morris Disability Questionnaire (RMDQ) scores from 0 to 24 and from 24 to 0 for the respective strategies. The cumulative number of patients at risk is presented below the x-axis for the corresponding strategy. The RR and 95% CI reported in each plot represent the overall results when the 2 strategies converge to include all 455 patients. Patients with baseline scores 10 mm or less or greater than 90 mm on the VAS, or with 2 or less or greater than 21 on the RMDQ, were not included in the plots to avoid extreme or undefined RRs attributable to small sample size. The plots were smoothed by using the moving average of RRs over successive 10-mm intervals of baseline VAS scores and 3-point intervals of baseline RMDQ scores (this smoothing obscured the large treatment effect observed in 186 patients with baseline VAS scores 50 mm or greater). *Abbreviations*: LBP, low back pain; NAR, number at risk.

tently yielded NNTs representing small or negative OMT effect sizes for back-specific functioning.

A comparison of the cumulative distribution functions for the strategies for targeting patient subgroups for OMT shows that the HTL strategy was clearly superior to LTH (*Table 2*). Using the HTL strategy and our criteria for treatment effect, the NNT cumulative distribution function identified more patients with large treatment effects for LBP intensity (n=294 [65%]) than did the RR cumulative distribution function based on the Cochrane Back Review Group criteria (n=186 [41%]).

Multivariate Analyses

Osteopathic manipulative treatment was the strongest multivariate factor associated with substantial improvement in LBP intensity (OR, 1.84; 95% CI, 1.24-2.72; *P*=.002) (*Table 3*). However, OMT was not associated with substantial improvement in back-specific functioning. Patients who were current cigarette smokers and those aged 50 to 69 years were less likely to experience substantial improvements in LBP intensity and back-specific functioning, respectively. None of the comorbid medical conditions studied, and neither prescription nor nonprescription medication use, was associated with substantial improvements in LBP intensity or back-specific functioning. There was no significant interaction between OMT and any of the categorical variables included in the multiple logistic regression model. The results observed in our sensitivity analysis for moderate improvement

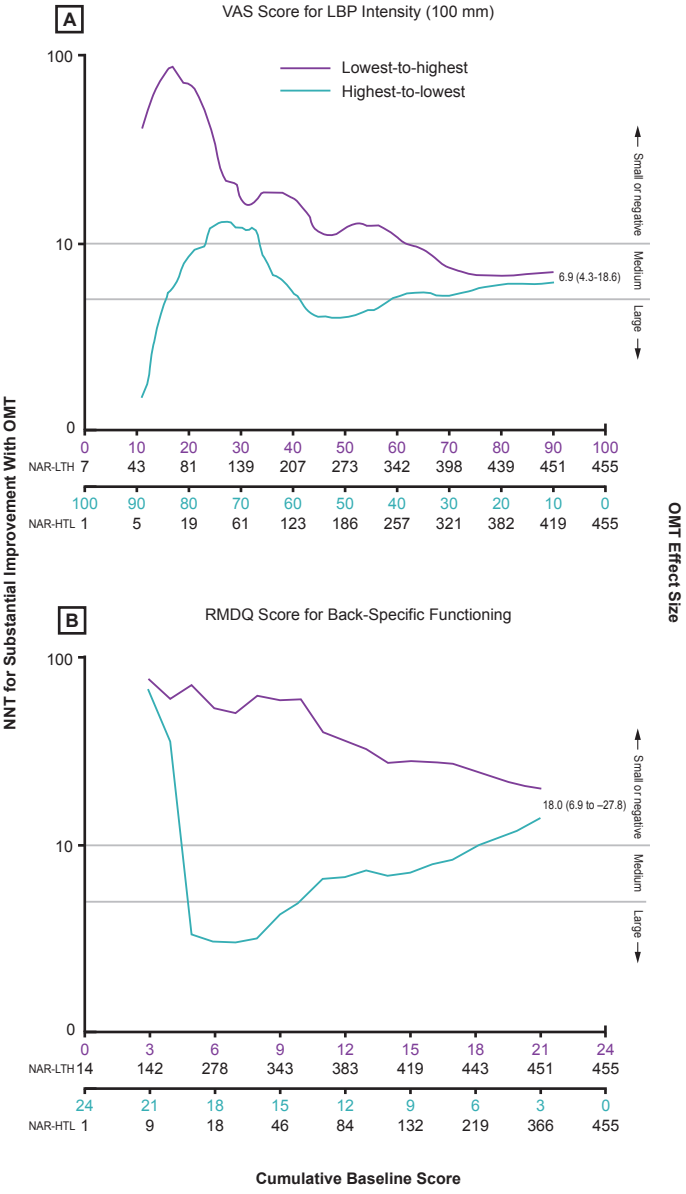


Figure 3.
Cumulative distribution functions for the number-needed-to-treat (NNT) for substantial improvement with osteopathic manipulative treatment (OMT). The data are plotted as the NNT for alternate strategies for targeting subgroups of patients for treatment according to cumulative baseline severity of symptoms (lowest-to-highest [LTH] vs highest-to-lowest [HTL]). The LTH strategy involved computing and plotting the NNT for 101 discrete points representing cumulative baseline visual analog scale (VAS) scores from 0 mm to 100 mm whereas the HTL strategy was based on scores from 100 mm to 0 mm. For back-specific functioning, the analyses and plots were based on 25 discrete points representing cumulative baseline Roland-Morris Disability Questionnaire (RMDQ) scores from 0 to 24 and from 24 to 0 for the respective strategies. The cumulative number of patients at risk is presented below the x-axis for the corresponding strategy. The NNT and 95% CI reported in each plot represent the overall results when the 2 strategies converge to include all 455 patients. The first and second confidence limits represent the range of best to worst NNT, respectively, with negative values indicating harm. Patients with baseline scores 10 mm or less or greater than 90 mm on the VAS, or with 2 or less or greater than 21 on the RMDQ, were not included in the plots to avoid extreme or undefined NNTs attributable to small sample size. The plots were smoothed by using the moving average of NNTs over successive 10-mm intervals of baseline VAS scores and 3-point intervals of baseline RMDQ scores. *Abbreviations*: LBP, low back pain; NAR, number at risk.

Table 2.
Comparison of Strategies for Targeting Patient Subgroups for Substantial Improvement With Osteopathic Manipulative Treatment (N=455)

	Medium Effect Size		Large Effect Size			*P* Value for	
Outcomes	Threshold for Response	No. At Risk (%)	Threshold for Response	No. at Risk (%)	AUC (95% CI)[a]	AUC Difference	Dominance
LBP Intensity[b]							
RR							
LTH	≥0 mm	455 (100)	≤4 mm	16 (4)	0.25 (0.24-0.26)	<.001	HTL
HTL	≥0 mm	455 (100)	≥50 mm	186 (41)	0.31 (0.30-0.33)		
NNT							
LTH	≥0 mm	455 (100)	…	…	0.20 (0.15-0.25)	<.001	HTL
HTL	≥0 mm	455 (100)	≥35 mm	294 (65)	0.07 (0.04-0.10)		
Back-Specific Functioning[c]							
RR							
LTH	…	…	…	…	0.21 (0.21-0.22)	.002	HTL
HTL	≥7	177 (39)	≥17	24 (5)	0.37 (0.27-0.47)		
NNT							
LTH	…	…	…	…	0.41 (0.30-0.53)	.007	HTL
HTL	≥7	177 (39)	≥16	36 (8)	0.19 (0.06-0.31)		

[a] The area under the curve (AUC) was computed using RRs or numbers-needed-to-treat (NNTs) over the entire range of cumulative baseline scores. Smaller AUCs represent better outcomes for NNT.
[b] The visual analog scale (VAS) is 100 mm, with 0 mm indicating no pain and 100 mm indicating worst possible pain.
[c] The Roland-Morris Disability Questionnaire (RMDQ) is a 24-point scale, with 0 indicating no disability and 24 indicating maximum disability.

Abbreviations: HTL, highest-to-lowest strategy; LBP, low back pain; LTH, lowest-to-highest strategy.

Table 3.
Multivariate Risk of Substantial Improvement in Chronic Low Back Pain (N=455)

	LBP Intensity[a]			Back-Specific Functioning[b]		
Variables	**No. (%)[c]**	**OR[d] (95% CI)**	***P* Value**	**No. (%)[c]**	**OR[d] (95% CI)**	***P* Value**
Baseline Patient Characteristics						
Age, y						
21-34	75 (45.5)	1	…	88 (53.3)	1	…
35-49	67 (40.9)	1.09 (0.68-1.76)	.72	82 (50.0)	1.01 (0.63-1.61)	.96
50-69	51 (40.5)	1.05 (0.60-1.85)	.87	45 (35.7)	0.55 (0.31-0.96)	.03
Sex						
Men	76 (44.4)	1	…	89 (52.0)	1	…
Women	117 (41.2)	0.95 (0.62-1.44)	.80	126 (44.4)	0.85 (0.56-1.28)	.43
Current smoker						
No	152 (45.2)	1	…	164 (48.8)	1	…
Yes	41 (34.5)	0.61 (0.38-0.98)	.04	51 (42.9)	0.83 (0.53-1.31)	.43
Duration of LBP >1 Year						
No	107 (47.1)	1	…	110 (48.5)	1	…
Yes	86 (37.7)	0.69 (0.47-1.03)	.07	105 (46.1)	1.07 (0.73-1.58)	.73
Previous hospitalization or surgery for LBP						
No	186 (43.4)	1	…	204 (47.6)	1	…
Yes	7 (26.9)	0.45 (0.17-1.17)	.10	11 (42.3)	1.10 (0.46-2.65)	.83
Comorbid Medical Conditions						
Hypertension						
No	161 (41.9)	1	…	184 (47.9)	1	…
Yes	32 (45.1)	1.53 (0.83-2.82)	.17	31 (43.7)	1.38 (0.76-2.53)	.29
Diabetes mellitus						
No	180 (42.8)	1	…	204 (48.5)	1	…
Yes	13 (38.2)	0.93 (0.41-2.11)	.86	11 (32.4)	0.72 (0.32-1.65)	.44

(continued)

(ie, minimally important change), including the cumulative distribution functions for RR and NNT and the multivariate analyses for improvement in LBP intensity and back-specific functioning, were generally comparable to those reported herein for substantial improvement.

Discussion

The OSTEOPATHIC Trial has previously shown that OMT is efficacious in achieving reductions in LBP intensity that meet the criteria for both substantial improvement and minimally important change.[10] The present responder analysis now indicates that patient subgroups may be targeted for response to OMT according to their baseline levels of LBP intensity and back-specific functioning. Extrapolating to the general population of patients with chronic LBP, our results suggest that sizeable subgroups of patients, perhaps as many as two-thirds, may be targeted for large treatment effects in substantially reducing LBP intensity. Correspondingly, about

Table 3 (continued).
Multivariate Risk of Substantial Improvement in Chronic Low Back Pain (N=455)

	LBP Intensity[a]			Back-Specific Functioning[b]		
Variables	**No. (%)[c]**	**OR[d] (95% CI)**	***P* Value**	**No. (%)[c]**	**OR[d] (95% CI)**	***P* Value**
Osteoarthritis						
No	183 (43.4)	1	…	204 (48.3)	1	…
Yes	10 (30.3)	0.64 (0.28-1.47)	.29	11 (33.3)	0.78 (0.35-1.74)	.54
Depression						
No	164 (44.9)	1	…	184 (50.4)	1	…
Yes	29 (32.2)	0.73 (0.42-1.30)	.29	31 (34.4)	0.63 (0.36-1.09)	.10
OMT						
Sham	79 (35.1)	1	…	100 (44.4)	1	…
Active	114 (49.6)	1.84 (1.24-2.72)	.002	115 (50.0)	1.28 (0.87-1.88)	.21
Co-treatments for LBP During Trial						
Prescription medication						
No	170 (45.0)	1	…	188 (49.7)	1	…
Yes	23 (29.9)	0.75 (0.41-1.39)	.36	27 (35.1)	0.79 (0.43-1.42)	.43
Nonprescription medication						
No	115 (46.4)	1	…	124 (50.0)	1	…
Yes	78 (37.7)	0.74 (0.49-1.12)	.15	91 (44.0)	0.90 (0.60-1.36)	.61
Adverse Event Reported During Trial						
No	182 (42.5)	1	…	206 (48.1)	1	…
Yes	11 (40.7)	1.18 (0.49-2.82)	.71	9 (33.3)	0.66 (0.27-1.59)	.35

[a] The visual analog scale (VAS) is 100 mm, with 0 mm indicating no pain and 100 mm indicating worst possible pain.
[b] The Roland-Morris Disability Questionnaire (RMDQ) is a 24-point scale, with 0 indicating no disability and 24 indicating maximum disability.
[c] The No. (%) represent those with the given characteristic among the 193 and 215 patients, respectively, who achieved substantial improvement in low back pain (LBP) intensity and back-specific functioning.
[d] The ORs are adjusted for the baseline values of LBP intensity and back-specific functioning and for each variable in the table. Baseline values of LBP and back-specific functioning were not significantly associated with substantial improvement in either outcome.

Abbreviation: OMT, osteopathic manipulative treatment.

four-tenths of patients may be targeted for medium treatment effects in substantially improving back-specific functioning with OMT.

To our knowledge, the OSTEOPATHIC Trial is the first major trial that has implemented the recommendation of the National Institutes of Health Task Force on Research Standards for Chronic Low Back Pain to report cumulative distribution functions of responses in treatment and control groups.[9] The present study demonstrates the feasibility of cumulative distribution functions for the RR and NNT as summary measures of efficacy with which to target patients with chronic LBP for a short course of OMT. The NNT emerged as a metric that may be used to supplement the more commonly used summary measures of efficacy. It may serve as a sensitive indicator of patient subgroups likely to experience reductions in LBP intensity with OMT as more standardized criteria for NNT interpretation in pain trials emerge. The use of the VAS and RMDQ and widely accepted thresholds of 30% and 50% reduction

for moderate and substantial improvement, respectively, facilitates corroboration of our findings and implementation in clinical practice.

The OSTEOPATHIC Trial is the largest single-site efficacy trial of spinal manipulation for chronic LBP based on a comparison with 26 trials reported in the Cochrane Review, including chiropractic and physical therapy studies.[5] Although focusing on efficacy facilitated tighter control of experimental design, our trial exhibited several pragmatic features that enhance the generalizability of its findings. These included limited exclusion criteria (eg, no thresholds for LBP intensity or back-specific functioning), clinically meaningful outcomes for patients, and intention-to-treat analysis.[26] Moreover, the OMT protocol included the 3 techniques commonly used by chiropractors, foreign-trained osteopaths, and physiotherapists, as agreed to in the UK BEAM trial.[13] The multivariate results and absence of interaction effects further suggest that OMT efficacy may not vary significantly according to such factors as patient demographic characteristics, LBP features, comorbid medical conditions, and use of prescription or nonprescription medication for LBP.

There are several potential limitations of our study. First, responder analysis was not planned when our trial was initially developed over 10 years ago. These a posteriori subgroup analyses were based on patient characteristics established before randomization. Hence, they are less vulnerable to biases than analyses based on variables derived after randomization. Nevertheless, it is possible that confounding variables may no longer have been distributed at random in the subgroups,[27] particularly in those with smaller numbers of patients at risk. Second, we used the last-observation-carried-forward to impute missing data. While other methods for data imputation have been used in the OSTEOPATHIC Trial, they have not yielded materially different results.[10,28] Third, the NNT is not widely used and reported as a measure of efficacy and, unlike the RR, there are no established guidelines for its interpretation in LBP research.[21]

Conclusion

The increasing use of magnetic resonance imaging, opioid prescribing, epidural steroidal injections, and spinal surgery has not improved outcomes or disability rates in patients with chronic LBP.[29] Our results indicate that OMT is more efficacious in treating chronic LBP than previously reported in the latest Cochrane review of spinal manipulation,[5] particularly in patient subgroups that may be easily identified by their baseline levels of LBP intensity. Thus, it appears reasonable to target the patient subgroups identified herein for a short course of OMT before proceeding to such other interventions. Patients with greater LBP intensity may represent an ideal population to target for OMT because they are most likely to accept the risks and costs of more invasive procedures such as lumbar surgery.[30] Additional research may also be warranted to explore how the subgroup findings reported herein may be combined with other subgrouping approaches to more effectively target patients with chronic LBP for treatment.

Author contributions

All authors provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Dr Licciardone drafted the article and revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published; and Dr Licciardone agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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