図　試験の流れ図

		適格性を評価する 1 回目ベースライン評価（n=504）		
			除外（n=165） 組入基準を満たさなかった：126 参加拒否：35 その他：4	
		適格性を評価する 1 回目ベースライン評価（n=339）		
			除外（n=67） 組入基準を満たさなかった：10 参加拒否：32 その他：25	
		無作為割り当て（n=272）		
SMT 群に割り当て（n=91） 治療実施：91		投薬治療群に割り当て（n=91） 治療実施：84 治療を実施せず：6 参加拒否：5 家族の問題および副作用の懸念：1		HEA 群に割り当て（n=91） 治療実施：91

介入段階 追跡不能例（n=3） 2 週目：0 4 週目：1 8 週目：1 12 週目：1 治療中止（n=2） 改善なし=:1 参加拒否：1 介入段階後 追跡不能例（n=21） 26 週目：7 52 週目：14		介入段階 追跡不能例（n=21） 2 週目：4 4 週目：5 8 週目：6 12 週目：6 治療中止（n=3） 妊娠=:1 参加拒否：2 介入段階後 追跡不能例（n=31） 26 週目：12 52 週目：19		介入段階 追跡不能例（n=13） 2 週目：2 4 週目：3 8 週目：4 12 週目：4 治療中止（n=3） 参加拒否：3 介入段階後 追跡不能例（n=22） 26 週目：10 52 週目：12
解析（n=91）		解析（n=90）		解析（n=91）

参加者が各タイムポイントでデータを提供しなかった場合には、追跡不能とした。治療を中止した患者は、追跡データを提供する機会があった。HEA=助言を伴う在宅運動；SMT=脊椎マニピュレーション療法。

表１　ベースライン時の人口学的特徴および臨床的特徴

特徴	SMT 群	投薬治療群	HEA 群
参加者数、 n			
平均年齢（SD)、年			
女性、%			
既婚または誰かと同居、%			
大学卒業者、%			
現在の喫煙者、%			
平均肥満度指数（SD)、kg/m²			
平均頸部疼痛期間（SD)、週間			
頸部疼痛の頻度（SD）*			
上肢への疼痛の放射、%			
頸部疼痛のため夜目覚める、%			
報告された頸部疼痛の原因			
外傷			
自動車事故			
余暇での事故			
業務上の事故			
明らかな原因足			
思い出せない			

その他†			
抑鬱の CES-D（SD）‡			
疼痛の変化に対する期待§			

CES-D=疫学研究用うつ病尺度；HEA=助言を伴う在宅運動；SMT=脊椎マニピュレーション療法。

＊　0（全く無い）から 5（常時）までの尺度で。

†　例えば、反復運動、ストレス、または睡眠時の姿勢。

‡　0 から 100 までの尺度で。

§　0（以前よりずっ良い状態）から 5（以前よりずっと悪い状態）までの尺度で。

表２　介入の詳細

集団と特徴	値
SMT 群	
参加者数、n	
平均来院回数（範囲）、n	
介入の具体的特徴、n（%）	
頸部 SMT	
胸部 SMT	
軟組織	
補助付きのストレッチ	
温パック	

冷パック	
処方薬	
投薬治療群	
参加者数、n	
平均来院回数（範囲）、n	
介入の具体的特徴、n（%）	
NSAID、オピオイド鎮痛薬、および筋弛緩剤	
NSAID、およびオピオイド鎮痛薬	
NSAID、および筋弛緩剤	
オピオイド鎮痛薬、および筋弛緩剤	
筋弛緩剤のみ	
HEA 群	
参加者数、n	
平均来院回数（範囲）、n	
介入の具体的特徴、n（%）	
運動指導	
教育（例えば、脊椎の構造）	
セルフケアに関する助言（例えば、疼痛管理）	
ADL に付いての指導（例えば、リフティング）	

処方薬	

ADL=日常生活動作；HEA=助言を伴う在宅運動；NSAID=非ステロイド系抗炎症薬；SMT=脊椎マニピュレーション療法。

表３　参加者自身の評価による疼痛におけるベースライからの変化の群間差

変数	SMT 群（n=91）	投薬治療群（n=90）	HEA 群（n=91）	群間差（95% CI）					
				SMT 群−投薬治療群	*P*値	SMT 群−HEA 群	*P*値	HEA 群−投薬治療群	*P*値
疼痛スコア*									
0 週目の平均疼痛スコア（SD）									
2 週目									
平均疼痛スコア（SD）									
0 週目からの平均変化（95% CI）									
4 週目									
平均疼痛スコア（SD）									
0 週目からの平均変化（95% CI）									
8 週目									
平均疼痛スコア（SD）									
0 週目からの平均変化（95% CI）									
12 週目									
平均疼痛スコア（SD）									

0 週目からの平均変化（95% CI）									
0 週目からの平均短期変化（95% CI）†									
26 週目									
平均疼痛スコア（SD）									
0 週目からの平均変化（95% CI）									
52 週目									
平均疼痛スコア（SD）									
0 週目からの平均変化（95% CI）									
0 週目からの平均長期変化‡									
疼痛の絶対的低下の割合									
12 週目									
≧50%低下									
≧75%低下									
100%低下									
26 週目									
≧50%低下									
≧75%低下									
100%低下									
52 週目									

≧50%低下									
≧75%低下									
100%低下									

HEA=助言を伴う在宅運動；SMT=脊椎マニピュレーション療法。

＊　0（頸部疼痛なし）から 10（考えられる最悪の頸部疼痛）までの尺度で。

†　2 週目、4 週目、8 週目、および 12 週目のデータに基づく群間差。

‡　2 週目、4 週目、8 週目、12 週目、26 週目、および 52 週目のデータに基づく群間差。

補足表 1　参加者自身の評価による頸部障害指標と薬剤使用におけるベースラインからの変化の群間差

変数	SMT 群	投薬治療群	HEA 群	群間差（95% CI）					
	（n=91）	（n=90）	（n=91）	SMT 群−投薬治療群	*P* 値	SMT 群−HEA 群	*P* 値	HEA 群−投薬治療群	*P* 値
頸部障害指標*									
0 週目の平均スコア（SD）									
2 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
4 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
8 週目									

平均スコア（SD）									
0 週目からの平均変化（95% CI）									
12 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
平均短期スコア †									
26 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
52 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
平均長期スコア ‡									
薬剤使用期間、日 §									
0 週目の平均（SD）									
2 週目									
平均（SD）									
0 週目からの平均変化（95% CI）									
4 週目									
平均（SD）									

0 週目からの平均変化（95% CI）									
8 週目									
平均（SD）									
0 週目からの平均変化（95% CI）									
12 週目									
平均（SD）									
0 週目からの平均変化（95% CI）									
平均短期使用期間†									
26 週目									
平均（SD）									
0 週目からの平均変化（95% CI）									
52 週目									
平均（SD）									
0 週目からの平均変化（95% CI）									
平均長期使用期間‡									

HEA=助言を伴う在宅運動；NA=該当なし；SMT=脊椎マニピュレーション療法。

＊　頸部疼痛に関連した 10 項目を含むアンケート。各項目を 0（障害なし）から 10（最大の障害）までの尺度で評価し、50 点満点のスコア合計を百分率点（0-100）に変換する。

†　2 週目、4 週目、8 週目、および 12 週目のデータに基づく群間差。

‡　2 週目、4 週目、8 週目、12 週目、26 週目、および 52 週目のデータに基づく群間差。

§　頸部疼痛に対して参加者が非処方薬または市販薬を服用した、1 週間のうちの日数（0 から 7 日）。最初の 12 週間は介入処方されていたため、短期または長期には投

薬治療群との比較は適応されない。

補足表２　参加者自身の評価による全体的改善と満足の群間差

変数	SMT 群	投薬治療群	HEA 群	群間差（95% CI）					
	（n=91）	（n=90）	（n=91）	SMT 群−投薬治療群	*P*値	SMT 群−HEA 群	*P*値	HEA 群−投薬治療群	*P*値
全体的改善スコアの平均（95% CI）†									
2 週目									
4 週目									
8 週目									
12 週目									
短期‡									
26 週目									
52 週目									
長期§									
満足度スコアの平均（95% CI）‖									
2 週目									
4 週目									
8 週目									
12 週目									
短期‡									

26 週目									
52 週目									
長期 §									

HEA=助言を伴う在宅運動；NA=該当なし；SMT=脊椎マニピュレーション療法。

＊　正の値は比較の第 1 の群を支持し、負の値は第 2 の群を支持する。

†　1（100%改善）から 5（0%改善）、10（100%悪化）までの 9 段階の尺度で測定した頸部疼痛の改善。

‡　2 週目、4 週目、8 週目、および 12 週目のデータに基づく群間差。

§　2 週目、4 週目、8 週目、12 週目、26 週目、および 52 週目のデータに基づく群間差。

頸部疼痛に対して参加者が非処方薬または市販薬を服用した、1 週間のうちの日数（0 から 7 日）。最初の 12 週間は介入処方されていたため、短期または長期には投薬治療群との比較は適応されない。

‖　1（これ以上はないほど完全に満足）から 4（満足でも不満足でもない））、7（これ以下はないほど完全に不満足）までの 7 段階の尺度で測定した治療による満足度。

補足表 3　SF-36 の身体的要素および精神的的要素のスコアにおけるベースラインからの変化の群間差*

SF-36 スコア	SMT 群	投薬治療群	HEA 群	群間差（95% CI）					
	（n=91）	（n=90）	（n=91）	SMT 群−投薬治療群	*P*値	SMT 群−HEA 群	*P*値	HEA 群−投薬治療群	*P*値
身体的要素									
0 週目の平均スコア（SD）									
2 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									

4 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
8 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
12 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
平均短期スコア †									
26 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
52 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
平均長期スコア ‡									
身体的要素									
0 週目の平均スコア（SD）									
2 週目									

平均スコア（SD）									
0 週目からの平均変化（95% CI）									
4 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
8 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
12 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
平均短期スコア †									
26 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
52 週目									
平均スコア（SD）									
0 週目からの平均変化（95% CI）									
平均長期スコア ‡									

HEA=助言を伴う在宅運動；NA=該当なし；SMT=脊椎マニピュレーション療法。

＊　スコアは、標準に基づく、50 の平均による線形 T スコア変換を用いた（SD, 10）。

† 2週目、4週目、8週目、および12週目のデータに基づく群間差。

‡ 2週目、4週目、8週目、12週目、26週目、および52週目のデータに基づく群間差。

補足表4 頸部可動域のベースラインからの変化の群間差*

頸部可動域	SMT群 (n=91)	投薬治療群 (n=90)	HEA群 (n=91)	群間差（95% CI）					
				SMT群−投薬治療群	*P*値	SMT群−HEA群	*P*値	HEA群−投薬治療群	*P*値
身体的要素									
屈曲と伸展†									
平均角度（SD）									
4週目									
平均角度（SD）									
0週目からの平均変化（95% CI）									
12週目									
平均角度（SD）									
0週目からの平均変化（95% CI）									
回旋‡									
平均角度（SD）									
4週目									
平均角度（SD）									

0 週目からの平均変化（95% CI）									
12 週目									
平均角度（SD）									
0 週目からの平均変化（95% CI）									
側屈§									
平均角度（SD）									
4 週目									
平均角度（SD）									
0 週目からの平均変化（95% CI）									
12 週目									
平均角度（SD）									
0 週目からの平均変化（95% CI）									

HEA=助言を伴う在宅運動；NA=該当なし；SMT=脊椎マニピュレーション療法。

＊　正常範囲の推定値は、参考文献 36 および 37 に基づいた。

†　正常範囲：110 ～ 120 度

‡　正常範囲：150 ～ 160 度

§　正常範囲：70 ～ 80 度

補足表 5　12 週間の治療期間中の有害事象*

事象	SMT 群 （n=91）	投薬治療群 （n=90）	HEA 群 （n=91）	群間差（95% CI）		
				SMT 群−投薬治療群	SMT 群−HEA 群	HEA 群−投薬治療群
疼痛の悪化						
頭痛						
凝り						
特定されず						
知覚異常						
吐き気						
捻髪音						
血圧の上昇						
緊張性尿失禁						
睡眠障害						
鬱血						
発疹						
認知症状						
口の乾燥						
胃腸症状						
眠気						
合計						

HEA=助言を伴う在宅運動；NA=該当なし；SMT=脊椎マニピュレーション療法。

＊　データは有害事象の数（パーセンテージ）である。治療の過程で 1 件以上の事象を報告した参加者。参加者は 1 種類上の事象を報告することができた。

† この群の 6 人の参加者は治療を受けたかったため解析から除外した。

Annals of Internal Medicine | ORIGINAL RESEARCH

Spinal Manipulation, Medication, or Home Exercise With Advice for Acute and Subacute Neck Pain

A Randomized Trial

Gert Bronfort, DC, PhD; Roni Evans, DC, MS; Alfred V. Anderson, DC, MD; Kenneth H. Svendsen, MS; Yiscah Bracha, MS; and Richard H. Grimm, MD, MPH, PhD

Background: Mechanical neck pain is a common condition that affects an estimated 70% of persons at some point in their lives. Little research exists to guide the choice of therapy for acute and subacute neck pain.

Objective: To determine the relative efficacy of spinal manipulation therapy (SMT), medication, and home exercise with advice (HEA) for acute and subacute neck pain in both the short and long term.

Design: Randomized, controlled trial. (ClinicalTrials.gov registration number: NCT00029770)

Setting: 1 university research center and 1 pain management clinic in Minnesota.

Participants: 272 persons aged 18 to 65 years who had nonspecific neck pain for 2 to 12 weeks.

Intervention: 12 weeks of SMT, medication, or HEA.

Measurements: The primary outcome was participant-rated pain, measured at 2, 4, 8, 12, 26, and 52 weeks after randomization. Secondary measures were self-reported disability, global improvement, medication use, satisfaction, general health status (Short Form-36 Health Survey physical and mental health scales), and adverse events. Blinded evaluation of neck motion was performed at 4 and 12 weeks.

Results: For pain, SMT had a statistically significant advantage over medication after 8, 12, 26, and 52 weeks ($P \leq 0.010$), and HEA was superior to medication at 26 weeks ($P = 0.02$). No important differences in pain were found between SMT and HEA at any time point. Results for most of the secondary outcomes were similar to those of the primary outcome.

Limitations: Participants and providers could not be blinded. No specific criteria for defining clinically important group differences were prespecified or available from the literature.

Conclusion: For participants with acute and subacute neck pain, SMT was more effective than medication in both the short and long term. However, a few instructional sessions of HEA resulted in similar outcomes at most time points.

Primary Funding Source: National Center for Complementary and Alternative Medicine, National Institutes of Health.

Ann Intern Med. 2012;156:1-10. www.annals.org
For author affiliations, see end of text.

Neck pain is a prevalent condition that nearly three quarters of persons experience at some point in their lives (1, 2). One of the most commonly reported symptoms in primary care settings (3, 4), neck pain results in millions of ambulatory health care visits each year and increasing health care costs (5–8). Although it is not life-threatening, neck pain can have a negative effect on productivity and overall quality of life (1, 9–11).

Chiropractors, physical therapists, osteopaths, and other health care providers commonly apply spinal manipulation, a manual therapy, for neck pain conditions (12), and home exercise programs and medications are also widely used (13). Recent Cochrane reviews (13, 14) report insufficient evidence to assess the effectiveness of commonly used medications or home exercise programs for the treatment of acute neck pain. The evidence for spinal manipulation is similarly limited, with only low-quality evidence supporting its use for neck pain of short duration (15).

Our goal was to test the hypothesis that spinal manipulation therapy (SMT) is more effective than medication or home exercise with advice (HEA) for acute and subacute neck pain.

METHODS

Setting

The trial was conducted from 2001 to 2007 in Minneapolis, Minnesota. Eligibility screening, randomization, and short-term data collection occurred at a university-affiliated research center; long-term data collection took place by mail. A university-affiliated outpatient clinic provided SMT and instruction for home exercise. Medical treatment was provided at a pain management clinic. The institutional review boards of Northwestern Health Sciences University and Hennepin County Medical Center

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Conversion of graphics into slides

Context

Persons with acute or subacute neck pain often turn to chiropractors and other practitioners of spinal manipulation for pain relief.

Contribution

This trial demonstrates that 12 weeks of spinal manipulation therapy (SMT) led to greater pain relief than medication up to 1 year after treatment. However, trial participants had as much pain relief with home exercise with advice (HEA) as with SMT over the same period.

Caution

Participants were unblinded to interventions.

Implication

For relief of acute or subacute neck pain, SMT and HEA seemed to be similarly effective and both were more effective than medication.

—The Editors

approved our study, and all participants gave written informed consent.

Participants

Participants were recruited by using mailings targeted to persons with neck pain who were registered with Blue Cross/Blue Shield Minnesota and through newspaper and radio advertisements. Interested persons were screened for eligibility at 2 baseline appointments by clinicians who were blinded to the randomization schedule. Inclusion criteria were age 18 to 65 years; primary symptom of mechanical, nonspecific neck pain equivalent to grades I or II according to the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders classification (16, 17); current neck pain of 2 to 12 weeks' duration; and a neck pain score of 3 or greater on a scale of 0 to 10. Participants were asked to refrain from seeking additional treatment for neck pain from nonstudy health care providers during the 12-week intervention.

Exclusion criteria were cervical spine instability, fracture, neck pain referred from peripheral joints or viscera, progressive neurologic deficits, existing cardiac disease requiring medical treatment, blood clotting disorders, diffuse idiopathic hyperostosis, inflammatory or destructive tissue changes of the cervical spine, infectious disease or other severe disabling health problems, substance abuse, pregnancy or breastfeeding, previous cervical spine surgery, and pending or current litigation. In addition, participants were excluded if they had received any of the study treatments in the past 3 months.

Randomization and Interventions

Participants were randomly assigned at the second baseline appointment by using permutated blocks of different sizes (18). The randomization schedule was prepared off-site by the study statistician before enrollment and was concealed from the investigators, treatment providers, and research staff by using consecutively numbered, sealed, opaque envelopes. As participants became eligible, envelopes were opened in consecutive order by a research staff member in the presence of the participant.

The intervention protocol was tested in a pilot study by our research team (19). Maximum treatment duration was 12 weeks. Treatment providers were trained in the study intervention protocols and were required to document treatment activities in standardized clinical records, which were routinely monitored by research staff to ensure protocol adherence.

SMT Group

Six chiropractors with a minimum of 5 years' experience served as the primary providers of treatment. Visits lasted 15 to 20 minutes and included a brief history and examination of the cervical and thoracic spine. The primary focus of treatment was manipulation of areas of the spine with segmental hypomobility by using diversified techniques, including low-amplitude spinal adjustments (a high-velocity type of joint thrust manipulation) and mobilization (a low-velocity type of joint oscillation) (20). The specific spinal level to be treated and the number of treatment sessions over the 12 weeks was left to the discretion of the provider, based on manual palpation of the spine and associated musculature and the participant's response to treatment (21). Adjunct therapy common to clinical practice included limited light soft-tissue massage, assisted stretching, and hot and cold packs to facilitate the manipulation treatment. Advice to stay active or modify activity was recommended as needed.

Medication Group

A licensed medical physician provided care to participants, with the focus of treatment on prescription medication. Visits lasted 15 to 20 minutes and included a brief history and examination. The first line of therapy was nonsteroidal anti-inflammatory drugs, acetaminophen, or both (22, 23). Participants who did not respond to or could not tolerate first-line therapy received narcotic medications. Muscle relaxants were also used. Advice to stay active or modify activity was issued as needed. The choice of medications and number of visits was made by the physician on the basis of the participant's history and response to treatment.

HEA Group

Home exercise with advice was provided in two 1-hour sessions, 1 to 2 weeks apart, at the university-affiliated outpatient clinic. Six therapists provided instruction to participants. The primary focus was simple self-mobilization exercise (gentle controlled movement) of the neck and shoulder joints, including neck retraction, exten-

sion, flexion, rotation, lateral bending motions, and scapular retraction, with no resistance (**Supplement**, available at www.annals.org). The delivery method was 1-on-1, and the program was individualized to each participant's abilities, tolerance, and activities of daily living. Participants were instructed to do 5 to 10 repetitions of each exercise up to 6 to 8 times per day. A booklet (24) and laminated cards of prescribed exercises were provided. Sessions were supplemented with information about the basic anatomy of the cervical spine and advice, including postural instructions and practical demonstrations of lifting, pushing, pulling, and other daily actions.

Outcomes and Measurements

We collected participant demographic and clinical characteristics at the initial baseline appointment by using self-report questionnaires, clinical history, and physical examinations. Self-reported outcomes (such as pain) were measured 6 times during the 12-week treatment period (at the 2 baseline appointments and 2, 4, 8, and 12 weeks after randomization). Outcomes were also collected twice during the posttreatment period (at weeks 26 and 52) by using a mailed questionnaire. All self-report questionnaires were completed by participants independent of influence from investigator, study staff, or treatment provider. Participants were asked in each questionnaire if anyone had attempted to influence their responses. Objective measures of cervical spine motion were measured at 4 and 12 weeks by 7 trained examiners who were masked to treatment assignment (25). Blinding was maintained by systematically instructing participants not to reveal treatment information and by ensuring that examiners had no exposure to activities in the outpatient clinics.

We chose participant-rated pain as the primary outcome measure a priori and used an 11-box numerical rating scale (range, 0 [no symptoms] to 10 [highest severity of pain]) (26–29). Secondary outcomes included the Neck Disability Index (30), global improvement (31–33), medication use (34), satisfaction with care (25, 34), the Short Form-36 Health Survey (SF-36) (35), and cervical spine motion (measured with a CA 6000 Spine Motion Analyzer [Orthopedic Systems, Union City, California]) (36, 37).

Before random assignment, participants were asked in the self-report questionnaire how they expected their neck pain to change in response to treatment, with choices of much better, better, no change, worse, and much worse. Participants were also asked to report additional health care use visits to nonstudy providers in the self-report questionnaires at all time points.

Participants were asked standardized questions at each treatment visit to assess side effects since the last visit, and responses were documented in the clinical record.

Statistical Analysis

Our sample size calculation was based on an ability to detect a 0.8-point difference between the highest and lowest group means in participant-rated neck pain (the primary outcome) at the end of 12 weeks of treatment. This difference was informed by previous neck pain trials conducted by our group (19, 25) and the ability to detect a small to medium effect size. We used an SD of 1.8 for our pain scale on the basis of our pilot study and estimates from the literature (25, 38). With a power of 0.90 and a 3-group design tested at an α level of 0.05 (2-tailed test), 75 participants per group were required (SPSS SamplePower 1.0, International Business Machines, Armonk, New York). To allow for a loss to follow-up rate of up to 15%, we aimed to recruit 90 participants per group for a total of 270 participants.

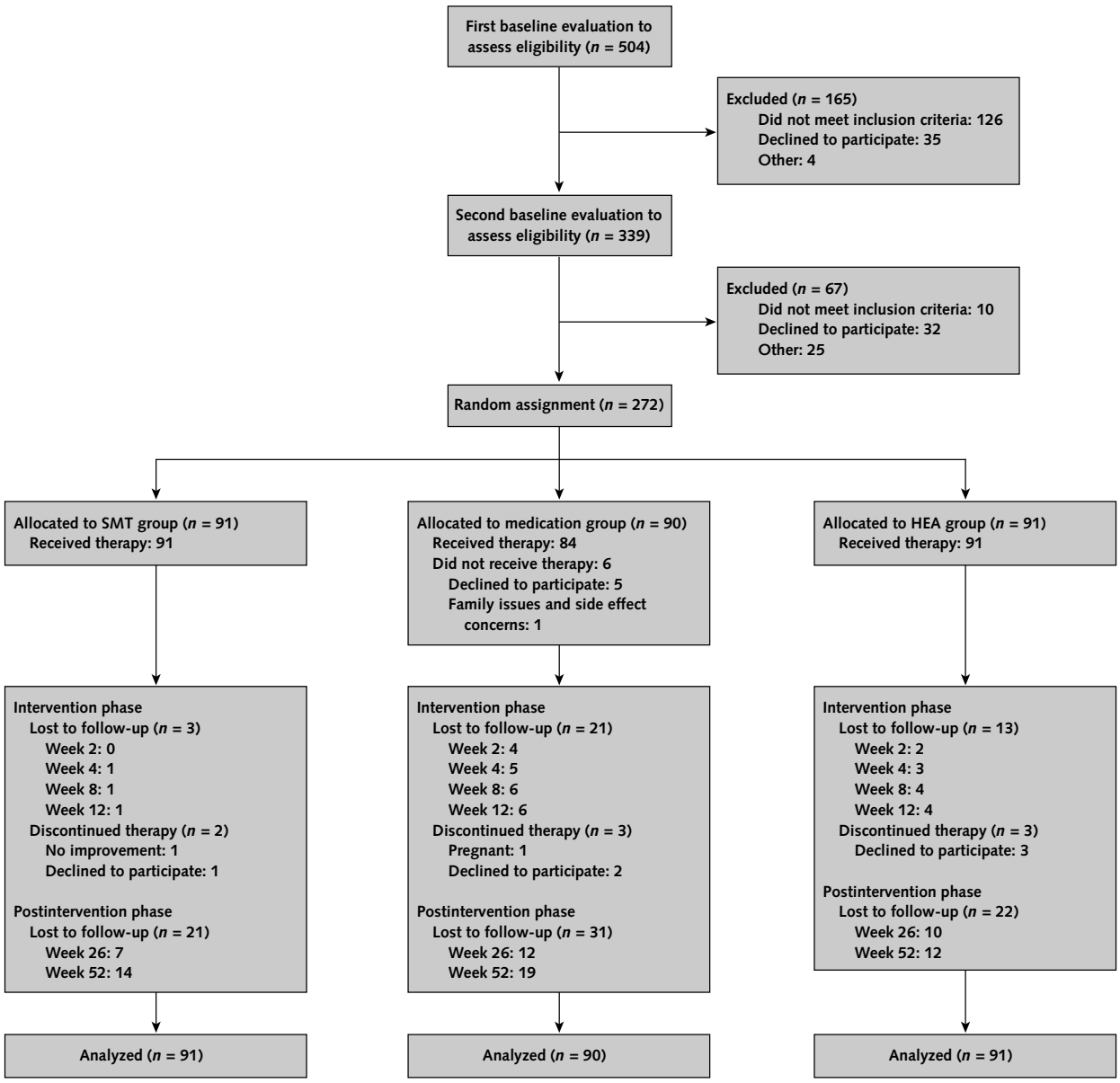
In primary analyses, we evaluated changes in neck pain between baseline and week 12 and performed longitudinal analyses by using data from weeks 2, 4, 8, and 12 (short-term outcome). In secondary (exploratory) analyses of both primary and secondary outcomes, we evaluated changes in participant-rated outcomes between baseline and weeks 2, 4, 8, 12, 26, and 52 and performed longitudinal analyses by using data from weeks 2, 4, 8, 12, 26, and 52 (long-term outcome). Both analyses were conducted by using linear mixed-model analysis with the MIXED procedure in SAS, version 9.1 (SAS Institute, Cary, North Carolina), with baseline values as outcomes (39–42). Clinical and demographic variables showing group differences at baseline were used as covariates in the analysis if they were at least moderately correlated with changes in outcomes (43, 44).

The study database was prepared by data managers who were blinded to study allocation. The intention-to-treat principle was adhered to by including all participants with baseline data in the analyses, regardless of loss to follow-up. To protect against increased risk for type I errors, we used the Fisher (protected) least-significant-difference test (45, 46). The mixed-model analysis included all participants who had at least baseline assessments. In the event of missing data, the reasons were explored and the pattern of the missing data was determined to select the best method of data imputation. The original analyses were then repeated as sensitivity analyses with fully imputed data by using the MI procedure in SAS, to assess the effect of the missing data (47–51). No prespecified thresholds for clinically important group differences were set because none has been established in the literature. To facilitate interpretation of the magnitude of group differences, responder analyses were conducted by group for pain reduction (absolute risk reduction) of 50%, 75%, and 100% (including 95% CIs) at the end of treatment and at 26- and 52-week follow-up (52–55).

Role of the Funding Source

Our trial was funded by the National Center for Complementary and Alternative Medicine, National Institutes of Health. The funding source had no role in the study design, collection, analysis, data interpretation, or writing of this article.

Figure. **Study flow diagram.**



Participants were lost to follow-up if they did not provide data at each time point. Patients who discontinued treatment had the opportunity to provide follow-up data. HEA = home exercise with advice; SMT = spinal manipulation therapy.

RESULTS

We evaluated 504 persons for eligibility, of whom 272 were randomly assigned: 90 to the medication group, 91 to the SMT group, and 91 to the HEA group. The **Figure** summarizes recruitment, participation, and attrition.

Table 1 summarizes the demographic and clinical characteristics of the randomly assigned participants. Potentially important between-group differences were noted for sex, duration of neck pain, pain during the night, and expectation of change in neck pain. **Table 2** provides details of the 3 study interventions.

Primary Outcomes

Improvement in participant-rated pain significantly differed with SMT compared with medication at 12 weeks (0.94 greater reduction in pain [95% CI, 0.37 to 1.51]; $P = 0.001$) and in longitudinal analyses that incorporated pain ratings every 2 weeks from baseline to 12 weeks (0.55 greater reduction in pain [CI, 0.10 to 1.00]; $P = 0.017$). At 12 weeks, a significantly higher absolute proportion of

Table 1. **Baseline Demographic and Clinical Characteristics**

Characteristic	SMT Group	Medication Group	HEA Group
Participants, *n*	91	90	91
Mean age (SD), *y*	48.3 (15.2)	46.8 (12.2)	48.6 (12.5)
Women, %	58.2	72.2	65.9
Married or living with someone, %	60.4	73.3	60.4
College graduate, %	55.0	48.9	52.8
Current smoker, %	13.2	14.4	17.6
Mean body mass index (SD), kg/m^2	27.6 (5.8)	27.9 (6.6)	26.4 (6.1)
Mean duration of neck pain (SD), *wk*	7.0 (3.2)	7.4 (3.0)	6.8 (3.2)
Frequency of neck pain (SD)*	3.5 (0.9)	3.3 (0.9)	3.7 (0.9)
Pain radiating to upper extremity, %	24.2	20.0	23.3
Awake at night because of neck pain, %	49.5	65.6	61.5
Reported cause of neck pain, %			
Trauma	29.7	22.2	16.5
Car accident	8.8	7.8	8.8
Leisure-time accident	16.5	12.2	5.5
Job accident	4.4	2.2	2.2
No apparent cause	45.1	48.9	50.5
Did not recall	5.5	8.9	6.6
Other†	19.8	20.0	26.4
CES-D score for depression (SD)‡	14.3 (12.7)	15.3 (11.0)	12.7 (9.6)
Expectation of change in pain (SD)§	1.5 (0.7)	1.8 (0.6)	1.9 (0.6)

CES-D = Center for Epidemiologic Studies Depression Scale; HEA = home exercise with advice; SMT = spinal manipulation therapy.
* On a scale of 0 (none of the time) to 5 (all of the time).
† For example, repetitive motion, stress, or sleep position.
‡ On a scale of 0 to 100.
§ On a scale of 1 (much better) to 5 (much worse).

the SMT group experienced reductions of pain of at least 50% (**Table 3**). Differences in participant-rated pain improvement between the SMT and HEA groups were smaller and not statistically significant. Differences between the HEA and medication groups were also not statistically significant, although a higher absolute proportion of the HEA group experienced reductions in pain of at least 75% at 12 weeks compared with the medication group.

Longer-term analyses showed similar findings. At 26 and 52 weeks, participant-rated pain improvement favored SMT over medication, but not SMT over HEA or HEA over medication, compared with baseline. A higher absolute proportion in the SMT group than in the medication group experienced reductions of pain of at least 50% at 26 but not 52 weeks. Those proportions did not differ at any time in comparisons of SMT and HEA, and a higher absolute proportion in the HEA group than in the medication group experienced reductions of pain of at least 75% at 26 but not 52 weeks.

Adjustment for baseline imbalances in sex, cause of pain, and depression did not change the group differences in pain outcomes.

Secondary Outcomes

Group differences in most secondary outcomes were similar to those of the primary outcomes (**Appendix Tables 1** to **4**, available at www.annals.org). Spinal manipulation therapy was superior to medication at the end of treatment and during follow-up in terms of global improvement, participant satisfaction, and SF-36–assessed

Table 2. **Details of Interventions**

Group and Characteristic	Value
SMT group	
Participants, *n*	91
Mean visits (range), *n*	15.3 (2–23)
Specific aspects of intervention, *n (%)*	
Cervical SMT	90 (99)
Thoracic SMT	56 (62)
Soft tissue	79 (87)
Assisted stretch	61 (67)
Hot packs	38 (42)
Cold packs	61 (67)
Prescription medication	0
Medication group	
Participants, *n*	84
Mean visits (range), *n*	4.8 (1–8)
Specific aspects of intervention, *n (%)*	
NSAID, opioid analgesic, and muscle relaxant	76 (90)
NSAID and opioid analgesic	3 (4)
NSAID and muscle relaxant	2 (2)
Opioid analgesic and muscle relaxant	1 (1)
Muscle relaxant only	1 (1)
HEA group	
Participants, *n*	91
Mean visits (range), *n*	2.0 (1–2)
Specific aspects of intervention, *n (%)*	
Exercise instruction	91 (100)
Education (e.g., spinal anatomy)	91 (100)
Self-care advice (e.g., pain management)	91 (100)
Instructions for ADLs (e.g., lifting)	88 (97)
Prescription medication	0

ADL = activity of daily living; HEA = home exercise with advice; NSAID = nonsteroidal anti-inflammatory drug; SMT = spinal manipulation therapy.

Table 3. **Between-Group Differences for Changes From Baseline in Participant-Rated Pain**

Variable	SMT Group (n = 91)	Medication Group (n = 90)	HEA Group (n = 91)
Pain score*			
Mean pain score (SD) at week 0	5.27 (1.57)	4.93 (1.49)	5.05 (1.64)
Week 2			
Mean pain score (SD)	3.77 (1.86)	3.62 (1.97)	3.47 (2.12)
Mean change from week 0 (95% CI)	1.51 (1.15 to 1.86)	1.28 (0.92 to 1.65)	1.57 (1.22 to 1.93)
Week 4			
Mean pain score (SD)	2.93 (2.02)	2.89 (1.83)	2.80 (2.15)
Mean change from week 0 (95% CI)	2.31 (1.90 to 2.73)	2.01 (1.68 to 2.35)	2.27 (1.85 to 2.69)
Week 8			
Mean pain score (SD)	2.01 (1.88)	2.39 (1.80)	2.22 (2.22)
Mean change from week 0 (95% CI)	3.24 (2.80 to 3.67)	2.50 (2.13 to 2.88)	2.85 (2.37 to 3.33)
Week 12			
Mean pain score (SD)	1.50 (1.70)	2.08 (1.65)	1.74 (1.84)
Mean change from week 0 (95% CI)	3.75 (3.34 to 4.16)	2.81 (2.41 to 3.20)	3.31 (2.88 to 3.74)
Mean short-term change from week 0†			
Week 26			
Mean pain score (SD)	1.90 (2.24)	2.33 (1.86)	1.77 (2.09)
Mean change from week 0 (95% CI)	3.30 (2.83 to 3.77)	2.52 (2.06 to 2.98)	3.21 (2.73 to 3.69)
Week 52			
Mean pain score (SD)	1.60 (1.53)	2.14 (1.85)	1.92 (2.34)
Mean change from week 0 (95% CI)	3.57 (3.13 to 4.00)	2.70 (2.20 to 3.20)	3.07 (2.46 to 3.69)
Mean long-term change from week 0‡			
Proportion with absolute reduction in pain			
Week 12			
≥50% reduction	82.2	69.0	77.0
≥75% reduction	56.7	33.3	48.3
100% reduction	32.2	13.1	29.9
Week 26			
≥50% reduction	75.0	59.0	71.6
≥75% reduction	53.6	30.8	49.4
100% reduction	36.9	19.2	34.6
Week 52			
≥50% reduction	81.8	69.0	69.6
≥75% reduction	53.2	38.0	49.4
100% reduction	27.3	16.9	36.7

HEA = home exercise with advice; SMT = spinal manipulation therapy.
* On a scale of 0 (no neck pain) to 10 (worst neck pain possible).
† Group differences based on data from weeks 2, 4, 8, and 12.
‡ Group differences based on data from weeks 2, 4, 8, 12, 26, and 52.

physical but not mental function; SMT was also superior to medication in measures of long-term medication use (1.26 fewer days per week of use at week 52 [CI, 0.53 to 1.99 days]; $P < 0.001$).

The SMT and HEA groups performed similarly on most of the secondary outcomes, although SMT performed better than HEA for satisfaction with care in both the short and long term. Home exercise with advice was superior to medication in both the short and long term for satisfaction with care and for long-term medication use (1.00 fewer days per week of use at week 52 [CI, 0.27 to 1.73 days]; $P = 0.008$).

Appendix Table 4 shows changes in cervical spine motion after 4 and 12 weeks. Overall, the greatest changes in cervical spine motion were observed in the HEA group. Results of the group differences in 3-dimensional cervical spine motion patterns will be reported elsewhere.

One of the participants indicated that someone tried to influence his responses. Because this was a week-52 questionnaire collected by mail independent of study staff, it was probably not of consequence.

Missing Data Analysis

Among the 272 participants, 219 (80.5%) provided data on neck pain at every visit. We considered loss to follow-up to be nonrandom for 12 participants, 6 of whom never commenced treatment (all in the medication group) and 6 of whom stopped participating in the study after they received treatment (2 in the medication group, 1 in the SMT group, and 3 in the HEA group). We first imputed values to the missing responses of these 12 participants by using the mean percentage reduction from baseline at all time points specific to the group to which they belonged. Then, we imputed the rest of the missing data during treatment and the 2 posttreatment follow-up time points by using the SAS multiple imputation strategy, on the assumption that the data were missing at random. The results of the analyses with imputed values changed the

Table 3—**Continued**

Between-Group Difference (95% CI)					
SMT Group Minus Medication Group	***P* Value**	**SMT Group Minus HEA Group**	***P* Value**	**HEA Group Minus Medication Group**	***P* Value**
0.22 (−0.35 to 0.79)	0.44	−0.07 (−0.63 to 0.50)	0.82	0.29 (−0.28 to 0.86)	0.32
0.30 (−0.27 to 0.87)	0.30	0.05 (−0.52 to 0.61)	0.87	0.25 (−0.32 to 0.83)	0.39
0.73 (0.16 to 1.30)	0.012	0.38 (−0.18 to 0.95)	0.185	0.35 (−0.22 to 0.92)	0.23
0.94 (0.37 to 1.51)	0.001	0.44 (−0.13 to 1.00)	0.130	0.50 (−0.07 to 1.08)	0.087
0.55 (0.10 to 1.00)	0.017	0.20 (−0.25 to 0.65)	0.38	0.35 (−0.10 to 0.80)	0.129
0.78 (0.20 to 1.36)	0.009	0.09 (−0.49 to 0.67)	0.76	0.69 (0.10 to 1.28)	0.021
0.87 (0.27 to 1.47)	0.005	0.49 (−0.10 to 1.08)	0.101	0.37 (−0.22 to 0.97)	0.22
0.64 (0.21 to 1.08)	0.004	0.23 (−0.20 to 0.66)	0.30	0.41 (−0.03 to 0.85)	0.066
13.2 (0.5 to 25.8)		5.2 (−6.7 to 17.1)		8.0 (−5.3 to 21.2)	
23.3 (9.0 to 37.7)		8.4 (−6.3 to 23.1)		14.9 (0.4 to 29.5)	
19.1 (7.1 to 31.2)		2.3 (−11.3 to 16.0)		16.8 (4.8 to 28.8)	
16.0 (1.7 to 30.3)		3.4 (−10.1 to 16.9)		12.6 (−2.1 to 27.3)	
22.8 (8.0 to 37.6)		4.2 (−11.1 to 19.4)		18.6 (3.7 to 33.6)	
17.7 (4.2 to 31.2)		2.3 (−12.3 to 17.0)		15.3 (1.8 to 28.9)	
12.8 (−1.0 to 26.6)		12.2 (−1.1 to 25.5)		0.6 (−14.2 to 15.4)	
15.2 (−0.7 to 31.1)		3.9 (−11.8 to 19.6)		11.3 (−4.4 to 27.1)	
10.4 (−2.9 to 23.6)		−9.4 (−24.0 to 5.1)		19.8 (6.1 to 33.6)	

estimates of group differences very little, and all statistically significant differences remained the same.

Nonstudy Treatments

During the 12-week intervention, 4 participants (3 in the medication group and 1 in the HEA group) reported visits to other health care providers for their neck pain. By week 52, about equal numbers of persons in each treatment group sought additional health care after completing the treatment phase (18 in the SMT group, 14 in the medication group, and 17 in the HEA group).

Adverse Events

No serious adverse events were reported in the study. Expected, nonserious adverse events that are typical to these treatments did occur and were all transient in nature, requiring little or no change to activity levels. Forty percent of the SMT group and 46% of the HEA group reported adverse events, primarily musculoskeletal pain. Paresthesia, stiffness, headache, and crepitus were less frequent (**Appendix Table 5**, available at www.annals.org). Sixty percent of participants in the medication group reported side effects, the most common being gastrointestinal symptoms and drowsiness. Dry mouth, cognitive disturbances, rash, congestion, and disturbed sleep were less commonly reported.

DISCUSSION

In the absence of available criteria for what constitute clinically important group differences, several factors should be considered in aggregate. This includes the statistical significance of the results of our primary efficacy analysis, as well as those of the responder and secondary outcomes analyses. The durability of the treatment effect, the safety and tolerability of the interventions, and the participant's ability and willingness to adhere to treatment should also be taken into account (56).

In this trial of SMT versus medication or HEA for the treatment of acute and subacute neck pain, SMT seemed more effective than medication according to various measures of neck pain and function. However, SMT demonstrated no apparent benefits over HEA. Spinal manipulation therapy and HEA led to similar short- and long-term outcomes, but participants who received medication seemed to fare worse, with a consistently higher use of pain med-

ication for neck pain throughout the trial's observation period. The performance of the HEA group, which has the potential for cost savings over both SMT and medication interventions, is noteworthy.

Participants and clinicians consider the potential for side effects when making treatment decisions. Although the frequency of reported side effects was similar among the 3 groups (41% to 58%), the nature of the side effects differed, with participants in the SMT and HEA groups reporting predominantly musculoskeletal events and those in the medication group reporting side effects that were more systemic in nature. Of note, participants in the medication group reported higher levels of medication use after the intervention.

Most participants had subacute neck pain that lasted more than 4 weeks, beyond the time when pain will probably resolve spontaneously, and evidence suggests that one half of persons with nonspecific neck pain continue to have neck pain 1 year after the original report (57). Although our trial did not have a placebo group, the observed results are unlikely to be due to natural history alone.

To date, few clinical trials have assessed the effectiveness of noninvasive interventions for acute and subacute neck pain not associated with whiplash; therefore, no evidence-informed first-line therapy for this type of neck pain has been established (12, 13).

We searched MEDLINE, EMBASE, CINAHL, and the Cochrane Library, using the terms *spinal manipulation* and *neck pain*, to identify all randomized trials published from 1960 to 2011 that evaluated SMT for acute or subacute neck pain. We found 3 trials (58–61). Our trial is most similar to that of Hoving and colleagues (58, 59), in which 75% of patients had neck pain of less than 12 weeks' duration. Six weeks of manual therapy (mainly spinal mobilization) was compared with usual medical care (advice, home exercise, and medication). The investigators found manual therapy to be superior to medical care, with reductions in pain and disability similar to what we observed at 8 weeks but less than what we observed at 12 weeks. Pool and colleagues (60) compared 6 weeks of manual therapy (up to 6 sessions) with 6 weeks of a behavioral-graded activity program (maximum of 18 sessions of 30 minutes each). At 3 months, the behavioral-graded activity program demonstrated slightly larger reductions in pain and disability than manual therapy; however, the magnitude of improvements in the behavioral program was similar to that found for SMT in our trial. Finally, Cleland and colleagues (61) found thrust mobilization and manipulation to be more effective than nonthrust manual treatment in patients with subacute neck pain. When considered in the context of the existing evidence, our results suggest that SMT and HEA both constitute viable treatment options for managing acute and subacute mechanical neck pain.

Our study has several strengths, including a rigorous concealed randomization procedure, use of recommended reliable outcome measures, masked objective outcomes assessors, and long-term postrandomization follow-up (6 and 12 months.) It also has limitations. First, participants and providers could not be blinded because of the nature of the treatments received and delivered. Second, no criteria are available to define clinically important group differences for the different outcomes. Finally, our study does not differentiate between the specific effects of treatment and the contextual (nonspecific) effects, including participant–provider interactions and expectations. This study was intended to be pragmatic in nature and to answer clinical questions regarding commonly used treatment approaches by approximating how they are delivered in practice.

For participants with acute and subacute neck pain, SMT was more effective than management with medication in both the short and long term; however, a few sessions of supervised instruction in HEA resulted in similar outcomes at most time points.

From Northwestern Health Sciences University, Pain Management and Rehabilitation Center, and Berman Center for Outcomes and Clinical Research at the Minneapolis Medical Research Foundation, Minneapolis, Minnesota.

Acknowledgment: The authors thank the study staff for dedicating substantial time and energy to ensure successful completion of the trial, as well as Brent Leininger, DC, and Jennifer Hart, MS, for their technical assistance in preparing this manuscript.

Grant Support: By the National Institutes of Health's National Center for Complementary and Alternative Medicine (grant R01 AT000707).

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-0299.

Reproducible Research Statement: *Study protocol and statistical code*: Available from Dr. Bronfort (e-mail, gbronfort@nwhealth.edu). *Data set*: Not available.

Requests for Single Reprints: Gert Bronfort, DC, PhD, Wolfe-Harris Center for Clinical Studies, Northwestern Health Sciences University, 2501 West 84th Street, Bloomington, MN 55431; e-mail, gbronfort@nwhealth.edu.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Bronfort and Evans: Wolfe-Harris Center for Clinical Studies, Northwestern Health Sciences University, 2501 West 84th Street, Bloomington, MN 55431.
Dr. Anderson: Medical Pain Management, 5775 Wayzata Boulevard, Suite 110, St. Louis Park, MN 55416.
Mr. Svendsen: 900 Forest Avenue, Birmingham, MI 48009.
Mr. Bracha: Division of Health Policy and Clinical Effectiveness, Cincinnati Children's Hospital, 3333 Burnet Avenue, MLC 5040, Cincinnati, OH 45229.
Dr. Grimm: Berman Center for Outcomes and Clinical Research, 825 South 8th Street, Suite 440, Minneapolis, MN 55404.

Author Contributions: Conception and design: G. Bronfort, R. Evans, R.H. Grimm.
Analysis and interpretation of the data: G. Bronfort, R. Evans, K.H. Svendsen, Y. Bracha, R.H. Grimm.
Drafting of the article: G. Bronfort, R. Evans, Y. Bracha, R.H. Grimm.
Critical revision of the article for important intellectual content: G. Bronfort, R. Evans, Y. Bracha, R.H. Grimm.
Final approval of the article: G. Bronfort, R. Evans, A.V. Anderson, Y. Bracha, R.H. Grimm.
Provision of study materials or patients: A.V. Anderson.
Statistical expertise: G. Bronfort, K.H. Svendsen, Y. Bracha, R.H. Grimm.
Obtaining of funding: G. Bronfort, R. Evans, R.H. Grimm.
Administrative, technical, or logistic support: G. Bronfort, R. Evans.
Collection and assembly of data: R. Evans, A.V. Anderson.

Appendix Table 1. Between-Group Differences for Changes From Baseline in Participant-Rated Neck Disability Index and Medication Use

Variable	SMT Group (n = 91)	Medication Group (n = 90)	HEA Group (n = 91)	Between-Group Difference (95% CI)					
				SMT Group Minus Medication Group	*P* Value	SMT Group Minus HEA Group	*P* Value	HEA Group Minus Medication Group	*P* Value
Neck disability index*									
Mean score (SD) at week 0	24.22 (9.71)	25.12 (9.67)	25.12 (9.79)						
Week 2									
Mean score (SD)	17.71 (9.66)	20.21 (10.53)	18.31 (10.21)						
Mean change from week 0 (95% CI)	6.51 (5.12 to 7.91)	4.84 (3.04 to 6.64)	6.81 (5.09 to 8.54)	1.67 (−0.82 to 4.17)	0.188	−0.30 (−2.77 to 2.18)	0.81	1.97 (−0.53 to 4.48)	0.123
Week 4									
Mean score (SD)	14.72 (9.67)	16.21 (9.38)	15.06 (10.26)						
Mean change from week 0 (95% CI)	9.44 (7.71 to 11.16)	8.89 (7.23 to 10.54)	10.01 (7.97 to 12.05)	0.55 (−1.95 to 3.06)	0.67	−0.57 (−3.06 to 1.92)	0.65	1.12 (−1.40 to 3.64)	0.38
Week 8									
Mean score (SD)	11.85 (8.51)	14.07 (8.57)	12.99 (10.45)						
Mean change from week 0 (95% CI)	12.30 (10.24 to 14.36)	11.08 (9.45 to 12.71)	12.14 (9.82 to 14.45)	1.22 (−1.29 to 3.72)	0.34	0.16 (−2.33 to 2.65)	0.90	1.06 (−1.47 to 3.58)	0.41
Week 12									
Mean score (SD)	9.20 (8.67)	12.33 (9.08)	11.08 (9.23)						
Mean change from week 0 (95% CI)	14.96 (12.90 to 17.01)	12.77 (10.65 to 14.89)	13.98 (11.76 to 16.20)	2.19 (−0.31 to 4.69)	0.087	0.98 (−1.51 to 3.47)	0.44	1.21 (−1.31 to 3.73)	0.35
Mean short-term score†				1.41 (−0.57 to 3.38)	0.162	0.07 (−1.89 to 2.03)	0.95	1.34 (−0.64 to 3.32)	0.185
Week 26									
Mean score (SD)	9.74 (10.91)	13.08 (11.52)	9.83 (10.33)						
Mean change from week 0 (95% CI)	14.39 (12.29 to 16.48)	11.79 (9.49 to 14.10)	14.75 (12.24 to 17.25)	2.59 (0.03 to 5.16)	0.047	−0.36 (−2.90 to 2.19)	0.78	2.95 (0.37 to 5.53)	0.025
Week 52									
Mean score (SD)	9.99 (8.41)	11.07 (11.28)	10.20 (10.60)						
Mean change from week 0 (95% CI)	13.81 (11.53 to 16.08)	13.62 (10.82 to 16.41)	14.34 (11.72 to 16.96)	0.19 (−2.45 to 2.82)	0.89	−0.53 (−3.12 to 2.06)	0.69	0.72 (−1.91 to 3.35)	0.59
Mean long-term score‡				1.40 (−0.51 to 3.31)	0.151	−0.10 (−2.00 to 1.80)	0.92	1.50 (−0.42 to 3.42)	0.12
Duration of medication use, *d*§									
Mean (SD) at week 0	2.38 (2.40)	2.44 (2.30)	2.65 (2.52)						
Week 2									
Mean (SD)	1.80 (2.20)	NA	1.78 (2.16)						
Mean change from week 0 (95% CI)	0.58 (0.18 to 0.97)	NA	0.87 (0.49 to 1.25)	NA		−0.29 (−0.96 to 0.38)	0.39	NA	
Week 4									
Mean (SD)	1.42 (2.02)	NA	1.59 (2.24)						
Mean change from week 0 (95% CI)	0.94 (0.52 to 1.36)	NA	1.07 (0.60 to 1.53)	NA		−0.13 (−0.80 to 0.54)	0.71	NA	
Week 8									
Mean (SD)	1.03 (1.67)	NA	1.26 (2.15)						
Mean change from week 0 (95% CI)	1.33 (0.85 to 1.81)	NA	1.41 (0.93 to 1.88)	NA		−0.08 (−0.75 to 0.60)	0.82	NA	
Week 12									
Mean (SD)	0.74 (1.58)	NA	1.24 (2.14)						
Mean change from week 0 (95% CI)	1.61 (1.09 to 2.13)	NA	1.42 (0.92 to 1.93)	NA		0.19 (−0.48 to 0.86)	0.58	NA	
Mean short-term duration of use†				NA		−0.08 (−0.61 to 0.45)	0.77	NA	
Week 26									
Mean (SD)	0.91 (1.88)	2.29 (2.54)	1.04 (2.15)						
Mean change from week 0 (95% CI)	1.38 (0.87 to 1.90)	0.18 (−0.41 to 0.78)	1.67 (1.14 to 2.20)	1.20 (0.50 to 1.90)	<0.001	−0.29 (−0.98 to 0.41)	0.42	1.49 (0.78 to 2.20)	<0.001
Week 52									
Mean (SD)	0.49 (1.14)	1.94 (2.01)	1.16 (2.08)						
Mean change from week 0 (95% CI)	1.82 (1.30 to 2.35)	0.56 (−0.12 to 1.25)	1.56 (1.07 to 2.05)	1.26 (0.53 to 1.99)	<0.001	0.26 (−0.45 to 0.97)	0.47	1.00 (0.27 to 1.73)	0.008
Mean long-term duration of use‡				NA		−0.06 (−0.57 to 0.46)	0.83	NA	

HEA = home exercise with advice; NA = not applicable; SMT = spinal manipulation therapy.

* Questionnaire containing 10 items relevant to neck pain. Each item is rated on a scale of 0 (no disability) to 5 (maximal disability); the total score out of 50 is converted to percentage points (0–100).

† Group differences based on data from weeks 2, 4, 8, and 12.

‡ Group differences based on data from weeks 2, 4, 8, 12, 26, and 52.

§ Number of days during the week (0 to 7 d) that participants have taken nonprescription or over-the-counter medication for neck pain. Because medication was a prescribed intervention during the first 12 wk, no comparisons with the medication group apply in the short or long term.

Appendix Table 2. **Between-Group Differences in Participant-Rated Global Improvement and Satisfaction**

Variable	SMT Group (n = 91)	Medication Group (n = 90)	HEA Group (n = 91)	Between-Group Difference (95% CI)					
				SMT Group Minus Medication Group*	*P* Value	SMT Group Minus HEA Group*	*P* Value	HEA Group Minus Medication Group*	*P* Value
Mean global improvement score (95% CI)†									
Week 2	3.48 (3.26 to 3.70)	3.93 (3.64 to 4.21)	3.31 (3.05 to 3.58)	0.44 (0.08 to 0.80)	0.02	−0.17 (−0.53 to 0.19)	0.36	0.61 (0.25 to 0.97)	0.001
Week 4	2.93 (2.64 to 3.21)	3.14 (2.88 to 3.41)	2.88 (2.63 to 3.12)	0.22 (−0.14 to 0.58)	0.24	−0.05 (−0.41 to 0.31)	0.79	0.27 (−0.10 to 0.63)	0.152
Week 8	2.29 (2.06 to 2.52)	2.54 (2.36 to 2.71)	2.47 (2.23 to 2.72)	0.24 (−0.12 to 0.61)	0.19	0.18 (−0.18 to 0.54)	0.33	0.06 (−0.30 to 0.43)	0.73
Week 12	1.99 (1.76 to 2.23)	2.41 (2.18 to 2.64)	2.17 (1.94 to 2.41)	0.42 (0.06 to 0.78)	0.02	0.18 (−0.18 to 0.54)	0.33	0.24 (−0.12 to 0.61)	0.194
Short term‡				0.33 (0.05 to 0.62)	0.02	0.04 (−0.25 to 0.32)	0.81	0.30 (0.01 to 0.58)	0.043
Week 26	2.18 (1.91 to 2.46)	2.58 (2.28 to 2.89)	2.21 (1.94 to 2.47)	0.40 (0.02 to 0.77)	0.04	0.02 (−0.35 to 0.39)	0.91	0.38 (0.00 to 0.76)	0.051
Week 52	2.22 (1.98 to 2.47)	2.57 (2.24 to 2.90)	2.43 (2.09 to 2.77)	0.35 (−0.04 to 0.74)	0.08	0.20 (−0.18 to 0.58)	0.29	0.14 (−0.25 to 0.53)	0.47
Long term§				0.34 (0.07 to 0.62)	0.01	0.06 (−0.21 to 0.34)	0.66	0.28 (0.01 to 0.56)	0.045
Mean satisfaction score (95% CI)‖									
Week 2	2.18 (1.97 to 2.38)	2.92 (2.67 to 3.16)	2.47 (2.28 to 2.66)	0.74 (0.46 to 1.03)	<0.001	0.30 (0.01 to 0.58)	0.039	0.45 (0.16 to 0.73)	0.002
Week 4	1.89 (1.69 to 2.09)	2.55 (2.31 to 2.79)	2.15 (1.97 to 2.34)	0.66 (0.38 to 0.95)	<0.001	0.26 (−0.02 to 0.55)	0.069	0.40 (0.11 to 0.69)	0.006
Week 8	1.66 (1.47 to 1.84)	2.38 (2.16 to 2.60)	2.08 (1.87 to 2.30)	0.72 (0.44 to 1.01)	<0.001	0.42 (0.14 to 0.71)	0.003	0.30 (0.01 to 0.59)	0.042
Week 12	1.54 (1.38 to 1.69)	2.18 (1.99 to 2.37)	1.89 (1.69 to 2.08)	0.64 (0.36 to 0.93)	<0.001	0.35 (0.07 to 0.64)	0.015	0.29 (0.00 to 0.58)	0.047
Short term‡				0.69 (0.47 to 0.92)	<0.001	0.33 (0.11 to 0.56)	0.003	0.36 (0.13 to 0.58)	0.002
Week 26	1.74 (1.50 to 1.97)	2.35 (2.07 to 2.63)	1.95 (1.73 to 2.17)	0.61 (0.31 to 0.91)	<0.001	0.21 (−0.08 to 0.50)	0.154	0.40 (0.10 to 0.70)	0.009
Week 52	1.67 (1.50 to 1.84)	2.48 (2.16 to 2.80)	2.06 (1.82 to 2.31)	0.81 (0.50 to 1.12)	<0.001	0.39 (0.09 to 0.69)	0.011	0.42 (0.11 to 0.73)	0.008
Long term§				0.70 (0.48 to 0.92)	<0.001	0.32 (0.11 to 0.54)	0.004	0.38 (0.16 to 0.59)	<0.001

HEA = home exercise with advice; SMT = spinal manipulation therapy.

* Positive values favor the first group in the comparison, and negative values favor the second group.

† Improvement in neck pain measured on a 9-point scale from 1 (100% improved) to 5 (0% improvement) to 9 (100% worse).

‡ Group differences based on data from weeks 2, 4, 8, and 12.

§ Group differences based on data from weeks 2, 4, 8, 12, 26, and 52.

‖ Satisfaction with care measured on a 7-point scale from 1 (completely satisfied, couldn't be better) to 4 (neither satisfied nor dissatisfied) to 7 (completely dissatisfied, couldn't be worse).

Appendix Table 3. **Between-Group Differences for Changes From Baseline in SF-36 Physical and Mental Component Scores***

SF-36 Score	SMT Group (n = 91)	Medication Group (n = 90)	HEA Group (n = 91)	Between-Group Difference (95% CI)					
				SMT Group Minus Medication Group	*P* Value	SMT Group Minus HEA Group	*P* Value	HEA Group Minus Medication Group	*P* Value
Physical component									
Mean score (SD) at week 0	45.36 (6.94)	46.27 (6.99)	45.31 (7.43)						
Week 2									
Mean score (SD)	47.42 (7.04)	48.29 (7.09)	48.90 (6.03)						
Mean change from week 0 (95% CI)	2.05 (1.16 to 2.94)	2.04 (1.11 to 2.96)	3.56 (2.57 to 4.55)	0.02 (−1.55 to 1.58)	0.98	−1.50 (−3.06 to 0.05)	0.058	1.52 (−0.05 to 3.09)	0.058
Week 4									
Mean score (SD)	49.38 (6.03)	49.07 (6.43)	49.77 (6.79)						
Mean change from week 0 (95% CI)	3.99 (2.95 to 5.04)	2.83 (1.71 to 3.95)	4.37 (3.11 to 5.64)	1.16 (−0.41 to 2.73)	0.148	−0.38 (−1.94 to 1.19)	0.64	1.54 (−0.04 to 3.12)	0.057
Week 8									
Mean score (SD)	51.25 (5.43)	50.48 (6.37)	51.01 (6.87)						
Mean change from week 0 (95% CI)	5.87 (4.64 to 7.09)	4.27 (3.04 to 5.49)	5.70 (4.32 to 7.08)	1.60 (0.02 to 3.18)	0.047	0.17 (−1.40 to 1.73)	0.83	1.43 (−0.15 to 3.02)	0.076
Week 12									
Mean score (SD)	52.46 (5.86)	51.57 (6.59)	51.98 (6.40)						
Mean change from week 0 (95% CI)	7.08 (5.81 to 8.36)	5.28 (4.00 to 6.57)	6.65 (5.26 to 8.03)	1.80 (0.22 to 3.37)	0.025	0.43 (−1.13 to 2.00)	0.59	1.36 (−0.22 to 2.95)	0.092
Mean short-term score†				1.14 (−0.10 to 2.38)	0.071	−0.32 (−1.55 to 0.91)	0.61	1.46 (0.22 to 2.71)	0.021
Week 26									
Mean score (SD)	52.58 (6.14)	51.16 (6.84)	52.91 (5.87)						
Mean change from week 0 (95% CI)	7.05 (5.80 to 8.31)	4.84 (3.39 to 6.29)	7.12 (5.66 to 8.58)	2.21 (0.57 to 3.84)	0.008	−0.07 (−1.68 to 1.54)	0.93	2.28 (0.63 to 3.93)	0.007
Week 52									
Mean score (SD)	52.51 (6.66)	51.13 (7.49)	52.48 (7.09)						
Mean change from week 0 (95% CI)	6.99 (5.37 to 8.61)	4.58 (2.71 to 6.46)	6.82 (5.14 to 8.50)	2.41 (0.71 to 4.11)	0.006	0.17 (−1.48 to 1.82)	0.84	2.24 (0.54 to 3.93)	0.010
Mean long-term score‡				1.53 (0.33 to 2.74)	0.013	−0.20 (−1.39 to 1.00)	0.75	1.73 (0.52 to 2.94)	0.005
Mental component									
Mean score (SD) at week 0	54.46 (7.83)	52.12 (8.75)	54.06 (6.94)						
Week 2									
Mean score (SD)	55.50 (6.92)	51.99 (8.98)	54.60 (7.70)						
Mean change from week 0 (95% CI)	1.04 (−0.24 to 2.32)	−0.07 (−1.23 to 1.09)	0.62 (−0.53 to 1.76)	1.11 (−0.69 to 2.91)	0.23	0.42 (−1.37 to 2.21)	0.64	0.69 (−1.13 to 2.50)	0.46
Week 4									
Mean score (SD)	55.81 (7.32)	53.29 (8.50)	55.33 (7.78)						
Mean change from week 0 (95% CI)	1.39 (0.06 to 2.72)	1.18 (−0.13 to 2.48)	1.31 (0.03 to 2.59)	0.21 (−1.60 to 2.03)	0.82	0.08 (−1.72 to 1.88)	0.93	0.13 (−1.69 to 1.96)	0.88
Week 8									
Mean score (SD)	56.52 (6.80)	53.80 (7.47)	55.94 (7.22)						
Mean change from week 0 (95% CI)	2.10 (0.82 to 3.39)	1.70 (0.25 to 3.15)	1.91 (0.69 to 3.14)	0.40 (−1.41 to 2.22)	0.67	0.19 (−1.61 to 1.99)	0.84	0.21 (−1.62 to 2.04)	0.82
Week 12									
Mean score (SD)	56.31 (7.64)	55.16 (6.65)	55.94 (6.77)						
Mean change from week 0 (95% CI)	1.89 (0.54 to 3.25)	3.08 (1.57 to 4.58)	1.95 (0.71 to 3.18)	−1.19 (−3.00 to 0.63)	0.20	−0.06 (−1.86 to 1.75)	0.95	−1.13 (−2.96 to 0.70)	0.22
Mean short-term score†				0.13 (−1.29 to 1.56)	0.85	0.16 (−1.26 to 1.58)	0.83	−0.02 (−1.46 to 1.41)	0.97
Week 26									
Mean score (SD)	55.55 (8.07)	54.65 (7.38)	54.93 (7.75)						
Mean change from week 0 (95% CI)	1.06 (−0.54 to 2.67)	2.28 (0.54 to 4.02)	0.79 (−0.70 to 2.27)	−1.21 (−3.10 to 0.67)	0.21	0.28 (−1.58 to 2.14)	0.77	−1.49 (−3.39 to 0.41)	0.124
Week 52									
Mean score (SD)	56.26 (6.48)	53.30 (9.33)	54.52 (9.26)						
Mean change from week 0 (95% CI)	1.41 (−0.17 to 2.99)	0.96 (−0.75 to 2.67)	0.27 (−1.63 to 2.16)	0.45 (−1.51 to 2.41)	0.65	1.14 (−0.75 to 3.04)	0.24	−0.69 (−2.65 to 1.26)	0.49
Mean long-term score‡				−0.04 (−1.42 to 1.35)	0.96	0.34 (−1.03 to 1.72)	0.62	−0.38 (−1.77 to 1.01)	0.59

HEA = home exercise with advice; SF-36 = Short Form-36 Health Survey; SMT = spinal manipulation therapy.

* Scores are norm-based, using a linear T-score transformation with a mean of 50 (SD, 10).

† Group differences based on data from weeks 2, 4, 8, and 12.

‡ Group differences based on data from weeks 2, 4, 8, 12, 26, and 52.

Appendix Table 4. **Between-Group Differences for Changes From Baseline in Cervical Range of Motion***

Plane of Motion	SMT Group (n = 91)	Medication Group (n = 90)	HEA Group (n = 91)	Between-Group Difference (95% CI)					
				SMT Group Minus Medication Group	*P* Value	SMT Group Minus HEA Group	*P* Value	HEA Group Minus Medication Group	*P* Value
Flexion and extension†									
Mean degrees (SD) at week 0	97.44 (18.56)	102.06 (18.85)	101.19 (18.01)						
Week 4									
Mean degrees (SD)	102.34 (17.86)	102.90 (16.02)	106.45 (18.32)						
Mean change from week 0 (95% CI)	4.20 (2.13 to 6.26)	0.97 (−1.17 to 3.12)	5.22 (3.13 to 7.31)	3.22 (0.36 to 6.09)	0.027	−1.02 (−3.85 to 1.80)	0.48	4.25 (1.39 to 7.11)	0.004
Week 12									
Mean degrees (SD)	104.06 (16.52)	104.15 (15.87)	107.89 (18.37)						
Mean change from week 0 (95% CI)	5.87 (3.53 to 8.20)	2.75 (0.32 to 5.19)	6.26 (3.87 to 8.66)	3.11 (0.23 to 5.99)	0.034	−0.40 (−3.24 to 2.45)	0.78	3.51 (0.62 to 6.40)	0.018
Rotation‡									
Mean degrees (SD) at week 0	118.29 (18.69)	122.43 (19.48)	120.21 (18.51)						
Week 4									
Mean degrees (SD)	122.00 (17.96)	125.98 (17.87)	125.50 (18.71)						
Mean change from week 0 (95% CI)	3.42 (1.11 to 5.72)	3.52 (1.13 to 5.91)	5.56 (3.24 to 7.89)	−0.10 (−3.64 to 3.43)	0.95	−2.15 (−5.64 to 1.34)	0.23	2.04 (−1.49 to 5.58)	0.26
Week 12									
Mean degrees (SD)	125.35 (18.26)	125.69 (17.19)	127.59 (18.48)						
Mean change from week 0 (95% CI)	6.89 (4.16 to 9.61)	3.93 (1.08 to 6.77)	7.53 (4.74 to 10.32)	2.96 (−0.60 to 6.52)	0.103	−0.64 (−4.15 to 2.88)	0.72	3.60 (0.03 to 7.17)	0.048
Lateral bending§									
Mean degrees (SD) at week 0	63.18 (14.90)	64.10 (14.15)	63.69 (16.95)						
Week 4									
Mean degrees (SD)	66.18 (17.84)	67.60 (14.11)	67.19 (17.63)						
Mean change from week 0 (95% CI)	2.92 (0.99 to 4.84)	3.50 (1.50 to 5.50)	3.75 (1.81 to 5.69)	−0.58 (−3.50 to 2.33)	0.69	−0.84 (−3.71 to 2.04)	0.57	0.25 (−2.66 to 3.17)	0.86
Week 12									
Mean degrees (SD)	69.91 (16.45)	68.63 (14.70)	69.67 (16.71)						
Mean change from week 0 (95% CI)	6.75 (4.63 to 8.88)	4.89 (2.68 to 7.09)	6.47 (4.29 to 8.65)	1.87 (−1.07 to 4.81)	0.21	0.28 (−2.64 to 3.20)	0.85	1.59 (−1.37 to 4.55)	0.29

HEA = home exercise with advice; SMT = spinal manipulation therapy.
* Estimates of normal range are based on references 36 and 37.
† Normal range, 110–120 degrees.
‡ Normal range, 150–160 degrees.
§ Normal range, 70–80 degrees.

Appendix Table 5. **Adverse Events During the 12-Week Treatment Period***

Event	SMT Group (n = 91)	Medication Group (n = 84)†	HEA Group (n = 91)	Absolute Difference (95% CI), *percentage points*		
				SMT Group Minus Medication Group	SMT Group Minus HEA Group	HEA Group Minus Medication Group
Aggravation of pain	28 (31)	0 (0)	37 (41)	31 (21 to 41)	−10 (−23 to 4)	41 (30 to 51)
Headache	5 (5)	0 (0)	3 (3)	5 (0 to 12)	2 (−5 to 9)	3 (−2 to 9)
Stiffness	5 (5)	0 (0)	4 (4)	5 (0 to 12)	1 (−6 to 8)	4 (−1 to 11)
Not specified	4 (4)	5 (6)	0 (0)	−2 (−9 to 6)	4 (0 to 11)	−6 (−13 to −1)
Paresthesia	2 (2)	0 (0)	3 (3)	2 (−3 to 8)	−1 (−7 to 5)	3 (−2 to 9)
Nausea	1 (1)	5 (6)	1 (1)	−5 (−12 to 1)	0 (0)	−5 (−12 to 1)
Crepitus	0 (0)	0 (0)	3 (3)	0 (0)	−3 (−9 to 1)	3 (−2 to 9)
Increased blood pressure	0 (0)	1 (1)	0 (0)	−1 (−6 to 3)	0 (0)	−1 (−6 to 3)
Stress incontinence	0 (0)	1 (1)	0 (0)	−1 (−6 to 3)	0 (0)	−1 (−6 to 3)
Disturbed sleep	0 (0)	4 (5)	0 (0)	−5 (−12 to 0)	0 (0)	−5 (−12 to 0)
Congestion	0 (0)	6 (7)	0 (0)	−7 (−15 to −2)	0 (0)	−7 (−15 to −2)
Rash	0 (0)	7 (8)	0 (0)	−8 (−16 to −3)	0 (0)	−8 (−16 to −3)
Cognitive symptoms	0 (0)	10 (12)	0 (0)	−12 (−21 to −5)	0 (0)	−12 (−21 to −5)
Dry mouth	0 (0)	10 (12)	0 (0)	−12 (−21 to −5)	0 (0)	−12 (−21 to −5)
Gastrointestinal symptoms	0 (0)	17 (20)	0 (0)	−20 (−30 to −12)	0 (0)	−20 (−30 to −12)
Drowsiness	0 (0)	18 (21)	0 (0)	−21 (−31 to −13)	0 (0)	−21 (−31 to −13)
Total	36 (40)	50 (60)	42 (46)	−20 (−34 to −5)	−6 (−20 to 8)	−13 (−27 to 1)

HEA = home exercise with advice; SMT = spinal manipulation therapy.
* Data are the numbers (percentages) of adverse events. Participants who reported an event at least once over the course of treatment; participants could report ≥1 type of event.
† We excluded 6 participants in this group from analysis because they received no treatment.