Systematic Review

Manipulation and Mobilization for Treating Chronic Nonspecific Neck Pain: A Systematic Review and Meta-Analysis for an Appropriateness Panel

Ian D. Coulter, PhD[1-3], Cindy Crawford, BA[1], Howard Vernon, DC, PhD[1,4], Eric L. Hurwitz, DC, PhD[1,5], Raheleh Khorsan, PhD[3,6], Marika Suttorp Booth, MS[1], and Patricia M. Herman, ND, PhD[1]

From: [1]RAND Corporation, Santa Monica, CA; [2]University of California Los Angeles, School of Dentistry, Los Angeles, CA; [3]Southern California University of Health Sciences, Whittier, CA; [4]Canadian Memorial Chiropractic College, Division of Research, Toronto, ON, Canada; [5]Office of Public Health Studies, University of Hawaii, Mānoa, Honolulu, HI; [6]Yo San University of Traditional Chinese Medicine, Los Angeles, CA

Address Correspondence: Ian D. Coulter, PhD RAND Corporation, 1776 Main Street, Santa Monica, CA 90407 E-mail: coulter@rand.org

Disclaimer: This project is funded by the National Center for Complementary and Integrative Health under Award Number U19AT007912 and does not necessarily represent the official views of the National Institutes of Health. All analyses of data, manuscript preparation, and presentation are the work solely of the authors and free of commercial input, influence, or bias.Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 10-22-2018
Revised manuscript received: 01-07-2019
Accepted for publication: 01-16-2019

Free full manuscript: www.painphysicianjournal.com

Background: Mobilization and manipulation therapies are widely used by patients with chronic nonspecific neck pain; however, questions remain around efficacy, dosing, and safety, as well as how these approaches compare to other therapies.

Objectives: Based on published trials, to determine the efficacy, effectiveness, and safety of various mobilization and manipulation therapies for treatment of chronic nonspecific neck pain.

Study Design: A systematic literature review and meta-analysis.

Methods: We identified studies published between January 2000 and September 2017, by searching multiple electronic databases, examining reference lists, and communicating with experts. We selected randomized controlled trials comparing manipulation and/or mobilization therapies to sham, no treatment, each other, and other active therapies, or when combined as multimodal therapeutic approaches. We assessed risk of bias by using the Scottish Intercollegiate Guidelines Network criteria. When possible, we pooled data using random-effects meta-analysis. Grading of Recommendations, Assessment, Development, and Evaluation was applied to determine the confidence in effect estimates. This project was funded by the National Center for Complementary and Integrative Health under award number U19AT007912 and ultimately used to inform an appropriateness panel.

Results: A total of 47 randomized trials (47 unique trials in 53 publications) were included in the systematic review. These studies were rated as having low risk of bias and included a total of 4,460 patients with nonspecific chronic neck pain who were being treated by a practitioner using various types of manipulation and/or mobilization interventions. A total of 37 trials were categorized as unimodal approaches and involved thrust or nonthrust compared with sham, no treatment, or other active comparators. Of these, only 6 trials with similar intervention styles, comparators, and outcome measures/timepoints were pooled for meta-analysis at 1, 3, and 6 months, showing a small effect in favor of thrust plus exercise compared to an exercise regimen alone for a reduction in pain and disability. Multimodal approaches appeared to be effective at reducing pain and improving function from the 10 studies evaluated. Health-related quality of life was seldom reported. Some 22/47 studies did not report or mention adverse events. Of the 25 that did, either no or minor events occurred.

Limitations: The current evidence is heterogeneous, and sample sizes are generally small.

Conclusions: Studies published since January 2000 provide low-moderate quality evidence that various types of manipulation and/or mobilization will reduce pain and improve function for chronic nonspecific neck pain compared to other interventions. It appears that multimodal approaches, in which multiple treatment approaches are integrated, might have the greatest potential impact. The studies comparing to no treatment or sham were mostly testing the effect of a single dose, which may or may not be helpful to inform practice. According to the published trials reviewed, manipulation and mobilization appear safe. However, given the low rate of serious adverse events, other types of studies with much larger sample sizes would be required to fully describe the safety of manipulation and/or mobilization for nonspecific chronic neck pain.

Key words: Chronic neck pain, nonspecific, chiropractic, manipulation, mobilization, systematic review, meta-analysis, appropriateness

Pain Physician 2019: 22:E55-E70

An estimated 66% of the population will suffer from neck pain at some point during their lifetime (1). In 2007, neck pain was the second most common reason cited by patients for using complementary and integrative medicine (CIM), preceded only by low back pain (2). The vast majority of neck pain is not due to organic pathology, and thus, has been termed "nonspecific" or "mechanical." Nonspecific neck pain is responsible for a significant proportion of direct health care costs, visits to health care providers, sick leave, and the related loss of productivity (3-5). Most nonspecific neck pain is not associated with major disease or with neurologic signs of nerve compression. For some patients, nonspecific neck pain rarely, if at all, interferes with daily activities; for others, nonspecific neck pain constitutes a major hindrance to daily functioning (6). More than one-third of people affected still have low grade symptoms or recurrences more than one year after treatment, often leading to chronic pain (7).

Many interventions are available for managing nonspecific chronic neck pain, including analgesics as prescribed by medical practitioners, physiotherapy, educational modalities, exercise, and manual therapy (4,6,8-10). Self-care management and educational modalities are usually the initial forms of treatment for nonspecific chronic neck pain. There is some evidence that educational videos are useful for patients with whiplash-related neck pain (11). There is little evidence that these types of modalities are more effective compared to other conservative therapies (6,12). Physiotherapy, exercise, and manual therapies such as massage, chiropractic, occupational, and osteopathic therapies, including spinal manipulation and mobilization, are used in isolation and in conjunction with other therapies to treat nonspecific neck pain.

There are several systematic reviews of manual therapies, such as spinal manipulation and mobilization, for the treatment of neck pain (5,8,13,14). Some reviews have found that there is no evidence or insufficient evidence that spinal manipulative therapy is superior to other standard treatments for patients with chronic neck pain (15). However, more recent systematic reviews on chronic neck pain, as well as chronic low back pain, suggest spinal manipulation and mobilization are "viable" options for treating pain and reducing disability (8). The Bone and Joint Decade 2000-2010 Task Force (12) found that mobilization or exercise sessions alone, or in combination with medications, are the most beneficial treatment for short term neck pain. Others have concluded that interventions commonly used by manual therapy practitioners, such as chiropractic care, improve outcomes for the treatment of chronic neck pain (16,17). The greatest increase in benefits has been suggested for multimodal approaches, in which multiple approaches are used together to treat chronic neck pain (16).

The long-term benefit of manual therapy is not well established in the literature. A systematic review of selected CIM therapies for neck and low back pain by Furlan et al (18), comparing CIM therapies to other active treatments (e.g., other CIM therapy, physiotherapy, pain medication, usual care) found that, "manipulation and mobilization effectiveness is variable depending on symptom duration, outcome, comparator, whether there is exercise or general practitioner care, and follow-up period. Although this variability can be considered inconsistent findings, the overall evidence suggests that manipulation and mobilization are an effective treatment modality compared to other therapies" (18). The findings of this systematic review regarding the effects of manipulation on neck pain appear to be consistent with both older and newer reviews (8,14).

The purpose of this systematic review was to evaluate the randomized controlled trials (RCTs) published from January 2000 through September 2017 on chronic nonspecific neck pain, comparing the effects of manipulation and/or mobilization as therapies to those of other active therapies (such as acupuncture, massage therapy, exercise, etc.) to sham or no treatment, and when combined with other therapies such as exercise or advice commonly seen in practice. The decision to begin with January 2000 was based on the fact that previous systematic reviews (SRs) existed up until that date and this represented a more rational use of our resources. The goal was to not only update the evidence base since these previous reviews reported earlier, but to better understand the effectiveness of the various types of manipulation and/or mobilization for treating chronic nonspecific neck pain, and the potential impact on patient-reported outcomes associated with pain, disability, and health-related quality of life (HRQoL). When there were subsets of data the authors felt were similar enough to pool, meta-analyses were attempted. This review was in support of a larger project investigating the appropriateness of manipulation/mobilization for the treatment of chronic low back pain and neck pain, funded by the National Center for Complementary and Integrative Health under award number U19AT007912. The systematic review was done to pres-

ent to a panel of experts who were making judgments about the appropriateness of using manipulation and/or mobilization for the treatment of nonspecific chronic neck pain under different clinical scenarios. This grant was a cooperative agreement and National Institutes of Health (NIH) also appointed an external advisory committee (EAC), who had the authority both to vote go/no go with regard to the planned systematic review and again to vote go/no go after reviewing the systematic review itself. The systematic review was then presented to an expert panel to use in their rating of the appropriateness of manipulation and/or mobilization for nonspecific chronic neck pain.

Methods

This systematic review and meta-analysis report adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Search Strategy and Data Sources

This systematic review builds on previous systematic reviews (up through 2000) that reported the evidence base for manipulation and mobilization for neck pain (8,15,19,20). We searched PubMed/MEDLINE, Cochrane, Embase, Cinahl, PsycInfo, and Index to Chiropractic Literature (ICL) for studies published between January 2000 and September 2017. In addition, we searched reference lists and consulted with subject matter experts. The search strategy was intentionally designed to be broad in nature without predefining the specific population (i.e., not using the words 'chronic' or 'nonspecific') or intervention (i.e., spanning multiple professions). In addition, there were no limitations placed on control/comparators, specific outcomes, or study designs, so that the breadth and variations across the research could be discovered, and the literature could inform the appropriate definitions and subgroups to consider for analysis. Because the NIH-funded project focused on both chronic nonspecific neck pain and chronic low back pain, we conducted the search to meet both needs. (Fig. 1 and Table 1)

Scoping Review

A scoping review of the literature informed the definitions and categorization of studies for systematic review. We categorized studies accordingly to the specific populations, interventions, control/comparators, patient reported outcomes, and study designs discovered in the literature base. We excluded studies clearly not related to neck pain or to an intervention involving mobilization and/or manipulation. We presented findings to an internal steering committee (ISC) as well as an EAC. With the help of these committees, evidence-informed definitions and specific eligibility criteria were devised based on the evidence base to be used in carrying out the systematic review and attempted meta-analysis (Table 1).

Study Selection

Six reviewers used study eligibility criteria to independently screen the literature in duplicate (Table 1). Disagreements about inclusion were resolved through discussion and consensus, or ultimately by the ISC. Eligibility criteria included: 1) a population experiencing chronic (21,22) and nonspecific (23) neck pain; 2) an intervention, with the involvement of a therapist, consisting of either (i) manipulation (labeled as thrust), (ii) mobilization (labeled as nonthrust), or (iii) a multimodal integrative practice including manipulation and/or mobilization components as part of the ap-

(Manipulation Osteopathic OR Chiropractic Manipulation OR Spinal Manipulation OR Musculoskeletal Manipulation OR Osteopathic Medicine OR Chiropractic OR manipulation orthopedic OR mobiliz* OR Manipulate OR manual therapy Or "Spinal Manipulative Therapy" OR SMT) and (back injury OR neck pain OR cervical pain OR neck ache OR low back pain OR low back ache OR spinal OR cervical vertebrae OR coccydynia OR sciatica OR spondylosis OR lumbago OR whiplash OR lumbar pain OR lumbar OR sacral OR neck pain OR neck pain* OR low* backache* OR back ache* OR neck pain* OR neck ache* OR cervical pain* OR cervical vertebra* OR low* back pain OR back injur* OR neck injury OR neck injur* OR neck ache* OR neckache* OR neck pain* OR cervical* OR sciatic*) AND ((Clinical Trial[ptyp] OR Pragmatic Clinical Trial[ptyp] OR Comparative Study[ptyp] OR Controlled Clinical Trial[ptyp] OR Evaluation Studies[ptyp] OR Multicenter Study[ptyp] OR Observational Study[ptyp] OR Randomized Controlled Trial[ptyp] OR Research Support, N I H, Extramural[ptyp] OR Research Support, Non U S Gov't[ptyp] OR Research Support, U S Gov't, Non P H S[ptyp] OR Research Support, U S Gov't, P H S[ptyp] OR Research Support, U.S. Government[ptyp] OR systematic[sb] OR Practice Guideline[ptyp] OR Meta-Analysis[ptyp] OR Guideline[ptyp] OR Research Support, N I H, Intramural[ptyp] OR Validation Studies[ptyp]) AND ("2000/01/01"[Pdat] : "2017/09/28"[Pdat]) AND Humans[Mesh] AND English[lang] AND adult[MeSH])

Fig. 1. *Search strategy.*
Note: Fig. 1 addresses search strategy for neck pain as well as low back pain studies. The findings of low back pain are not reported here (32). Because the Center of Excellence for Research in CAM (CERC) project was focused on both chronic neck pain as well as chronic low back pain, the search was executed to meet both needs together to streamline the effort.

Table 1. *Eligibility criteria*.

Eligibility Criteria	Reference Standard Definition	Scope Driven Evidence-Informed Definition
Population "chronic" neck pain	According to the Pain Management Task Force, (21) chronic pain can be described as ongoing or recurrent pain, lasting beyond the usual course of acute illness or injury or more than 3-6 months, and which adversely affects the individual's well-being. In 2014, the NIH Task Force on Research Standards for Low Back (22) recommended defining chronicity of pain as: "How long has back pain been an ongoing problem for you? (2) How often has low-back pain been an ongoing problem for you over the past 6 months? A response of greater than 3 months to question 1, and a response of "at least half the days in the past 6 months" to question 2 would define chronic low back pain."	The majority of studies defined chronicity based on the duration of pain symptoms for 12 weeks or more. Therefore, a similar definition of chronicity (≥ 12 weeks) was adopted, and studies were categorized as those patients with >12 weeks, a mean duration of 6 months, and those with >12 months pain duration.
Population "non-specific"	Non-specific pain is defined as pain not attributable to a recognizable, known specific pathology (23) (e.g., infection, tumor, osteoporosis, fracture, structural deformity, rheumatoid arthritis, radicular syndrome, etc.). Therefore, the etiology of the pain is often unknown and it is not categorized with a major pathogenic etiology.	The existing literature does not use standard terminology to report "non-specific" chronic pain. In order to guide the eligibility of studies, the following terms were specified to be outside the scope of "non-specific:" specific conditions, i.e., cancer, rheumatoid arthritis, fibromyalgia, spondylolisthesis (displacement of vertebra) and spinal stenosis (narrowing of spinal canal), temporomandibular disorders, ankylosing spondylitis, headaches as sole or principal condition including cervicogenic headache, etc. Consensus among the internal steering committee specified the following exemptions: osteoarthritis, whiplash, radiculopathy, neck pain "of mechanical origin," pain associated with vertigo, cervico-brachial pain syndrome, spondylosis, trauma-induced pain, disc herniation, cervicobrachial, cervico-craniofacial pain, and "occupational" neck pain.
Interventions mobilization or manipulation	Bronfort et al. defines mobilization as "the application of manual force to the spinal joints within the passive range of joint motion that does not involve a thrust (p. 336)."(8) The RAND report by Coulter et al. defines mobilization as "controlled, judiciously applied force of low velocity and variable amplitude directed to spinal joint segment(s)" (p. xi).(15,19,20) Spinal manipulation is defined as "the application of high-velocity, low amplitude manual thrusts to the spinal joints slightly beyond the passive range of joint motion," by Bronfort et al.,(8) where the RAND report by Coulter et al. defines spinal manipulation as "a controlled, judiciously applied dynamic thrust adjustment, that may include combined extension and rotation of the upper cervical spinal segments, or low-velocity and low-amplitude force with the use of a short or long lever directed to spinal joint segments within patient tolerance" (p. xi).	The interventions in this systematic review consist of manipulation and/or mobilization in chiropractic settings and other non-invasive therapies including osteopathy, manual therapy and physical therapy. For simplicity, interventions were categorized into thrust and non-thrust interventions. When combined with other active interventions, they were labeled as "programs".
Control/ comparator(s)	This review focused on any intervention being compared to mobilization or manipulation, including any active therapy (i.e., exercise, physical therapy), manipulation (thrust), mobilization (nonthrust), sham, no-treatment, usual or standard care.	For purpose of analysis, controls/comparisons were categorized as active, sham, or no treatment, or as direct comparisons between various thrust or non-thrust interventions.
Outcome(s)	Although pain reduction was predefined as the primary outcome of interest, the most commonly reported pain-related, patient reported outcomes that affect health status were determined through a scoping review and thus pooled to determine which could be assessed.	Patient-reported outcomes that the majority of studies include to date: pain intensity/severity (as measured by a VAS or NRS scale) disability (as measured by the Neck Disability Index (NDI), health-related quality of life (HRQoL) as measured by the SF-36/SF-12 and/or safety.
Study Design(s)	All study designs were considered for the purposes of scoping the literature.	Randomized controlled trials were included in the systematic review and meta-analysis.

proach, labeled as a "program" if the observed effect could not be attributed directly to the unimodal thrust or nonthrust intervention (e.g., a study of chiropractic plus acupuncture vs. usual care would be multimodal and labeled as a "program" because chiropractic would serve as an adjunctive therapy to acupuncture, separate from chiropractic plus exercise vs. exercise in which the observed effect could be attributed to the addition of chiropractic); 3) compared to sham, no treatment or any other active therapies, such as exercise, physiotherapy, or physical therapy; and 4) at least one outcome measuring a reduction in pain intensity/severity. Although all study designs were captured for the scoping of the literature, only RCTs involving adult human subjects (aged ≥ 18 years) were considered for this systematic review and meta-analysis (Table 1).

For simplicity and because eligible studies included many types and styles of therapies, the authors chose to refer to the manipulation therapies as "thrust" and mobilization therapies as "nonthrust." The studies describing programs and in which the effects could not be attributed to thrust or nonthrust alone (multimodal studies) were separated from those studies in which the effect could be attributed to thrust or nonthrust (unimodal studies) for the remainder of the systematic review methods and to describe the quality of the evidence for included studies.

Quality Assessment and Data Extraction

Risk of bias was assessed independently by 6 reviewers in duplicate using the Scottish Intercollegiate Guidelines Network (SIGN 50) checklist for RCTs (24). We assessed external and model validity using the External Validity Assessment Tool (EVAT) (25), which measures the generalizability of research to other individuals (external validity) and settings (model validity) outside a study's confines. We extracted data to describe each included study, including the population, intervention, control/comparators, and outcomes at specific timepoints and across various prescribed doses of treatment.

Data Synthesis and Analysis

Studies were grouped and labeled according to: 1) duration of chronic pain (i.e., at least 3 months, 6 months, and 12 months); and 2) studies considered unimodal with intervention arms consisting of thrust or nonthrust compared to a sham, no treatment, another active intervention, or a head-to head comparison, or separately, when combined as a multimodal approach. This grouping exercise allowed for the comparison of interventions. It was also an attempt to reduce heterogeneity.

We extracted data from studies when available for sample size, and mean and standard deviation for each treatment group in pain intensity, disability, and HRQoL outcomes at each timepoint: closest to one month, 3 months, and 6 months. We computed an unbiased estimate using the Hedges' effect size (26) and 95% lower and upper limits, regardless of whether a study was eligible for meta-analysis for all studies categorized as unimodal (Appendix Table 1). A negative effect size indicated a reduction in pain intensity or disability, and favored manipulation or mobilization. For HRQoL, a positive effect size indicated an increase in HRQoL with treatment at those timepoints and favored manipulation or mobilization.

A minimum of 3 studies with sufficient homogeneity was considered for meta-analysis. Single treatment studies (one dose over one day), as well as multimodal interventions in which the effects of manipulation/mobilization could not be distinguished from the total program, were excluded from any attempted pooling for meta-analysis. For subsets in which authors felt studies were similar enough to pool and data were available, standardized mean differences (SMD) were computed using Comprehensive Meta-Analysis software, Version 3.3.070 (CMA; Biostat, Englewood, NJ). Meta-analyses of SMD were performed with the generic inverse model of REVMAN (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). We used random effects models; statistical heterogeneity was examined by I^2 with low, moderate, and high I^2 values of 25%, 50%, and 75%, respectively. We assessed publication bias using the Begg adjusted rank correlation test (27) and the Egger regression asymmetry test (28). Pooled effect sizes for pain and disability outcomes were translated into the visual analog scale (VAS, 0-100) using a standard deviation of 25 points, and the neck disability index (NDI, 0-50) using a standard deviation of 12.5 points, respectively for clinical interpretation (29,30). For constructing forest plots, a negative effect size indicated a reduction in pain intensity or disability and favored manipulation or mobilization; therefore, the thrust is on the left side (-) column and active on the right. For HRQoL, a positive effect size indicated an increase in HRQoL with treatment at those timepoints and favored manipulation or mobilization. Therefore, the effect is on the right side for this outcome (+).

Regardless of whether studies were included in the meta-analysis or not, we followed the Grading of Recom-

mendations, Assessment, Development, and Evaluation approach, to determine our confidence in the effects reported and overall quality of the literature (31).

Results

Our search of multiple databases for studies of both low back and neck pain yielded 7,460 records (Fig. 2). The systematic review for chronic low back pain has already been published (32). We report here only on the 47 unique randomized trials (53 publications total) eligible for evaluation related to chronic nonspecific neck pain. Of these, 37 unique trials (42 publications) (33-74) were identified as unimodal in which the effect of manipulation and/or mobilization could be distinguished

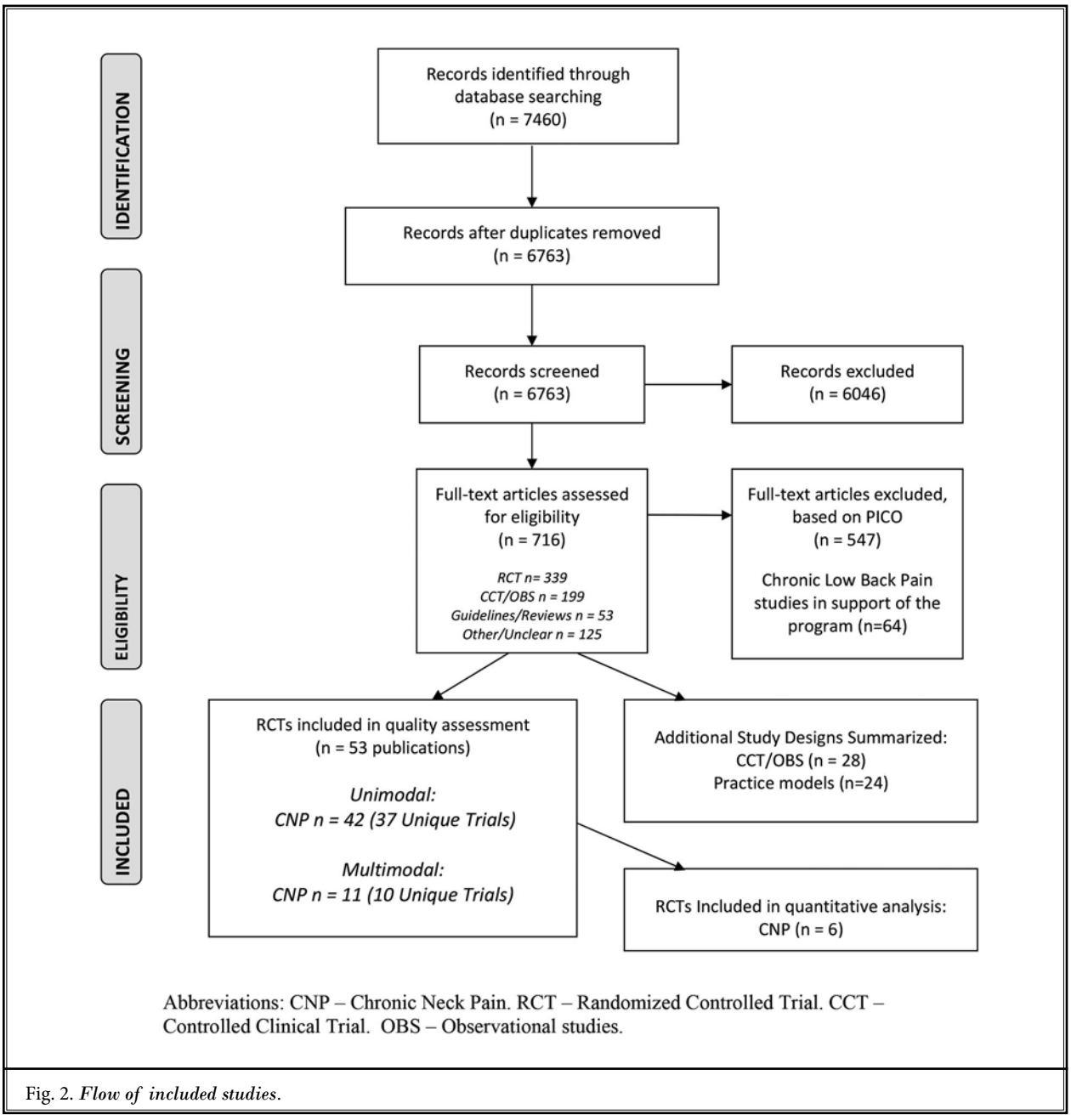

Fig. 2. *Flow of included studies.*

from that of the comparator. Ten trials (11 publications) (75-85) were multimodal studies that were designed more as "programs." All the studies were included in the qualitative analysis.

Study Characteristics

Characteristics of included studies are detailed in Appendix Tables 1 and 2. The 47 included trials examining either a uni- or multimodal intervention of thrust and/or nonthrust for patients with chronic nonspecific neck pain were published between January 2000 and September 2015. No studies meeting the eligibility criteria were found between January 2016 and September 2017. The total number of patients across the 47 trials was 4,460, ranging from 16 in the smallest to 409 in the largest study. The average age of the patients was approximately 40 years, ranging from ages 19-65 years. The studies included more men than women. For unimodal and multimodal studies separately, average duration of chronic pain ranged from 3 months or more in 63% and 40% studies, > 6 months in 5% and 20%, and greater than one year in 32% and 40% of included trials, respectively.

Of the 37 unimodal studies, 46% were identified as thrust interventions, 31% as nonthrust interventions, 19% included both thrust and nonthrust intervention arms, and 4% used a combination of both thrust and nonthrust as the intervention. The multimodal studies included combination therapies, such as chiropractic care, manual and physical therapy combined with commonly prescribed exercises, massage, ultrasound, education, or advice in which the effect of the thrust or nonthrust could not be distinguished from that of the program. The treatment period of studies was not consistent and ranged from one day to across 4 months with as few as a single treatment to up to 20 treatments over 12 weeks (Appendix Tables 1 and 2).

Studies reported outcomes related to pain intensity/severity, disability, and HRQoL. The most common outcome measures used were the pain intensity VAS, the NDI, and the Short Form-36 (SF-36) (Appendix Tables 1 and 2).

Methodological Quality

According to the SIGN 50 criteria used to assess the risk of bias, 18 of the 37 unimodal studies were judged to be of high quality (++), 16 of acceptable quality (+), and 3 of low quality (0) (Appendix Table 1). The number of studies that were judged either well covered or adequately addressed for SIGN 50 criteria included baseline similarities between groups (36/37) at the start of the trial, relevant outcomes measured using valid and reliable methods (35/37), dropout rates (35/37), intention-to-treat analysis (30/37), an appropriate and clearly focused question (37/37), randomization process (34/37), allocation concealment (27/37), blinding (31/37), and group differences (33/37). When treatment was conducted at multiple sites, 4 out of the 5 multisite studies did not mention if results were comparable across sites (Table 2). The 10 unique studies evaluating multimodal approaches for chronic neck pain were all rated for risk of bias as acceptable quality (+) according to SIGN 50 RCT criteria (75-80,82-85) (Appendix Table 2). Categories that were poorly addressed include multisite similarities (6/10) and group differences (6/10) (Table 2).

In general, we judged that all EVAT categories were adequately addressed in terms of the recruitment and participation of those intended for study. However, the staff, places, and facilities in which the treatment was being delivered were not always clearly described to the reader (16/37 unimodal studies and 3/10 multimodal studies). Several types of practitioners delivered the treatment including physical therapists, chiropractors, and massage therapy students, and in some studies, multiple therapists delivered the interventions. Treatments were commonly conducted at multiple locations, as one would often see in real-life practice, including private clinics, hospitals, and universities (Table 2).

Adverse Events

Of the 37 unimodal RCTs, 12 reported that no adverse events occurred during the study; 10 reported minor adverse events, typically transient increases in pain in the area of treatment or overall soreness. The remaining 15 studies did not provide any information on adverse events. Of the 10 multimodal studies, 2 reported minor adverse events such as muscle soreness or increased pain or tiredness; one study reported that no adverse events had occurred during the study. The remaining 7 did not describe any adverse events or mention whether they occurred during the study (Appendix Tables 1 and 2).

Multimodal Studies

We did not attempt meta-analysis for the multimodal studies given the heterogeneity and varying combinations of interventions being used for each program. Overall, regardless of intervention types, half (n = 5/10) of the studies (76,78,79,81-83) reported a positive effect on pain outcomes; studies with nonthrust inter-

Table 2. *Quality assessment of included studies.*

Percentage (n)	Unimodal Studies				Multimodal Studies			
SIGN Criteria	Poor	Adequate	Well	NA	Poor	Adequate	Well	NA
Appropriate and clearly focused question	-	54% (20)	46% (17)	-	10% (1)	60% (6)	30%(3)	-
Randomization	8% (3)	70% (26)	22% (8)	-	10% (1)	80% (8)	10% (1)	-
Allocation concealment	27% (10)	57% (21)	16% (6)	-	20% (2)	80% (8)	-	-
Blinding	16% (6)	81% (30)	3% (1)		10% (1)	90% (9)	-	-
Percentage of dropouts	5% (2)	22% (8)	73% (27)	-	-	40% (4)	60% (6)	-
Baseline similarities	3% (1)	35% (13)	62% (23)	-	10% (1)	60% (6)	30% (3)	-
Group differences	11% (4)	86% (32)	3% (1)	-	60% (6)	40% (4)	-	-
Outcome reliability/validity	5% (2)	22% (8)	73% (27)	-	-	70% (7)	30% (3)	-
Intention-to-treat analyses	19% (7)	16% (6)	65% (24)	-	10% (1)	20% (2)	70% (7)	-
Multi-site similarities	11% (4)	-	3% (1)	86% (32)	60% (6)	-	-	40% (4)
EVAT Criteria	Poor	Adequate	Well	NA	Poor	Adequate	Well	NA
Recruitment	8% (3)	92% (34)	-	-	-	100% (10)	-	-
Participation	14% (5)	49% (18)	37% (14)	-	10% (1)	80% (8)	10% (1)	-
Model Validity	43% (16)	35% (13)	-	22% (8)	30% (3)	50% (5)	10% (1)	10% (1)

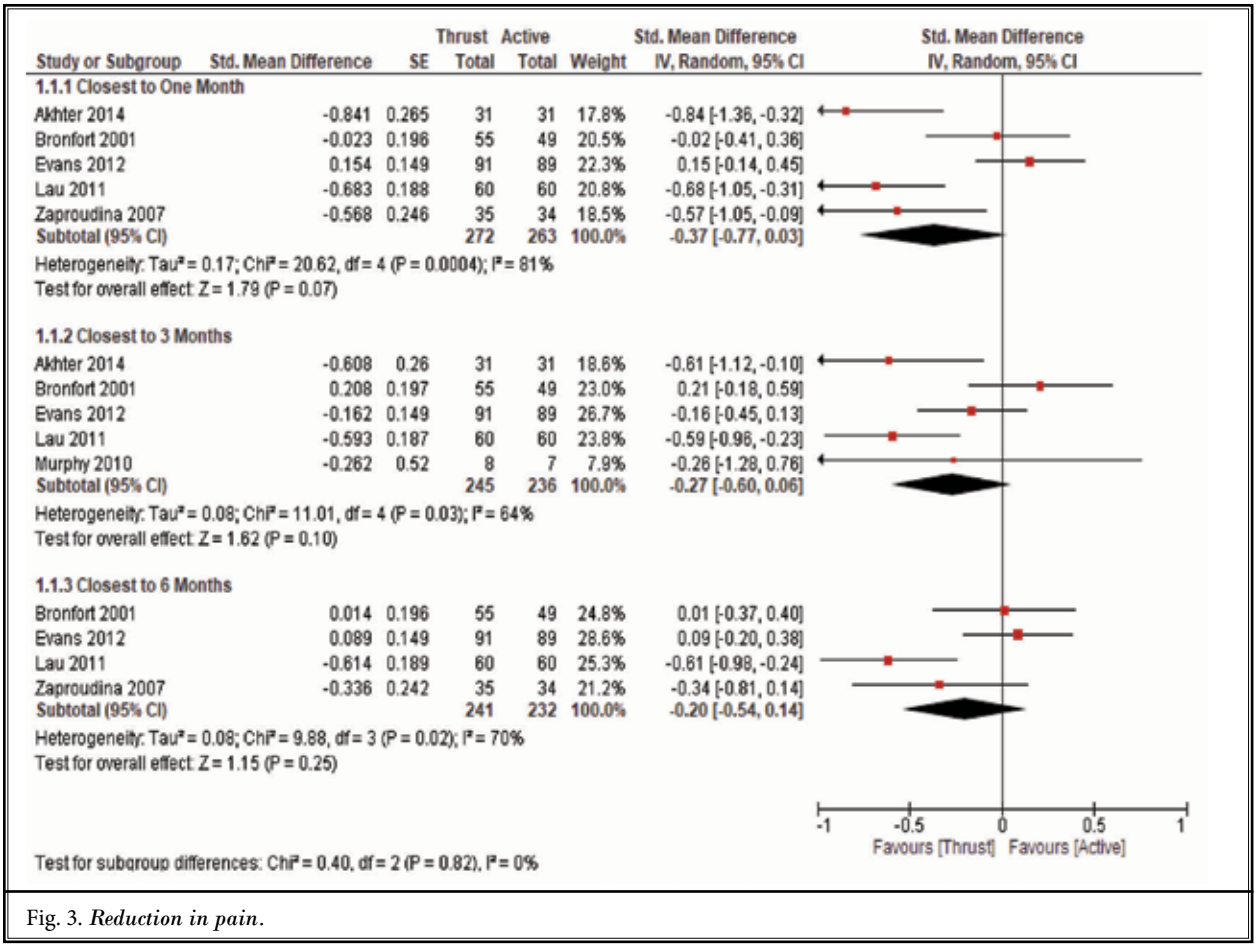

Fig. 3. *Reduction in pain.*

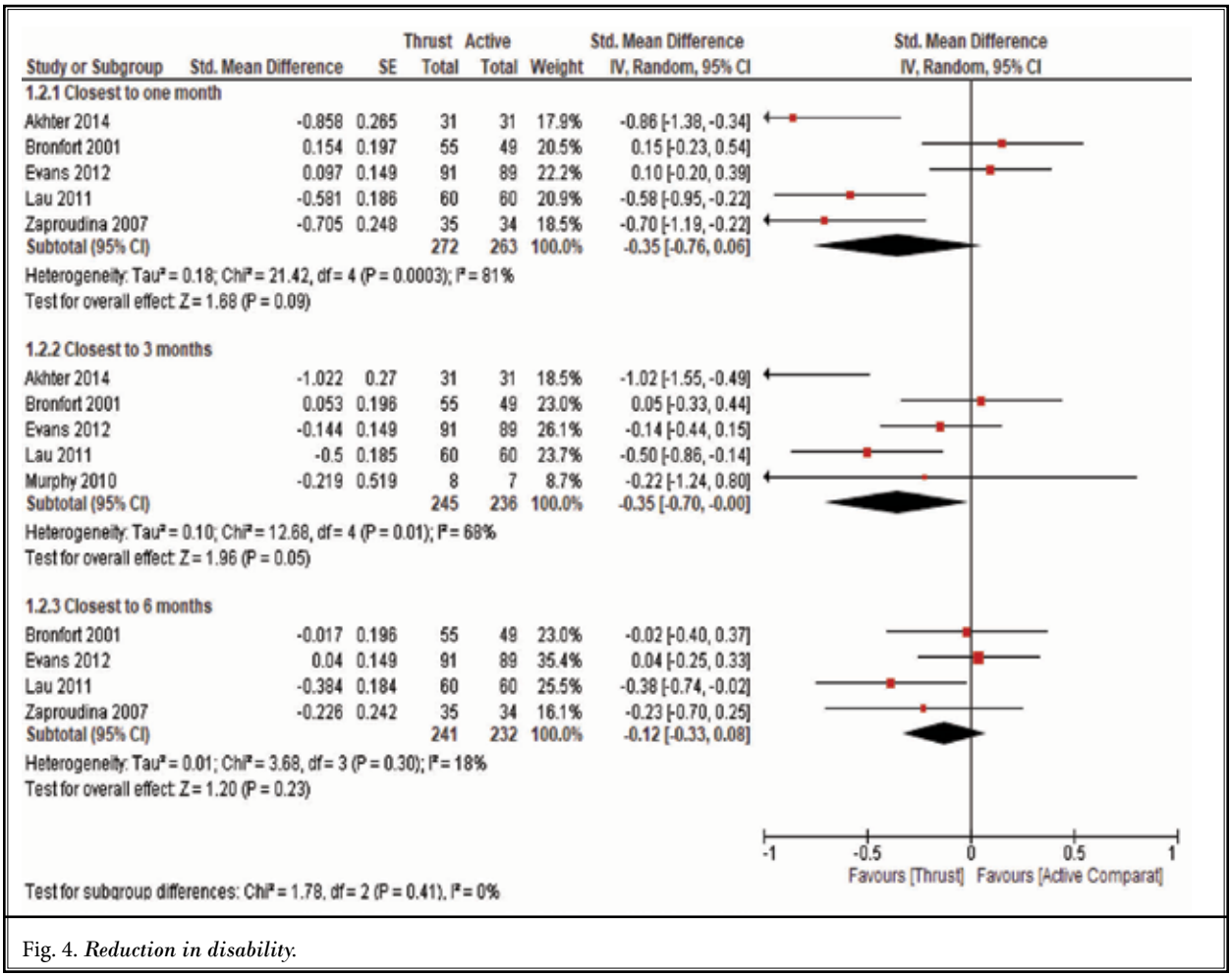

Fig. 4. *Reduction in disability.*

ventions trended toward greater pain reductions than did interventions with thrust. Of the 8 studies measuring disability as an outcome, 7 reported improved function using a multimodal approach; only one study assessed HRQoL as an outcome (Appendix Table 2).

Unimodal Studies

The unimodal studies published since January 2000 comparing thrust to either sham (n = 5) or no treatment (n = 3) included treatment of one dose/one day (n = 5/8 studies) or varied in duration or types of interventions/comparators, which prevented pooling. These studies have small samples and show mixed results for a reduction in pain; only one study measured disability and 2 studied HRQoL. The studies comparing nonthrust to either sham or no treatment (n = 4) were all of one dose/one day treatment; 3 of the 4 studies did not show any immediate reduction in pain; only one study assessed disability as an outcome. The studies comparing nonthrust to active comparators were also either one dose/one day treatment or compared interventions too different to pool (n = 4). There were also studies comparing different styles or doses of thrust and/or nonthrust (Appendix Table 1).

There were 6 studies the authors believed could be combined and compared thrust interventions that included an exercise regimen to exercise alone at timepoints closest to 1, 3, and 6 months follow-up. The authors believed meta-analysis could be attempted for the outcomes of pain, disability, and HRQoL (Figs. 3-5). The pooled SMD across 5 studies (535 patients) closest to one month showed a nonstatistically significant reduction in pain in favor of thrust plus exercise versus exercise regimen alone (SMD = –0.37; 95% confidence

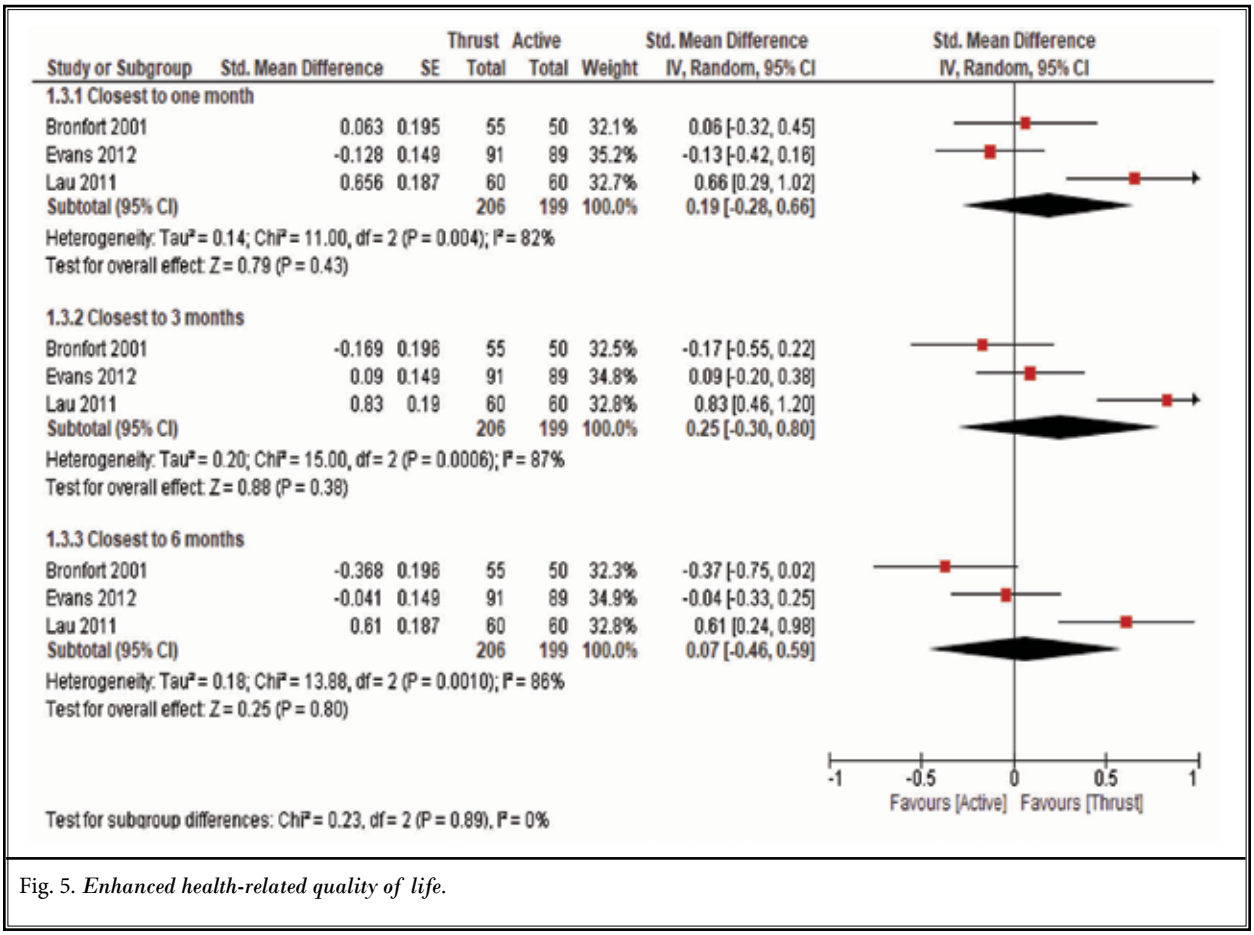

Fig. 5. *Enhanced health-related quality of life.*

interval [CI], –0.77 to 0.03; *P* = 0.07; I^2 = 81%). Translated into the VAS, this equates to a 9.25-point change on a 0-100 scale. A similar effect is noted (SMD = –0.27; 95% CI, –0.60 to 0.06; *P* = 0.10; I^2 = 64%) at 3 months across 5 studies (481 patients); at 6 months even less of an effect is observed across 4 trials (473 patients) (SMD = –0.20; 95% CI, –0.54 to 0.14; *P* = 0.25; I^2 = 70%) (Fig. 3). Across these same studies, meta-analysis produced similar results for a reduction in disability. At the timepoint nearest one month, a nonstatistically significant reduction in disability favored thrust plus exercise compared to exercise alone (SMD = –0.35; 95% CI, –0.76 to 0.06; *P* = 0.09; I^2 = 81%). Translated into the NDI, this equates to a 4.4-point change on a 0-50 scale. SMD for a reduction in disability at 3 months (SMD = –0.35; 95% CI, –0.70 to 0.00; *P* = 0.05; I^2 = 68%), and at 6 months across 3 trials (473 patients) (SMD = –0.12; 95% CI, –0.33 to 0.08; *P* = 0.23; I^2 = 18%) (Fig. 4). HRQoL was pooled across 3 studies closest to 1, 3, and 6 months (405 patients); at one month (SMD = 0.19; 95% CI, –0.28 to 0.66; *P* = 0.43; I^2 = 82%); at 3 months (SMD = 0.25; 95% CI, –0.30 to 0.80; *P* = 0.38; I^2 = 87%), and at 6 months (SMD = 0.07; 95% CI, –0.46 to 0.59; *P* = 0.80; I^2 = 86%) (Fig. 5).

Confidence in the Effect Estimates

Overall, risk of bias was not of serious concern across all studies evaluated for systematic review. Methodological quality of studies since 2000 is adequate. However, heterogeneity was of serious concern for this systematic review, and results are not consistent across included studies. Clinical heterogeneity hindered our ability to pool attempted subsets or categories of studies and comparators as well as varying intervention approaches, treatment doses, and duration of studies reported in the literature. There were only 6 studies for which the authors judged meta-analysis to be feasible. The studies looked at the effect of thrust plus exercise versus exercise alone at timepoints of 1, 3, and 6 months. As expected, we detected a statistically significant degree of heterogeneity in these pooled

studies' analyses except for closest to 6 months for disability when the studies similarly report small or no effect favoring either approach. Outcomes measures, however, appear consistent, and report the VAS, NDI, and SF-36 tools at varying timepoints. Sample sizes remained small across studies. Although the studies were directly related to our research question, inconsistency and small sample size contributed to overall imprecision. We did not detect any publication bias according to either the Begg or Egger tests according to groupings (data not shown). Considering these factors, our confidence in the effect estimates are limited, and we graded the overall literature pool as low to moderate quality evidence. Our evaluation and Appendix Tables 1 and 2 display these different approaches preventing pooling.

Discussion

There is low to moderate quality evidence that various types of manipulation and/or mobilization will reduce pain and improve function for chronic nonspecific neck pain compared to other interventions. Many of the previous reviews of chronic nonspecific neck pain report evidence in favor of manipulation and mobilization for patients with chronic neck pain. However, most of these studies also report that methodological flaws render the evidence insufficient or inconclusive, making it inappropriate to conclude that manipulation and/or mobilization are more effective compared to usual care or other CIM therapies.

We relied on the evidence from previous reviews (8,15,19,20) as a starting point for this review. The Shekelle and Coulter (15) review found that there is greater evidence for manipulation and mobilization of chronic low back pain compared to chronic neck pain. Both the Bronfort et al (8) systematic review and the Shekelle and Coulter (15) systematic review emphasized the need for future trials to examine well-defined subgroups of patients, and to further assess the value of manipulation and mobilization to establish the optimal number of treatment visits. In 2010, Gross et al (5) published a Cochrane Review on manipulation and mobilization of neck pain. The Gross et al (5) review reported conclusions similar to those in our review and in the Bronfort et al (8) systematic review (i.e., moderate evidence that thrust/nonthrust is equal to or superior to general practitioner management for short-term pain reduction for chronic neck pain patients).

Other systematic reviews (12,86) have also found that therapies involving manual therapy (thrust/nonthrust) and exercise are more effective than other noninvasive alternative strategies for patients with chronic neck pain. Vernon et al (87,88) published 2 systematic reviews on neck pain. They indicated moderate to high quality evidence in support of spinal manipulation or mobilization for chronic nonspecific neck pain (8,15,19,20,87).

Strengths and Limitations

Although this review builds on previous efforts, it adds to the literature base by including both manipulation and mobilization interventions not only in chiropractic settings, but in other noninvasive therapy settings such as osteopathy, manual therapy, and physical therapy. We attempted to sort the literature in the most homogeneous fashion, predefining eligibility criteria and specifying precise definitions with subject matter experts. Still, few studies could be pooled for meta-analysis. The methodological quality of studies published since 2000 appears to be adequate overall; few studies suffered from methodological flaws that would risk biasing the reported results. However, the studies remain heterogeneous in terms of dose, styles of interventions, controls/comparators being used across studies, and chronicity of patients is not always consistently defined across studies included. We attempted to create homogeneous subsets of data through the current analysis. Doing so may have reduced the power of calculations when only a small number of studies could be pooled. Further research is likely to have an important impact on the evidence.

Most systematic reviews that evaluate treatment efficacy for musculoskeletal disorders such as chronic neck pain give preference to including unimodal rather than multimodal approaches. As noted previously, studies with unimodal approaches can better isolate (statistically) the individual effects of mobilization and manipulation. In contrast, assessing the effect of multimodal programs can be problematic, especially when meta-analysis is desired. However, multimodal programs may better represent "real-world" clinical practice and may translate to clearer clinical knowledge (89).

The approaches used in the multimodal intervention studies are heterogeneous between, and in some cases within, individual studies. Some studies evaluate a specific standard program; some evaluate classification-based approaches in which patients are assigned therapies based on an assessment of the etiology of their

pain; and some are pragmatic trials that allow practitioners to choose specific treatments for each patient. Because the study of multimodal programs is more difficult than that for unimodal interventions, largely owing to their heterogeneity, it is difficult to interpret the evidence. However, these types of approaches are more likely what one would see in practice (90). As groups such as chiropractors are accepted more widely in such treatment settings and hospitals, the norm is likely to be multimodal care. The majority of nonthrust multimodal studies trended toward showing significant pain reduction results compared to that of the thrust multimodal studies. However, additional treatment modalities (e.g., prescribed exercises, stretches, massage, ultrasound, education, or advice) were used in conjunction with manual manipulation and mobilization treatments, so the causal link between treatment and clinical effect cannot be substantiated. This trend is also in contrast to the unimodal studies, in which thrust interventions may appear to be more effective than nonthrust in reducing pain intensity.

The research to support manipulation and mobilization as a treatment for chronic nonspecific neck pain is complicated and trying to dissect it to draw specific conclusions proved challenging. Stakeholders, including physicians and their patients, should have an active voice at the table when identifying what will be most impactful to them and building future research agendas. This review can serve as a guide to the categories of studies with strength areas for treating chronic neck pain with manipulation and mobilization, and the settings in which multimodal approaches were incorporated in which there may be an increased benefit to the patient.

Although the focus of this review was on randomized trials, it is important to note that available research on manipulation and mobilization for the treatment of chronic nonspecific neck pain encompasses study designs other than the randomized controlled trial (e.g., cohort studies [both perspective and retrospective], observational studies, and others). The use of observational studies is important for building the evidence base in which randomized trials are lacking or are insufficient for the task (e.g., assessing adverse effects, identifying best practices, and understanding disparities in access to and delivery of health care services).

Conclusions

There is low to moderate quality evidence that various types of manipulation and/or mobilization will reduce pain and improve function for chronic nonspecific neck pain compared to other interventions. The methodological quality of the reported trials from 2000 to 2017 is adequate to evaluate. The studies remain heterogeneous in terms of dosing, duration of treatment, interventions, and comparators. For these reasons, it remains a challenge to draw conclusions and have confidence in any estimated effect that could be confirmed as a benefit of mobilization and manipulation alone for chronic neck pain beyond other therapies. Based only on the trial literature to date, these therapies do appear to be safe. However, large longitudinal studies are needed to establish safety.

Acknowledgments

The authors would like to acknowledge the following individuals for their technical and administrative support throughout the project: Cindy Lentino, Viviane Enslein, Chris Baur, John Bingham, Holly Chittum, Laurie Davidson, and Judy Bearer.

Author contributions: Dr. Ian Coulter had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses. Drs. Coulter, Vernon, Hurwitz, and Herman—with the support of Ms. Crawford and Dr. Khorsan—designed the study protocol. Ms. Crawford, Ms. Booth, and Dr. Khorsan managed the literature searches and summaries of previous related work and wrote the first draft of the manuscript. Drs. Coulter, Vernon, Hurwitz, and Herman provided revision for intellectual content and final approval of the manuscript.

Appendix

Appendix Table 1

Appendix Table 2

To view pdf with Appendix links active, visit
Pain Physician journal website
to access manuscript pdf.

References

1. Cote P, Cassidy JD, Carroll L; The Saskatchewan Health and Back Pain Survey. The prevalence of neck pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1689-1698.
2. Martin BI, Gerkovich MM, Deyo RA, Sherman KJ, Cherkin DC, Lind BK, Goertz CM, Lafferty WE. The association of complementary and alternative medicine use and health care expenditures for back and neck problems. *Med Care* 2012; 50:1029-1036.
3. Borghouts JA, Koes BW, Vondeling H, Bouter LM. Cost-of-illness of neck pain in The Netherlands in 1996. *Pain* 1999; 80:629-636.
4. Korthals-de Bos IB, Hoving JL, van Tulder MW, Rutten-van Molken MP, Ader HJ, de Vet HC, Koes BW, Vondeling H, Bouter LM. Cost effectiveness of physiotherapy, manual therapy, and general practitioner care for neck pain: Economic evaluation alongside a randomised controlled trial. *BMJ* 2003; 326:911.
5. Gross A, Miller J, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N, Haines T, Bronfort G, Hoving JL. Manipulation or mobilisation for neck pain: A Cochrane Review. *Man Ther* 2010; 15:315-333.
6. Evans G. Identifying and treating the causes of neck pain. *Med Clin North Am* 2014; 98:645-661.
7. Cohen S, Hooten W. Advances in the diagnosis and management of neck pain. *BMJ* 2017; 358.
8. Bronfort G, Haas M, Evans RL, Bouter LM. Efficacy of spinal manipulation and mobilization for low back pain and neck pain: A systematic review and best evidence synthesis. *Spine J* 2004; 4:335-356.
9. Peloso P, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie S; Cervical Overview Group. Medicinal and injection therapies for mechanical neck disorders. *Cochrane Database Syst Rev* 2007; 3:CD000319.
10. Carragee EJ, Hurwitz EL, Cheng I, Carroll LJ, Nordin M, Guzman J, Peloso P, Holm LW, Cote P, Hogg-Johnson S, van der Velde G, Cassidy JD, Haldeman S; Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Treatment of neck pain: Injections and surgical interventions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine* 2008; 33(4 Suppl):S153-169.
11. Brison RJ, Hartling L, Dostaler S, Leger A, Rowe BH, Stiell I, Pickett W. A randomized controlled trial of an educational intervention to prevent the chronic pain of whiplash associated disorders following rear-end motor vehicle collisions. *Spine* 2005; 30:1799-1807.
12. Hurwitz EL, Carragee EJ, van der Velde G, Carroll LJ, Nordin M, Guzman J, Peloso PM, Holm LW, Cote P, Hogg-Johnson S, Cassidy JD, Haldeman S; Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Treatment of neck pain: Noninvasive interventions: Results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. *Spine* 2008; 33(4 Suppl):S123-152.
13. Schroeder J, Kaplan L, Fischer DJ, Skelly AC. The outcomes of manipulation or mobilization therapy compared with physical therapy or exercise for neck pain: A systematic review. *Evid Based Spine Care J* 2013; 4:30-41.
14. Gross A, Langevin P, Burnie SJ, Bédard-Brochu MS, Empey B, Dugas E, Faber-Dobrescu M, Andres C, Graham N, Goldsmith CH, Brønfort G, Hoving JL, LeBlanc F. Manipulation and mobilization for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database Syst Rev* 2015; 9:CD004249.
15. Shekelle PG, Coulter I. Cervical spine manipulation: Summary report of a systematic review of the literature and a multidisciplinary expert panel. *J Spinal Disord* 1997; 10:223-228.
16. Bryans R, Decina P, Descarreaux M, Duranleau M, Marcoux H, Potter B, Ruegg RP, Shaw L, Watkin R, White E. Evidence-based guidelines for the chiropractic treatment of adults with neck pain. *J Manipulative Physiol Ther* 2014; 37:42-63.
17. Vincent K, Maigne JY, Fischhoff C, Lanlo O, Dagenais S. Systematic review of manual therapies for nonspecific neck pain. *Joint Bone Spine* 2013; 80:508-515.
18. Furlan AD, Yazdi F, Tsertsvadze A, Gross A, Van Tulder M, Santaguida L, Gagnier J, Ammendolia C, Dryden T, Doucette S, Skidmore B, Daniel R, Ostermann T, Tsouros S. A systematic review and meta-analysis of efficacy, cost-effectiveness, and safety of selected complementary and alternative medicine for neck and low-back pain. *Evid Based Complement Alternat Med* 2012; 2012:953139.
19. Shekelle PG, Adams AH, Chassin MR, Hurwitz EL, Brook RH. Spinal manipulation for low-back pain. *Ann Intern Med* 1992; 117:590-598.
20. Shekelle PG, Hurwitz EL, Coulter I, Adams AH, Genovese B, Brook RH. The appropriateness of chiropractic spinal manipulation for low back pain: A pilot study. *J Manipulative Physiol Ther* 1995; 18:265-270.
21. Office of the Army Surgeon General: Pain Management Task Force. *Pain Management Task Force Final Report: Providing a Standardized DoD and VHA Vision and Approach to Pain Management to Optimize the Care for Warriors and their Families*. Washington, DC: Office of the Army Surgeon General; 2010.
22. Deyo RA, Dworkin SF, Amtmann D, Andersson G, Borenstein D, Carragee E, Carrino J, Chou R, Cook K, DeLitto A, Goertz C, Khalsa P, Loeser J, Mackey S, Panagis J, Rainville J, Tosteson T, Turk D, Von Korff M, Weiner DK. Report of the NIH Task Force on research standards for chronic low back pain. *J Pain* 2014; 15:569-585.
23. Maher C, Underwood M, Buchbinder R. Non-specific low back pain. *Lancet* 2017; 389:736-747.
24. Scottish Intercollegiate Guidelines Network. *Sign 50: A Guideline Developer's Handbook*. 2010 [cited 2015 Jan 1]; Available from: www.sign.ac.uk/. Accessed March 10, 2019.
25. Khorsan R, Crawford C. How to assess the external validity and model validity of therapeutic trials: A conceptual approach to systematic review methodology. *Evid Based Complement Alternat Med* 2014; 2014:694804.
26. Hedges LV, Olkin I. *Statistical Methods for Meta-Analysis*. Orlando, FL: Academic Press; 1985.
27. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; 50:1088-1101.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997; 315:629-634.
29. Assendelft WJ, Morton SC, Yu EI, Suttorp MJ, Shekelle PG. Spinal manipulative therapy for low back pain. A me-

ta-analysis of effectiveness relative to other therapies. *Ann Intern Med* 2003; 138:871-881.

30. Vernon H. The Neck Disability Index: State of the art, 1991-2008. *J Manipulative Physiol Ther* 2008; 31:491-502.
31. GRADE Working Group. *Grading of Recommendations Assessment, Development and Evaluation (GRADE)*. November 30, 2011; Available from: www.gradeworkinggroup.org/. Accessed March 10, 2019.
32. Coulter ID, Crawford C, Hurwitz EL, Vernon H, Khorsan R, Suttorp Booth M, Herman PM. Manipulation and mobilization for treating chronic low back pain: A systematic review and meta-analysis. *Spine J* 2018; 18:866-879.
33. Akhter S, Khan M, Ali SS, Soomro RR. Role of manual therapy with exercise regime versus exercise regime alone in the management of non-specific chronic neck pain. *Pak J Pharm Sci* 2014; 27(6 Suppl):2125-2128.
34. Aquino RL, Caires PM, Furtado FC, Loureiro AV, Ferreira PH, Ferreira ML. Applying joint mobilization at different cervical vertebral levels does not influence immediate pain reduction in patients with chronic neck pain: A randomized clinical trial. *J Man Manip Ther* 2009; 17:95-100.
35. Briem K, Huijbregts P, Thorsteinsdottir M. Immediate effects of inhibitive distraction on active range of cervical flexion in patients with neck pain: A pilot study. *J Man Manip Ther* 2007; 15:82-92.
36. Bronfort G, Evans R, Nelson B, Aker PD, Goldsmith CH, Vernon H. A randomized clinical trial of exercise and spinal manipulation for patients with chronic neck pain. *Spine (Phila Pa 1976)* 2001; 26:788-797; discussion 798-799.
37. Cleland JA, Childs JD, McRae M, Palmer JA, Stowell T. Immediate effects of thoracic manipulation in patients with neck pain: A randomized clinical trial. *Man Ther* 2005; 10:127-135.
38. Dunning JR, Cleland JA, Waldrop MA, Arnot C, Young I, Turner M, Sigurdsson G. Upper cervical and upper thoracic thrust manipulation versus nonthrust mobilization in patients with mechanical neck pain: A multicenter randomized clinical trial. *J Orthop Sports Phys Ther* 2012; 42:5-18.
39. Dziedzic K, Hill J, Lewis M, Sim J, Daniels J, Hay EM. Effectiveness of manual therapy or pulsed shortwave diathermy in addition to advice and exercise for neck disorders: A pragmatic randomized controlled trial in physical therapy clinics. *Arthritis Rheum* 2005; 53:214-222.
40. Escortell-Mayor E, Riesgo-Fuertes R, Garrido-Elustondo S, Asunsolo-Del Barco A, Diaz-Pulido B, Blanco-Diaz M, Bejerano-Alvarez E. Primary care randomized clinical trial: Manual therapy effectiveness in comparison with TENS in patients with neck pain. *Man Ther* 2011; 16:66-73.
41. Evans R, Bronfort G, Nelson B, Goldsmith CH. Two-year follow-up of a randomized clinical trial of spinal manipulation and two types of exercise for patients with chronic neck pain. *Spine (Phila Pa 1976)* 2002; 27:2383-2389.
42. Evans R, Bronfort G, Schulz C, Maiers M, Bracha Y, Svendsen K, Grimm R, Garvey T, Transfeldt E. Supervised exercise with and without spinal manipulation performs similarly and better than home exercise for chronic neck pain: A randomized controlled trial. *Spine* 2012; 37:903-914.
43. Hemmila HM. Bone setting for prolonged neck pain: A randomized clinical trial. *J Manipulative Physiol Ther* 2005; 28:508-515.
44. Hurwitz EL, Goldstein MS, Morgenstern H, Chiang LM. The impact of psychosocial factors on neck pain and disability outcomes among primary care patients: Results from the UCLA Neck Pain Study. *Disabil Rehabil* 2006; 28:1319-1329.
45. Hurwitz EL, Morgenstern H, Harber P, Kominski GF, Yu F, Adams AH. A randomized trial of chiropractic manipulation and mobilization for patients with neck pain: Clinical outcomes from the UCLA neck-pain study. *Am J Public Health* 2002; 92:1634-1641.
46. Hurwitz EL, Morgenstern H, Vassilaki M, Chiang L. Adverse reactions to chiropractic treatment and their effects on satisfaction and clinical outcomes among patients enrolled in the UCLA Neck Pain Study. *J Manipulative Physiol Ther* 2004; 27:16-25.
47. Hurwitz EL, Morgenstern H, Vassilaki M, Chiang L. Frequency and clinical predictors of adverse reactions to chiropractic care in the UCLA Neck Pain Study. *Spine* 2005; 30:1477-1484.
48. Izquierdo Perez H, Alonso Perez JL, Gil Martinez A, La Touche R, Lerma-Lara S, Commeaux Gonzalez N, Arribas Perez H, Bishop MD, Fernandez-Carnero J. Is one better than another? A randomized clinical trial of manual therapy for patients with chronic neck pain. *Man Ther* 2014; 19:215-221.
49. Kanlayanaphotporn R, Chiradejnant A, Vachalathiti R. The immediate effects of mobilization technique on pain and range of motion in patients presenting with unilateral neck pain: A randomized controlled trial. *Arch Phys Med Rehabil* 2009; 90:187-192.
50. Kanlayanaphotporn R, Chiradejnant A, Vachalathiti R. Immediate effects of the central posteroanterior mobilization technique on pain and range of motion in patients with mechanical neck pain. *Disabil Rehabil* 2010; 32:622-628.
51. Klein R, Bareis A, Schneider A, Linde K. Strain-counterstrain to treat restrictions of the mobility of the cervical spine in patients with neck pain: A sham-controlled randomized trial. *Complement Ther Med* 2013; 21:1-7.
52. Lau HM, Wing Chiu TT, Lam TH. The effectiveness of thoracic manipulation on patients with chronic mechanical neck pain: A randomized controlled trial. *Man Ther* 2011; 16:141-147.
53. Lin JH, Shen T, Chung RCK, Chiu TTW. The effectiveness of Long's manipulation on patients with chronic mechanical neck pain: A randomized controlled trial. *Man Ther* 2013; 18:308-315.
54. Lluch E, Schomacher J, Gizzi L, Petzke F, Seegar D, Falla D. Immediate effects of active cranio-cervical flexion exercise versus passive mobilisation of the upper cervical spine on pain and performance on the cranio-cervical flexion test. *Man Ther* 2014; 19:25-31.
55. Lopez-Lopez A, Alonso Perez JL, Gonzalez Gutierez JL, La Touche R, Lerma Lara S, Izquierdo H, Fernandez-Carnero J. Mobilization versus manipulations versus sustain apophyseal natural glide techniques and interaction with psychological factors for patients with chronic neck pain: Randomized controlled trial. *Eur J Phys Rehabil Med* 2015; 51:121-132.
56. Madson TJ, Cieslak KR, Gay RE. Joint mobilization vs massage for chronic mechanical neck pain: A pilot study to assess recruitment strategies and estimate outcome measure variability. *J Manipulative Physiol Ther* 2010; 33:644-651.
57. Marks M, Schottker-Koniger T, Probst A. Efficacy of cervical spine mobilization versus peripheral nerve slider techniques in cervicobrachial pain syndrome: A randomized clinical trial. *J Phys Ther* 2011; 4:9-17.
58. Martel J, Dugas C, Dubois JD, Descar-

reaux M. A randomised controlled trial of preventive spinal manipulation with and without a home exercise program for patients with chronic neck pain. *BMC Musculoskelet Disord* 2011; 12:41.

59. Martinez-Segura R, De-la-Llave-Rincon AI, Ortega-Santiago R, Cleland JA, Fernandez-de-las-Penas C. Immediate changes in widespread pressure pain sensitivity, neck pain, and cervical range of motion after cervical or thoracic thrust manipulation in patients with bilateral chronic mechanical neck pain: A randomized clinical trial. *J Orthop Sports Phys Ther* 2012; 42:806-814.
60. Martínez-Segura R, Fernández-de-las-Peñas C, Ruiz-Sáez M, López-Jiménez C, Rodríguez-Blanco C. Immediate effects on neck pain and active range of motion after a single cervical high-velocity low-amplitude manipulation in subjects presenting with mechanical neck pain: A randomized controlled trial. *J Manipulative Physiol Ther* 2006; 29:511-517.
61. Murphy B, Taylor HH, Marshall P. The effect of spinal manipulation on the efficacy of a rehabilitation protocol for patients with chronic neck pain: A pilot study. *J Manipulative Physiol Ther* 2010; 33:168-177.
62. Pires PF, Packer AC, Dibai-Filho AV, Rodrigues-Bigaton D. Immediate and short-term effects of upper thoracic manipulation on myoelectric activity of sternocleidomastoid muscles in young women with chronic neck pain: A randomized blind clinical trial. *J Manipulative Physiol Ther* 2015; 38:555-563.
63. Saavedra-Hernandez M, Arroyo-Morales M, Cantarero-Villanueva I, Fernandez-Lao C, Castro-Sanchez AM, Puentedura EJ, Fernandez-de-las-Penas C. Short-term effects of spinal thrust joint manipulation in patients with chronic neck pain: A randomized clinical trial. *Clin Rehabil* 2013; 27:504-512.
64. Saavedra-Hernández M, Castro-Sánchez AM, Arroyo-Morales M, Cleland JA, Lara-Palomo I, Fernández-de-las-Peñas C. Short-term effects of kinesio taping versus cervical thrust manipulation in patients with mechanical neck pain: A randomized clinical trial. *J Orthop Sports Phys Ther* 2012; 42:724-730.
65. Saayman L, Hay C, Abrahamse H. Chiropractic manipulative therapy and low-level laser therapy in the management of cervical facet dysfunction: A randomized controlled study. *J Manipulative Physiol Ther* 2011; 34:153-163.
66. Salom-Moreno J, Ortega-Santiago R, Cleland JA, Palacios-Cena M, Truyols-Dominguez S, Fernandez-de-las-Penas C. Immediate changes in neck pain intensity and widespread pressure pain sensitivity in patients with bilateral chronic mechanical neck pain: A randomized controlled trial of thoracic thrust manipulation vs non-thrust mobilization. *J Manipulative Physiol Ther* 2014; 37:312-319.
67. Schwerla F, Bischoff A, Nurnberger A, Genter P, Guillaume JP, Resch KL. Osteopathic treatment of patients with chronic non-specific neck pain: A randomised controlled trial of efficacy. *Forsch Komplementmed* 2008; 15:138-145.
68. Sillevis R, Cleland J. Immediate effects of the audible pop from a thoracic spine thrust manipulation on the autonomic nervous system and pain: A secondary analysis of a randomized clinical trial. *J Manipulative Physiol Ther* 2011; 34:37-45.
69. Sillevis R, Cleland J, Hellman M, Beekhuizen K. Immediate effects of a thoracic spine thrust manipulation on the autonomic nervous system: A randomized clinical trial. *J Man Manip Ther* 2010; 18:181-190.
70. Snodgrass SJ, Rivett DA, Sterling M, Vicenzino B. Dose optimization for spinal treatment effectiveness: A randomized controlled trial investigating the effects of high and low mobilization forces in patients with neck pain. *J Orthop Sports Phys Ther* 2014; 44:141-152.
71. Suvarnnato T, Puntumetakul R, Kaber D, Boucaut R, Boonphakob Y, Arayawichanon P, Chatchawan U. The effects of thoracic manipulation versus mobilization for chronic neck pain: A randomized controlled trial pilot study. *J Phys Ther Sci* 2013; 25:865-871.
72. Vernon HT, Triano JJ, Ross JK, Tran SK, Soave DM, Dinulos M.D. Validation of a novel sham cervical manipulation procedure. *Spine J* 2012; 12:1021-1028.
73. Wood TG, Collaca CJ, Matthews R. A pilot randomized clinical trial on the relative effect of instrumental (MFMA) versus manual (HVLA) manipulation in the treatment of cervical spine dysfunction. *J Manipulative Physiol Ther* 2001; 24:260-271.
74. Zaproudina N, Hanninen OO, Airaksinen O. Effectiveness of traditional bone setting in chronic neck pain: Randomized clinical trial. *J Manipulative Physiol Ther* 2007; 30:432-437.
75. Allan M, Brantingham JW, Menezes A. Stretching as an adjunct to chiropractic manipulation of chronic neck pain--before, after or not at all? A prospective randomized controlled clinical trial. *Eur J Chiropr* 2003; 50:41-52.
76. Allison GT, Nagy BM, Hall T. A randomized clinical trial of manual therapy for cervico-brachial pain syndrome: A pilot study. *Man Ther* 2002; 7:95-102.
77. Gustavsson C, Denison E, Koch Lv. Self-management of persistent neck pain: A randomized controlled trial of a multi-component group intervention in primary health care. *Eur J Pain* 2010; 14:630.e1-630.e11.
78. Klaber Moffett JA, Jackson DA, Richmond S, Hahn S, Coulton S, Farrin A, Manca A, Torgerson DJ. Randomised trial of a brief physiotherapy intervention compared with usual physiotherapy for neck pain patients: Outcomes and patients' preference. *BMJ* 2005; 330:75.
79. Nee RJ, Vicenzino B, Jull GA, Cleland JA, Coppieters MW. Neural tissue management provides immediate clinically relevant benefits without harmful effects for patients with nerve-related neck and arm pain: A randomised trial. *J Physiother* 2012; 58:23-31.
80. Palmgren PJ, Sandstrom PJ, Lundqvist FJ, Heikkila H. Improvement after chiropractic care in cervicocephalic kinesthetic sensibility and subjective pain intensity in patients with nontraumatic chronic neck pain. *J Manipulative Physiol Ther* 2006; 29:100-106.
81. Skillgate E, Bohman T, Holm LW, Vingard E, Alfredsson L. The long-term effects of naprapathic manual therapy on back and neck pain: Results from a pragmatic randomized controlled trial. *BMC Musculoskelet Disord* 2010; 11:26.
82. Skillgate E, Vingard E, Alfredsson L. Naprapathic manual therapy or evidence-based care for back and neck pain: A randomized, controlled trial. *Clin J Pain* 2007; 23:431-439.
83. Walker MJ, Boyles RE, Young BA, Strunce JB, Garber MB, Whitman JM, Deyle G, Wainner RS. The effectiveness of manual physical therapy and exercise for mechanical neck pain: A randomized clinical trial. *Spine (Phila Pa 1976)* 2008; 33:2371-2378.
84. Ylinen J, Kautiainen H, Wiren K, Hakkinen A. Stretching exercises vs manual therapy in treatment of chronic neck pain: A randomized, controlled cross-over trial. *J Rehabil Med* 2007; 39:126-132.

85. Young IA, Michener LA, Cleland JA, Aguilera AJ, Snyder AR. Manual therapy, exercise, and traction for patients with cervical radiculopathy: A randomized clinical trial. *Phys Ther* 2009; 89:632-642.
86. Miller J, Gross A, D'Sylva J, Burnie SJ, Goldsmith CH, Graham N, Haines T, Bronfort G, Hoving JL. Manual therapy and exercise for neck pain: A systematic review. *Man Ther* 2010; 15:334-354.
87. Vernon H, Humphreys K, Hagino C. Chronic mechanical neck pain in adults treated by manual therapy: A systematic review of change scores in randomized clinical trials. *J Manipulative Physiol Ther* 2007; 30:215-227.
88. Vernon H, Humphreys BK. Manual therapy for neck pain: An overview of randomized clinical trials and systematic reviews. *Eura Medicophys* 2007; 43:91-118.
89. Jull G, Moore A. Systematic reviews assessing multimodal treatments. *Man Ther* 2010; 15:303-304.
90. Goertz CM, Long CR, Vining RD, Pohlman KA, Kane B, Corber L, Walter J, Coulter I. Assessment of chiropractic treatment for active duty, U.S. military personnel with low back pain: Study protocol for a randomized controlled trial. *Trials* 2016; 17:70.