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

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Abstract

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

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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.

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.

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.

Keywords

Chronic neck pain; nonspecific; chiropractic; manipulation; mobilization; systematic review; meta-analysis; appropriateness

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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 present 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 approach, 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 Co-chrane 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 Recommendations, 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 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 interventions 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 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/non-thrust) 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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APPENDIX

Appendix Table 1

Appendix Table 2

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

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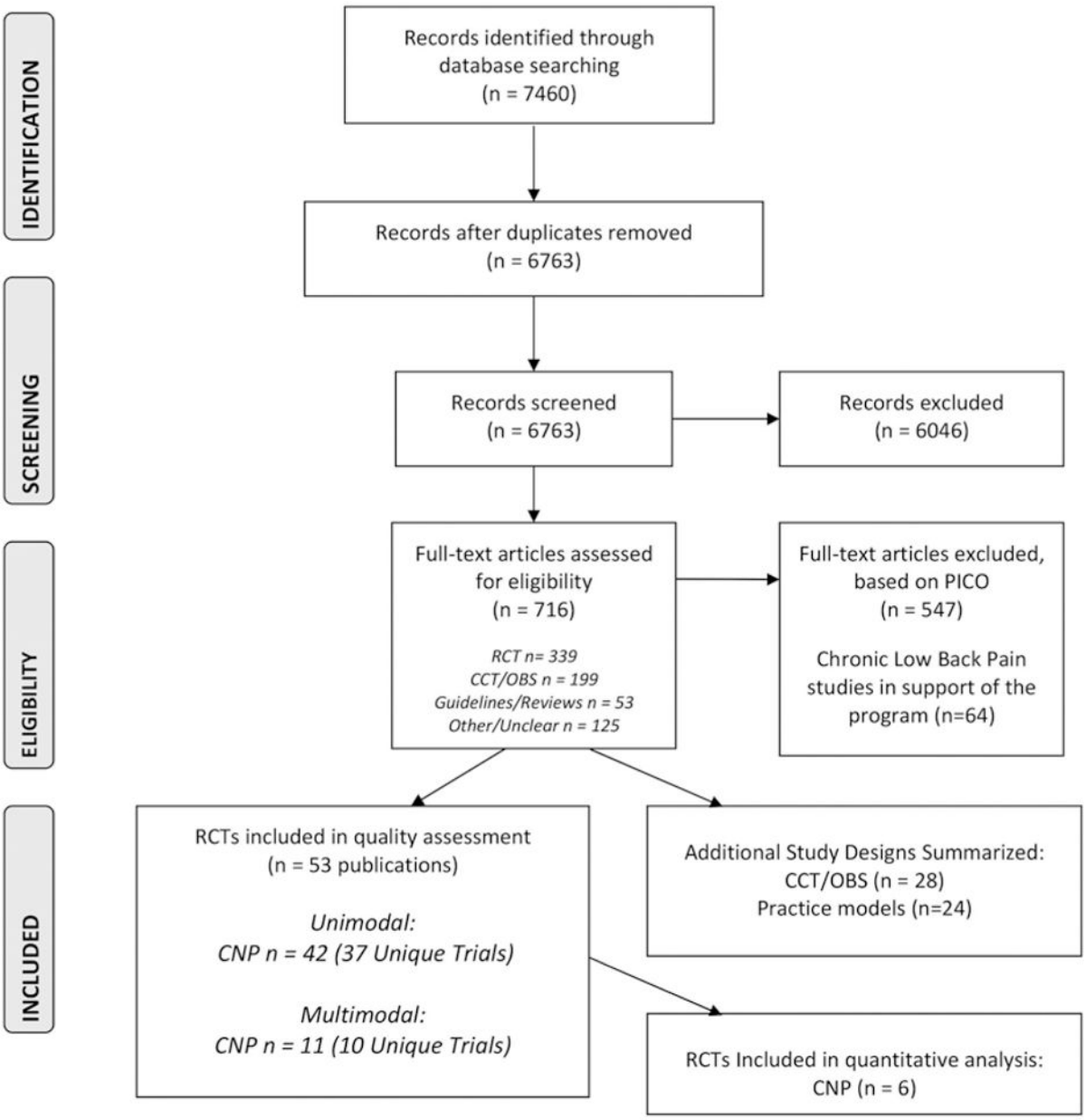
(Manipulation Osteopathic OR Chiropractic Manipulation OR Spinal Manipulation OR Musculoskeletal Manipulation OR Osteopathic Medicine OR Chiropractic OR manipulation orthopedic OR mobiliz* OR Manipulate OR manual therapy Or "Spinal Manipulative Therapy" OR SMT) and (back injury OR neck pain OR cervical 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.



Abbreviations: CNP – Chronic Neck Pain. RCT – Randomized Controlled Trial. CCT – Controlled Clinical Trial. OBS – Observational studies.

Fig. 2.
Flow of included studies.

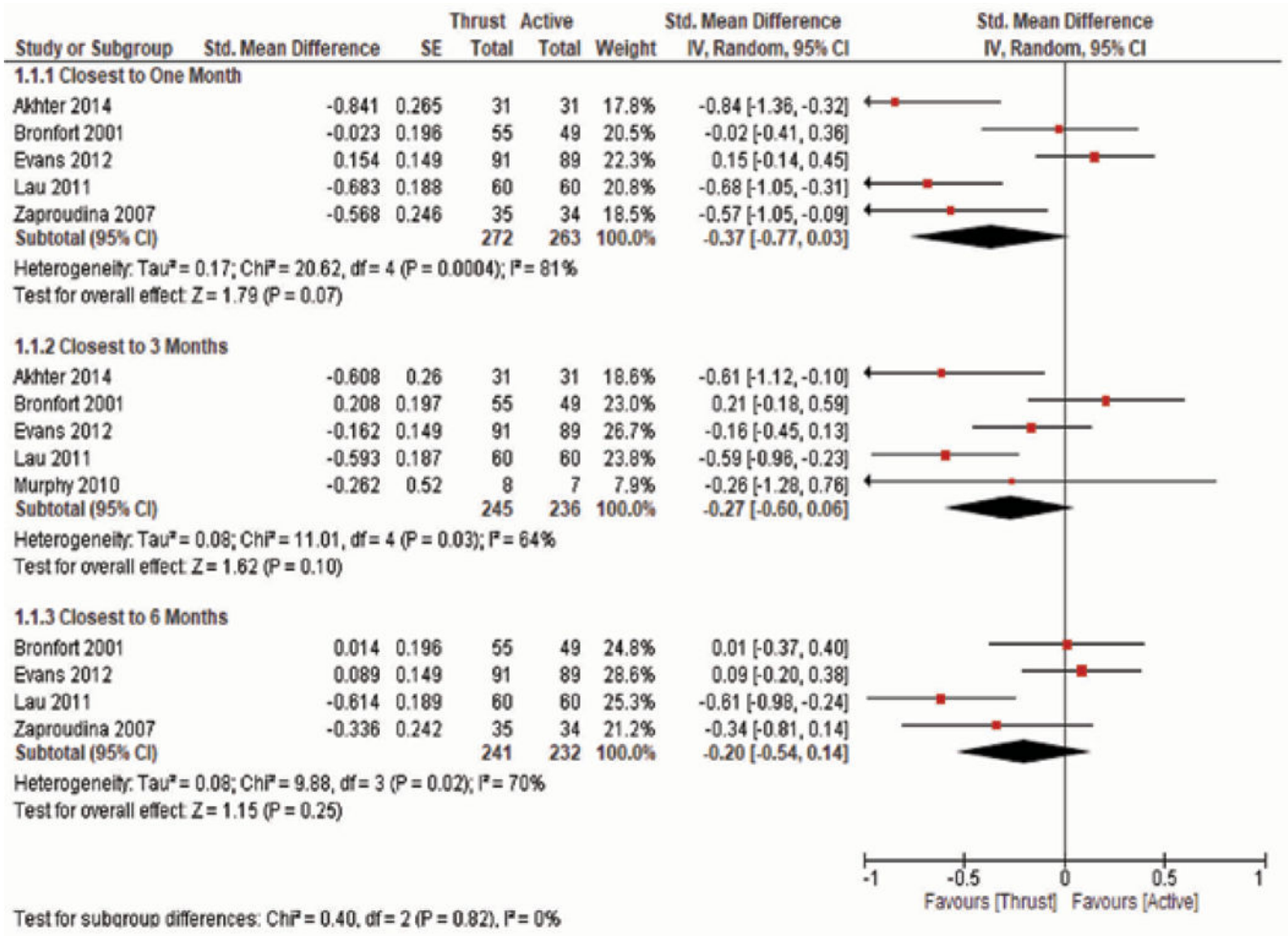


Fig. 3.
Reduction in pain.

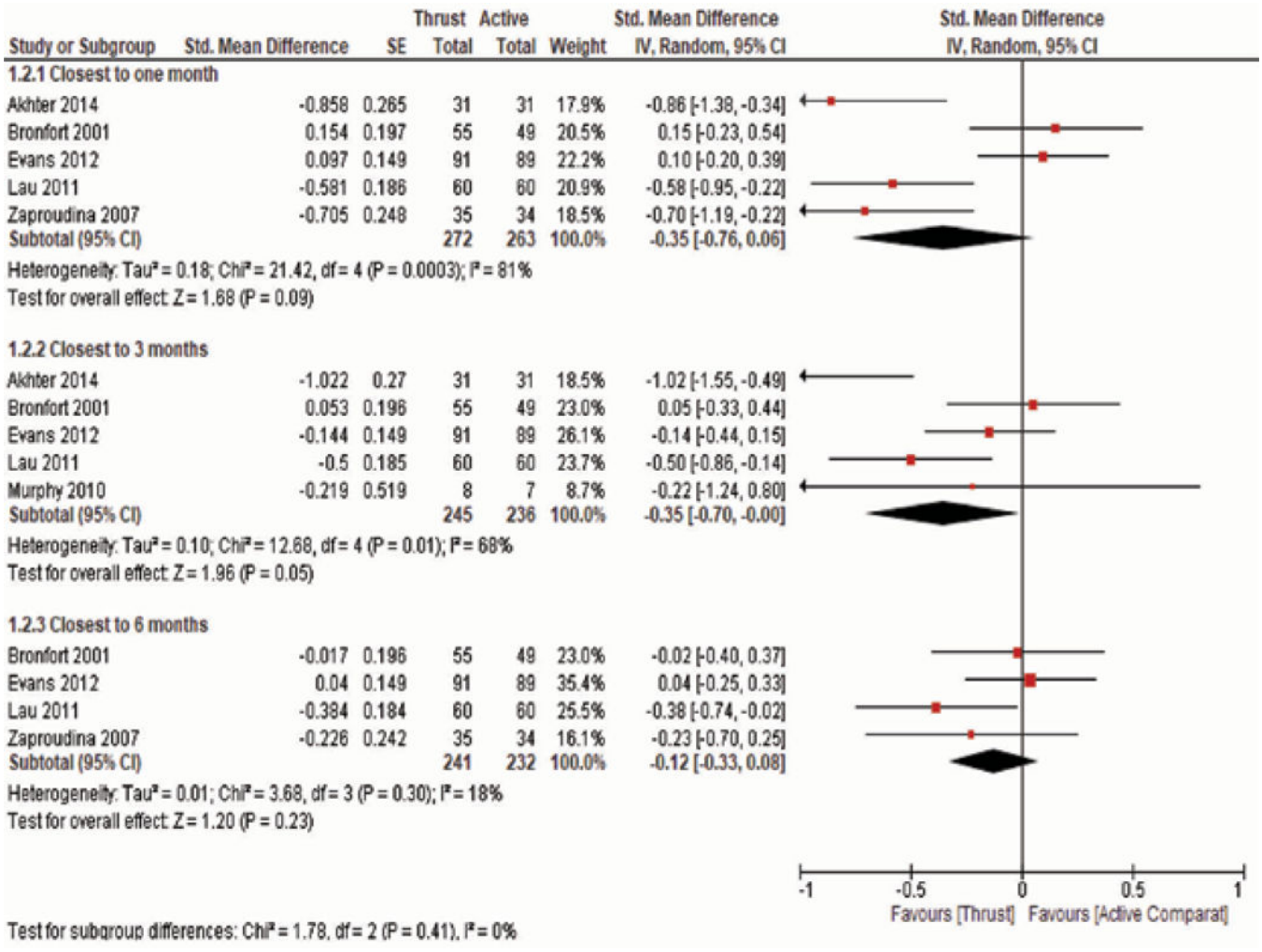


Fig. 4.
Reduction in disability.

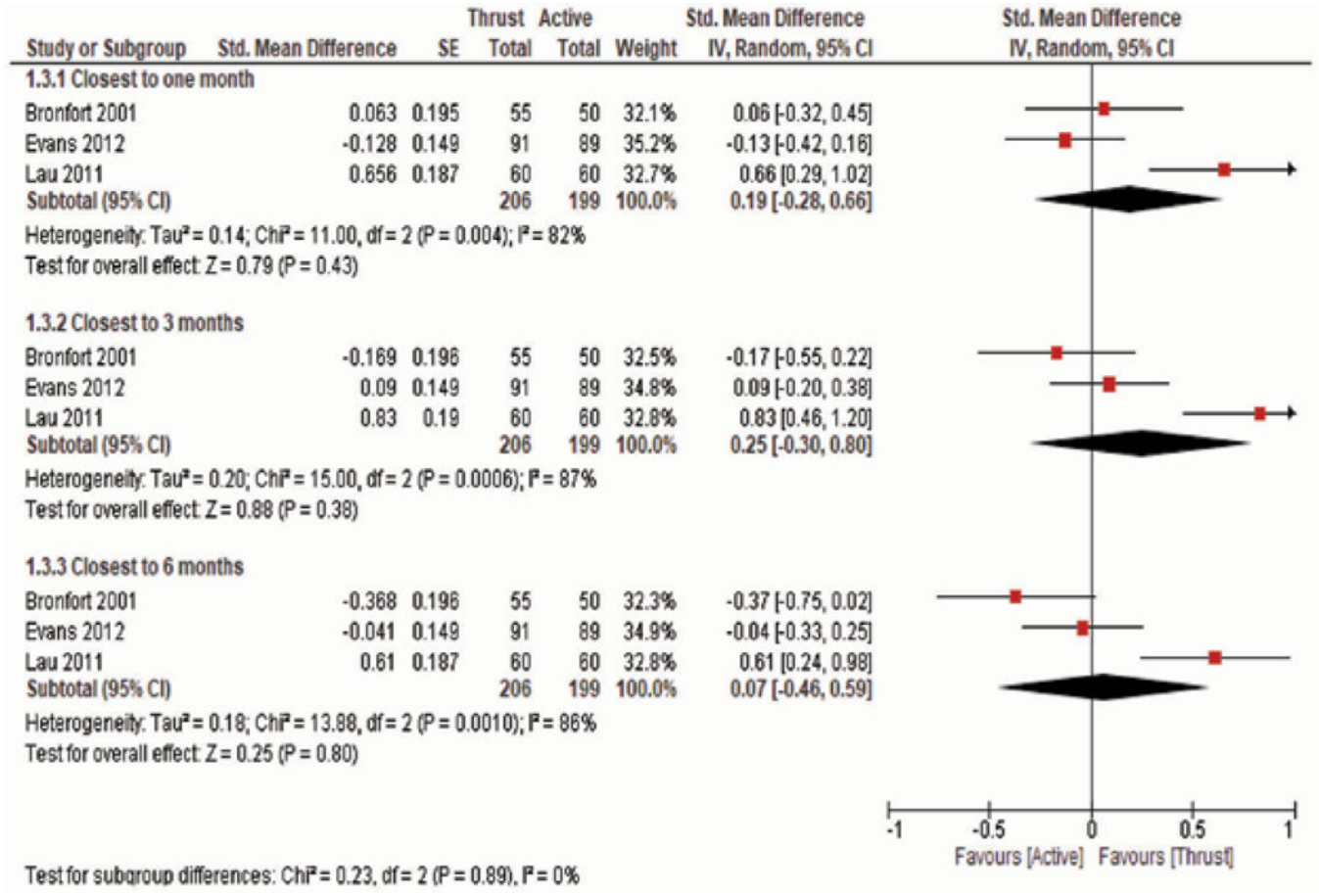


Fig. 5.
Enhanced health-related quality of life.

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.

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)