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Manual Therapy for Chronic Non-Cancer Back and Neck Pain: A Review of Clinical Effectiveness

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Abbreviations

AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CI	confidence interval
MD	mean difference
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SF-12	12-Item Short Form Health Survey
SF-36	36-Item Short Form Health Survey
SMD	standardized mean difference

Context and Policy Issues

Back and neck pain are major health problems that are leading causes of years lived with disability and significant sources of societal burden due to their associated direct (e.g., health care costs directly related to the treatment of neck or back pain) and indirect costs (e.g., costs resulting from loss of productivity).1 The one-year prevalence of low back pain is estimated at 38%,2 while estimates for the one-year prevalence of neck pain range between 30% and 50%.3 Although a proportion of individuals with back or neck pain may recover over a short period of time, many will experience chronic pain that may last months or years.4,5 The duration of pain is used to classify an individual's condition as either acute (symptoms lasting less than 12 weeks) or chronic (symptoms lasting more than 12 weeks).6,7

Common causes of back or neck pain include disk herniation, muscle strains, compression fracture, lumbar and cervical spinal stenosis or other forms of nerve compression, whiplash, sciatica, osteoarthritis, and spondylolisthesis.[8-10] Though back and neck pain may differ in their affected region and underlying etiologies, individuals who report symptoms of either condition may be offered similar therapeutic options. Pharmacological interventions include acetaminophen, non-steroidal anti-inflammatory drugs, opioids, systemic corticosteroids, and skeletal muscle relaxants.[11] Non-pharmacological interventions include exercise, psychological therapies, patient education, multidisciplinary rehabilitation, acupuncture, transcutaneous electrical nerve stimulation, and manual therapy.[11-15] Despite these numerous options, the long-term efficacy and safety of many interventions for the treatment of back and neck pain is not well-established.[11,16,17]

Manual therapy is a physical treatment applied by skilled clinicians (e.g., physiotherapists, chiropractors, osteopaths) that directly or indirectly targets a variety of anatomical structures of the musculoskeletal system.[18] The goal of manual therapy is to increase range of motion, improve tissue extensibility, induce relaxation, modulate pain, and reduce swelling or inflammation.[19] Manual therapy constitutes a wide variety of different techniques, such as: manipulation, mobilization, traction, and soft-tissue therapies (e.g., massage).[20]

CADTH has conducted a series of reports regarding the use of manual therapy for neck or lower back pain.[21-24] Two CADTH reports, published in 2017, reviewed the evidence for neck[24] and lower back[23] pain separately. The current report will update components of these previous CADTH reports[23,24] by summarizing the evidence regarding the clinical effectiveness of manual therapy for persistent or chronic non-cancer back and neck pain published since 2017.

Research Question

What is the clinical effectiveness of manual therapy for chronic non-cancer back and neck pain?

Key Findings

Four systematic reviews with meta-analyses (that included 27 unique relevant primary studies) were identified regarding the clinical effectiveness of manual therapy for adults with chronic non-cancer back and neck pain.

The systematic reviews were largely well-conducted (despite the methodological limitations of their included primary studies), and all evaluated the clinical effectiveness of various manual therapies compared with sham interventions (i.e., placebo) or no treatment. The effectiveness of manual therapy for chronic non-cancer back and neck pain was unclear due to variation in findings, significant clinical heterogeneity (e.g., differences in type of manual therapy, frequency and duration of treatments, length of follow-up), and concerns with the methodological quality of relevant primary studies. In most cases, treatment with manual therapy did not result in statistically significant differences when compared to sham therapy or no treatment in adults with persistent or chronic non-cancer back and neck pain; however, there was some evidence that suggested treatment with manual therapies improved pain, functional status, and health-related quality of life. Overall, manual therapies and their comparators (sham treatment or no treatment) were well-tolerated but were associated with mild transient adverse events such as discomfort and tiredness.

No evidence was identified regarding the comparative clinical effectiveness of manual therapies versus pharmacological interventions for adults with chronic non-cancer back and neck pain. The limitations of the included literature (e.g., high risk of performance bias due to a lack of blinding, lack of long-term follow-up data, substantial heterogeneity) should be considered when interpreting the findings of this report.

Methods

Literature Search Methods

This report makes use of a literature search developed for two previous CADTH reports.[21,22] In both reports,[21,22] a limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were manual therapies, neck pain, and back pain. Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and October 2, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed

for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with chronic non-cancer back or neck pain (or both), excluding pregnant populations
Intervention	Manual therapy, including manipulation, mobilization, traction, and soft tissue therapy
Comparator	Pharmacological interventions No treatment (e.g., waitlist, sham interventions) Usual care (if usual care is pharmacological interventions only)
Outcomes	Clinical effectiveness (e.g., pain reduction, functional performance, quality of life, disability level, safety, global impression of recovery, adverse events, skin reactions)
Study Designs	Health technology assessments and systematic reviews

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, they were included in the two previous 2017 CADTH reports on this topic,[23,24] or were published prior to 2017. Additionally, systematic reviews that had relevant included studies fully captured in other, more recent or more comprehensive (i.e., outcome data from relevant primary studies was more completely summarized) systematic reviews were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised by one reviewer using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) II.[25] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 488 citations were identified in the literature searches conducted as part of the two previous CADTH reports.[21,22] Following screening of titles and abstracts, 479 citations were excluded and nine potentially relevant reports from the electronic searches were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature searches for full-text review. Of these nine potentially relevant articles, five publications were excluded for various reasons, while four publications met the inclusion criteria and were included in this report. These comprised four systematic reviews with meta-analyses. Appendix 1 presents the PRISMA[26] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Four relevant systematic reviews with meta-analyses[27-30] were identified for inclusion in this review. No relevant health technology assessments were identified. Detailed study characteristics are available in Appendix 2, Table 3.

The four included systematic reviews[27-30] had objectives and inclusion criteria that were broader than the current report (i.e., wider in scope). Specifically, all four systematic

reviews[27-30] included primary studies that compared manual therapies versus non-pharmacological active interventions (e.g., exercise, acupuncture, physiotherapy) in addition to those that compared manual therapies versus sham therapy or no treatment. Additionally, one systematic review[28] was not specific to manual therapies, but instead included studies on all available interventions to manage non-specific low back pain in older adults (e.g., manual therapy, exercise, acupuncture, thermotherapy, pharmacological agents, percutaneous neurostimulation). Only the characteristics and results of the subset of relevant studies will be described in this report.

Study Design

The authors of the Coulter et al. 2019 systematic review and meta-analysis[27] included randomized controlled trials (RCTs) published between January 2000 and September 2017. A total of 53 RCTs were included in the systematic review[27] (11 RCTs[31-41] were relevant to the current report). The Nascimento et al.[28] systematic review and meta-analysis (published in 2019) searched for RCTs in peer-reviewed journals up to September 2018. The authors included 18 RCTs (one RCT[42] was relevant to the current report). The systematic review published in 2019 by Rubinstein et al.[29] searched for RCTs published up to May, 2018. Of the 47 RCTs included and summarized in the systematic review,[29] nine[43-51] were relevant to the current report. The authors of the Coulter et al. 2018 systematic review and meta-analysis[30] included RCTs published between January 2000 and March 2017. The review included 64 RCTs (eight RCTs[46-48,52-56] were relevant to the current report). In total, the systematic reviews[27-30] included 27 unique clinical studies[31-56] that were relevant to the current report.

The relevant primary study overlap between these systematic reviews[27-30] is summarized in Appendix 5, Table 7. Findings from primary studies included in multiple systematic reviews were only summarized once. Specifically, if the findings from a primary study were pooled in meta-analytic results extracted from a systematic review, the findings of that study were not also summarized narratively. If the findings were not pooled in an extracted meta-analysis, the results from the primary were narratively described once (i.e., they were not reported in duplicate from multiple systematic reviews).

Country of Origin

The included systematic reviews had first authors located in Canada,[28] the Netherlands,[29] and the United States.[27,30]

Patient Population

One systematic review[27] included primary studies that recruited adults (≥18 years of age) with chronic and non-specific neck pain relating to osteoarthritis, whiplash, radiculopathy, vertigo, cervico-brachial pain syndrome, spondylosis, trauma, disc herniation, cervicobrachial, cervico-craniofacial pain, or neck pain of occupational or mechanical origin. The three remaining systematic reviews[28-30] were specific to patient populations with low back pain. The Nascimento et al.[28] review included studies that enrolled older adults (≥60 years of age) with non-specific low back pain. The review by Rubinstein et al.[29] studied adult (≥18 years of age) populations where at least 50% of trial participants had chronic low back pain. The review excluded individuals whose pain was related to pregnancy, recent surgery, or serious pathology. The authors of the fourth systematic review[30] included studies that recruited adults (≥18 years of age) with chronic and non-specific low back pain related to osteoarthritis, sciatica, radiculopathy, spondylosis, sacroiliac joint syndrome, trauma, disc herniation, pelvic anteversion, or low back pain of occupational or mechanical

origin. In all systematic reviews,[27-30] non-specific pain referred to pain that was not attributable to specific conditions (e.g., cancer, rheumatoid arthritis, fibromyalgia, spondylolisthesis, spinal stenosis, temporomandibular disorders, ankylosing spondylitis, compression fracture). Overall, a total of 2,781 participants were included in the 27 unique relevant clinical studies (2,160 with back pain, 621 with neck pain).[31-56] The complete characteristics of participants from relevant clinical studies[31-56] (e.g., age, sex, severity and duration of back or neck pain) was not obtainable from the systematic reviews.[27-30]

Interventions and Comparators

The four systematic reviews[27-30] included primary studies that investigated a wide variety of manual therapies for the treatment of neck or back pain. Relevant to the current report, all four systematic reviews[27-30] included RCTs that compared manual therapies (including manipulation, mobilization, traction, and soft tissue therapy) to no treatment or sham interventions. No studies were identified that compared manual therapies to pharmacological interventions. Two systematic reviews[27,30] were specific to manipulation and mobilization techniques in chiropractic settings, one systematic review[28] included studies on all available interventions to manage non-specific low back pain (including spinal manipulative therapy), and the systematic review by Rubinstein et al.[29] included studies on spinal manipulative therapies. A summary of the interventions and comparators used in relevant primary studies,[31-56] as described in the included systematic reviews,[27-30] is provided in Table 2.

Table 2: Interventions and Comparators used in Relevant Primary Studies from the Included Systematic Reviews[27-30]

Primary Study Citation	Intervention(s)	Comparator(s)
Back Pain[28-30]		
Krekoukiasa et al., 2017[51] (N = 50)	- Spinal manipulative therapy (mobilization; 5 sessions over 5 weeks; duration was NR)	- Sham therapy (5 sessions over 5 weeks; duration was NR)
Xia et al., 2016[50] (N = 150)	- Group 1: Thrust spinal manipulative therapy (4 sessions over 2 weeks; duration was NR) - Group 2: Non-thrust spinal manipulative therapy (4 sessions over 2 weeks; duration was NR)	- No treatment (waiting list)
Hidalgo et al., 2015[45] (N = 32)	- Spinal manipulative therapy (Mulligan mobilization; 1 session; duration was NR)	- Sham therapy (1 session; duration was NR)
Bialosky et al., 2014[43] (N = 637)	- Spinal manipulative therapy (8 sessions over 4 to 8 weeks; duration of sessions was NR)	- Sham therapy (8 sessions over 4 to 8 weeks; duration was NR)
Dougherty et al., 2014[42] (N = 136)	- High-velocity, low-amplitude spinal manipulation and/or flexion distraction therapy and/or mobilization alone (based on the clinicians' judgement; 8 sessions over 4 weeks; duration was NR)	- Sham therapy (8 sessions over 4 weeks; 11 minutes per session)
Licciardone et al., 2013[46] (N = 455)	- Thrust osteopathic manipulative treatment (6 sessions over 8 weeks; 15 minutes per session)	- Sham therapy (6 sessions over 8 weeks; 15 minutes per session)

Primary Study Citation	Intervention(s)	Comparator(s)
Senna and Machaly, 2011[48] (N = 60)	- Group 1: Non-maintained spinal manipulation therapy (12 sessions over 1 month; duration was NR) - Group 2: Maintained spinal manipulation therapy (12 sessions over 1 month followed by a session every 2 weeks for 9 months; duration was NR)	- Sham therapy (12 sessions over 1 month; duration was NR)
Bicalho et al., 2010[52] (N = 40)	- Thrust high-velocity spinal manipulation (1 session; duration was NR)	- No treatment
Hondras et al., 2009[54] (N = 240)	- Group 1: Thrust high-velocity, low-amplitude spinal manipulation (3 sessions over 6 weeks; 30 minutes per session) - Group 2: Non-thrust low-velocity, variable-amplitude spinal mobilization (3 sessions over 6 weeks; 30 minutes per session)	- No treatment
Paatelma et al., 2008[56] (N = 134)	- Thrust osteopathic manipulative treatment (3 to 7 sessions; time period and duration were NR)	- No treatment
Ghroubi et al., 2007[44] (N = 64)	- Spinal manipulative therapy (4 sessions over 4 weeks; duration was NR)	- Sham therapy (4 sessions over 4 weeks; duration was NR)
Konstantinou et al., 2007[55] (N = 26)	- Non-thrust mobilization and movements (1 session; 3-minute duration)	- Sham therapy (1 session; 3-minute duration)
Licciardone et al., 2003[47] (N = 91)	- Thrust osteopathic manipulative treatment (7 sessions over 5 months; 15 to 30 minutes per session)	- Sham therapy (7 sessions over 5 months; duration was NR) - No treatment
Goodsell et al., 2000[53] (N = 26)	- Non-thrust central posteroanterior mobilization (1 session; 3-minute duration)	- No treatment
Waagen et al., 1986[49] (N = 19)	- Spinal manipulative therapy (6 sessions over 2 weeks; duration was NR)	- Sham therapy (6 sessions over 2 weeks; duration was NR)
Neck Pain[27]		
Pires et al., 2015[36] (N = 32)	- Thrust upper thoracic spine manipulation (1 session; duration was NR)	- Sham therapy (1 session; duration was NR)
Snodgrass et al., 2014[39] (N = 64)	- Non-thrust high force mobilization (1 session; 3 sets of 1-minute duration)	- Sham therapy (1 session; 3 sets of 1-minute duration)
Klein et al., 2013[34] (N = 61)	- Non-thrust strain-counterstrain therapy (1 session; duration was NR)	- Sham therapy (1 session; duration was NR)
Suvarnnato et al., 2013[40] (N = 39)	- Group 1: Thrust thoracic manipulation (1 session; 2-minute duration) - Group 2: Non-thrust thoracic mobilization (1 session; 2-minute duration)	- No treatment
Vernon et al., 2012[41] (N = 67)	- Thrust cervical manipulation (1 session; duration was NR)	- Sham therapy (1 session; duration was NR)

Primary Study Citation	Intervention(s)	Comparator(s)
Martel et al., 2011[35] (N = 98)	- Thrust spinal manipulation therapy (4 sessions over 4 months; 10 to 15 minutes per session)	- No treatment
Sillevis et al., 2010[38] (N = 101)	- Thrust manipulative therapy (1 session; duration was NR)	- Sham therapy (1 session; duration was NR)
Schwerla et al., 2008[37] (N = 41)	- Thrust osteopathic treatment (9 sessions over 10 weeks; 30 minutes per session)	- Sham therapy (9 sessions over 10 weeks; 45 minutes per session)
Briem et al., 2007[31] (N = 40)	- Non-thrust inhibitive distraction (1 session; 3-minute duration)	- Sham therapy (1 session; 3-minute duration)
Cleland et al., 2005[32] (N = 36)	- Thrust thoracic manipulation (1 session; duration was NR)	- Sham therapy (1 session; duration was NR)
Hemmilä, 2005[33] (N = 42)	- Thrust bone setting (5 sessions over 5 weeks; 30 minutes per session)	- No treatment

N = number of participants; NR = not reported.

Note: Studies are presented in reverse chronological and alphabetical order. "Duration" refers to duration of individual sessions.

Outcomes

All four systematic reviews[27-30] included studies that evaluated outcomes relating to pain and disability or functional status. In addition, three systematic reviews[27,29,30] reported on adverse events, while two systematic reviews[27,30] also summarized data relating to health-related quality of life. Various scales or questionnaires were used in the relevant RCTs[31-56] in the included systematic reviews for assessing pain (the Million Index, the Neck Pain and Disability Scale, the Numeric Pain Rating Scale, the Northwick Park Pain Questionnaire, and the Visual Analogue Scale), functional status or disability (the Roland Morris Disability Questionnaire, the Neck Disability Index, and the Oswestry Disability Index), or health-related quality of life (the 12-Item Short Form Health Survey [SF-12] and the 36-Item Short Form Health Survey [SF-36]). A brief description of the outcome assessment scales used in the relevant primary studies[31-56] is provided in Appendix 2, Table 4. No information on the minimal clinically important difference for any of these outcome assessment scales was available within the included systematic reviews.[27-30]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of the included publications are provided in Appendix 3, Table 5.

The three included systematic reviews[27-30] were generally well-conducted according to AMSTAR II criteria. The reviews[27-30] had clearly defined objectives and inclusion criteria, searched multiple databases, described the article selection process, conducted article selection in duplicate, provided a list of included studies, and assessed the risk of bias of included primary studies using appropriate techniques. The review methods for two systematic reviews[28,29] were prospectively registered in a published protocol (with the Cochrane Collaboration or PROSPERO), decreasing the risk for selective reporting. Key search terms and search strategies were provided in all four reviews,[27-30] increasing their reproducibility. All four systematic reviews[27-30] performed meta-analyses using appropriate methods for the statistical combination of results and assessed heterogeneity when suitable (using I^2 statistics). However, pooled estimates from three systematic reviews[27,28,30] could

not be extracted for the current report as the pooled data presented in the Forest plots included RCTs that were not relevant under our inclusion criteria. Publication bias was assessed by the authors of each included systematic review using various methods (e.g., Egger and Begg tests, funnel plots, examination of trial registries) and in all cases no indicators of publication bias were identified. Finally, the authors of all four systematic reviews[27-30] disclosed their sources of funding and any potential conflicts of interest (which were considered unlikely to have influenced the findings of the reviews).

As for methodological limitations, the literature search strategies of all four reviews[27-30] did not include grey literature searches, increasing the risk for missing relevant, non-indexed studies. None of the reviews[27-30] included a list of excluded studies; however, reasons for exclusion were described. The authors of three systematic reviews[27,28,30] did not conduct data extraction in duplicate, increasing the risk for inconsistencies in this process. In addition, the authors of all reviews[27-30] limited their eligible study designs to RCTs only. Although this is assumed to be related to the principle that RCTs provide the highest-quality of evidence of primary study designs,[57] no justification for this decision was explicitly stated. Three systematic reviews[27,28,30] did not report the sources of funding for the included primary studies. Finally, the countries in which relevant primary studies were conducted were not described in any of the reviews;[27-30] therefore, the generalizability of the findings to the Canadian setting was unclear.

Summary of Findings

The overall findings of the included studies are highlighted below. Detailed summaries of the main findings are available in Appendix 4, Table 6.

Clinical Effectiveness of Manual Therapy for Back Pain

Pain

Evidence regarding the clinical effectiveness of manual therapy for the treatment of back pain was available from 15 primary studies[42-56] within three systematic reviews.[28-30]

The systematic review by Rubinstein et al.[29] included four meta-analyses that pooled data from eight relevant RCTs[43-49,51] comparing spinal manipulative therapy versus sham therapy with respect to back pain at various follow-up durations. The meta-analytic results (reported as mean difference [MD] between groups) suggested that there were no statistically significant differences in pain severity between participants treated with spinal manipulative therapy and sham therapy at one-month (MD [95% CI] = −7.55 [−19.86 to 4.76]; participants = 831; 8 RCTs[43-49,51]), three-month (MD [95% CI] = −2.06 [−8.87 to 2.74]; participants = 573; 3 RCTs[46-48]), six-month (MD [95% CI] = 0.96 [−6.34 to 8.26]; participants = 114; 2 RCTs[47,48]), or 12-month (MD [95% CI] = 0.20 [−5.33 to 5.73]; participants = 63; 1 RCT[48]) follow-ups. In addition to these meta-analytic findings, three RCTs[42,52,55] that compared manual therapies to sham therapy were narratively summarized in two systematic reviews.[28,30] Dougherty et al.[42] reported no significant differences in low back pain (measured with the Visual Analogue Scale) at short-term (up to six weeks after randomization) or intermediate-term (more than six weeks and less than 12 months after randomization) follow-ups between individuals treated with spinal manipulative therapy or sham treatment. Similarly, Konstantinou et al.[55] concluded that there were no significant differences in pain (as measured with the Visual Analogue Scale) post-treatment between study participants who received mobilization with movements or sham therapy. The RCT by Bicalho et al.[52] reported significant improvements in pain (measured with the Visual

Analogue Scale) for participants treated with high-velocity spinal manipulation compared to those who received sham manipulation.

Six RCTs[43,47,50,53,54,56] summarized within two systematic reviews[29,30] compared manual therapies versus no treatment. Xia et al.[50] reported statistically significant improvements in pain for participants who received thrust or non-thrust spinal manipulative therapy at one-month follow-up compared to those who received no treatment. Similarly, the findings of a study by Goodsell et al.[53] study suggested that participants who received central posteroanterior mobilization had significant improvements in pain post-treatment compared to those who received no treatment. Licciardone et al.[47] reported that participants who received osteopathic manipulative treatment had significant improvements in pain (measured with the Visual Analogue Scale) post-treatment, at three- and six-month follow-up compared to those who received no treatment. The three remaining RCTs[43,54,56] did not detect statistically significant differences between participants who received various manual therapies or no treatment.

Overall, evidence from three[47,50,53] out of six RCTs[43,47,50,53,54,56] suggested that manual therapy may improve back pain in adults compared to no treatment, while the three remaining RCTs[43,54,56] showed no difference between manual therapy and no treatment with respect to pain. Of the 11 RCTs[42-49,51,52,55] that compared manual therapy versus sham therapy, three RCTs[48,51,52] showed improvement in those treated with manual therapy, while eight RCTs[42-47,49,55] did not show any statistically significant differences in chronic non-cancer back pain in adults.

Disability or functional status

Ten RCTs[42,43,45-48,50,51,54,56] from three included systematic reviews[28-30] investigated the effectiveness of manual therapies for the improvement of disability or functional status in adults with back pain.

The systematic review by Rubinstein et al.[29] included four meta-analyses that pooled data from six relevant RCTs[43,45-48,51] comparing spinal manipulative therapy versus sham therapy with respect to functional status at various follow-up durations. The meta-analytic results suggested that participants treated with spinal manipulative therapy experienced statistically significant improvements in functional status at one-month (SMD [95% CI] = −0.74 [−1.39 to −0.10]; participants = 738; 6 RCTs[43,45-48,51]) follow-up. There were no statistically significant differences in functional status between participants treated with spinal manipulative therapy and sham therapy at three-month (SMD [95% CI] = −0.15 [−0.32 to 0.01]; participants = 573; 3 RCTs[46-48]), six-month (SMD [95% CI] = −0.12 [−0.50 to 0.25]; participants = 114; 2 RCTs[47,48]), or 12-month (SMD [95% CI] = −0.19 [−0.69 to 0.31]; participants = 63; 1 RCT[48]) follow-ups. In addition to these meta-analytic findings, one RCT[42] that compared spinal manipulation therapy to sham therapy was narratively summarized in one systematic review.[28] The authors of this study[42] concluded that there were no statistically significant differences between participants who received spinal manipulation therapy or sham therapy with respect to disability (measured using the Oswestry Disability Index) at short-term (up to six weeks after randomization) or intermediate-term (more than six weeks and less than 12 months after randomization) follow-ups.

Four RCTs[43,50,54,56] summarized within two systematic reviews[29,30] compared various manual therapies versus no treatment. The RCT by Xia et al.[50] reported statistically significant improvements in functional status for participants who received thrust or non-

thrust spinal manipulative therapy at one-month follow-up compared to those who received no treatment. The three remaining RCTs[43,54,56] did not detect statistically significant differences between participants who received various manual therapies or no treatment.

Overall, evidence from six RCTs[43,45-48,51] suggested that manual therapy (specifically spinal manipulative therapy) improved functional status in adults with back pain compared to sham therapy at one-month follow-up; however, there were no statistically significant differences between those treated with manual therapies and sham therapies at subsequent follow-ups. Of the four RCTs[43,50,54,56] that compared manual therapies versus no treatment, one RCT[50] showed improvement in functional status in those treated with manual therapy, while three RCTs[43,54,56] did not show any statistically significant differences in functional status in adults with chronic non-cancer back pain.

Health-related quality of life

Information regarding the effectiveness of manual therapy with respect to health-related quality of life in adults with back pain was available in four RCTs[46-48,54] summarized in one systematic review.[30] Senna and Machaly[48] concluded that participants treated with spinal manipulation therapy had significant improvements in health-related quality of life (measured using the SF-36) compared to those who received sham therapy. Conversely, two RCTs[46,47] did not detect statistically significant differences in health-related quality of life (as measured with the SF-36) between individuals who received osteopathic manipulative treatment or sham therapy. The findings of the Hondras et al.[54] RCT suggested there were no significant differences in health-related quality of life (as measured with the SF-36) post-treatment between participants who received high-velocity low amplitude spinal manipulation, low-velocity variable amplitude spinal mobilization, or no treatment; however, the authors of another RCT[47] noted that participants who received osteopathic manipulative treatment reported significant improvements in health-related quality of life (measured with the SF-36) post-treatment compared to those who received no treatment.

Adverse events

Information relating to adverse events associated with manual therapy for the treatment of adults with back pain was available from three RCTs[46,48,54] within one systematic review.[30] Hondras et al.[54] reported that 20 of 240 study participants experienced side effects that were resolved within six days (the type of side effects were not described in the systematic review). The authors of a second RCT[46] noted that adverse events were reported by 27 of 455 study participants. Finally, an unreported number of participants in the RCT by Senna and Machaly[48] experienced local discomfort and tiredness. The distribution of these adverse events between treatment groups was not reported for any of the three RCTs[46,48,54] within in the systematic review.[30]

Clinical Effectiveness of Manual Therapy for Neck Pain

Pain

Evidence regarding the clinical effectiveness of manual therapy for the treatment of neck pain was available from 11 RCTs[31-41] within one systematic review.[27]

Eight RCTs[31,32,34,36-39,41] compared various manual therapies (e.g., inhibitive distraction, strain-counterstrain therapy, upper thoracic spine manipulation, cervical manipulation therapy, high force mobilization) versus sham therapy that was intended to mimic the active treatment (i.e., placebo). Of these eight studies, six RCTs[31,34,36,38,39,41] reported no

statistically significant differences between treatment with a manual therapy or sham therapy with respect to pain. The findings of two RCTs suggested that participants who received thoracic manipulation[32] or osteopathic treatment[37] experienced statistically significant improvements in pain compared to those who received sham therapy.

Three RCTs[33,35,40] allocated participants to receive various manual therapies (e.g., spinal manipulation therapy, single thoracic manipulation, bone setting therapy) or no treatment. Two of these studies[35,40] concluded that there were no statistically significant differences between participants who were received treatment with various manual therapies or who did not receive any treatment at all. The findings of the third RCT[33] reported that participants who were treated with bone setting therapy had improvements in pain at five weeks, three months, and six months compared to participants who received no treatment.

Overall, evidence from two[32,37] out of eight RCTs[31,32,34,36-39,41] suggested that manual therapy may improve neck pain in adults compared to sham therapy, while the six[31,34,36,38,39,41] remaining RCTs showed no difference between manual therapy and sham therapy with respect to neck pain. Of the three RCTs[33,35,40] that compared manual therapy versus no treatment, one RCT[33] showed improvement in those treated with manual therapy, while two RCTs[35,40] did not show any statistically significant difference in chronic non-cancer neck pain in adults.

Disability

Two RCTs[35,39] from one included systematic review[27] investigated the effectiveness of manual therapies with respect to disability in adults with neck pain. The findings of one RCT[39] suggested that there were no significant differences between participants treated with high force mobilization or sham therapy with respect to disability (measured with the Neck Disability Index). Similarly, the authors of the second RCT[35] suggested that participants who received spinal manipulation therapy had no significant improvements in disability mid-trial or post-treatment (measured using the Neck Pain Disability Index) compared to those who received no treatment.

Health-related quality of life

The effect of manual therapy on health-related quality of life in adults with neck pain was examined in two RCTs[35,37] summarized in one systematic review.[27] Schwerla et al.[37] concluded that participants in their trial who were provided with osteopathic treatment reported significant improvements in health-related quality of life (measured with the SF-36) compared to those who were given sham therapy. Conversely, Martel et al.[35] reported that participants treated with spinal manipulation therapy had no significant improvements in health-related quality of life (measured using the SF-12) compared to those who received no treatment.

Adverse events

Information relating to adverse events associated with manual therapy for the treatment of adults with neck pain was available from six RCTs[32,34,35,37,39,41] within one systematic review.[27] The authors of three RCTs[32,35,39] stated that no participants who received various manual therapies reported any adverse events. Four participants who received strain-counterstrain therapy and one who received sham therapy (out of a total of 61 participants) in the RCT by Klein et al.[34] experienced mild transient adverse events (the statistical significance of this finding was not reported). Some participants in the RCTs by Schwerla et

al.[37] and Vernon et al.[41] experienced tiredness or mild pain lasting less than 24 hours, respectively; however, the number of participants who were affected was not reported.

Limitations

A number of limitations were identified in the critical appraisal (Appendix 3, Table 5), however, additional limitations exist.

While the included systematic reviews[27-30] were generally well-conducted according to AMSTAR II criteria, the underlying evidence from relevant RCTs was rated as being of very low to moderate quality in many cases (as assessed by the authors of the systematic reviews). Common methodological limitations from the RCTs were inadequate methods of participant randomization and allocation concealment, the open-label status of studies (i.e., unblinded subjects, therapists, and outcome assessors), inadequate follow-up durations (often limited to a few days or weeks despite the target condition of chronic pain), and the risk for attrition bias due to unequal dropout rates across intervention groups. Any quality issues from the primary studies cause uncertainty in the findings presented in the systematic reviews.

There was significant clinical heterogeneity amongst included studies. The four systematic reviews[27-30] combined data across primary studies that differed in many aspects, such as: type of manual therapy, frequency of treatment, duration of treatment, patient populations, and length of follow-up. Additionally, statistical heterogeneity was quantified (using I^2 statistics) in the meta-analytic results extracted from the Rubinstein et al.[29] review. I^2 values indicated considerable heterogeneity for the outcome of pain at one month (I^2 = 96%) and functional status at one month (I^2 = 91%) for the comparison of spinal manipulative therapy and sham treatment. The appropriateness of combining such heterogeneous data is unclear.

Assessed outcomes lacked standardization (i.e., scales used to measure pain and disability varied across primary studies) and apart from the Rubinstein et al.[29] review, there was little discussion around minimum clinically important differences. A statistically significant improvement in outcome scores does not necessarily translate into clinically meaningful change for patients.

No evidence regarding the comparative clinical effectiveness of manual therapy versus pharmacological interventions for chronic non-cancer back and neck pain in adults was identified.

Conclusions and Implications for Decision or Policy Making

This review was comprised of four systematic reviews with meta-analyses[27-30] regarding the clinical effectiveness of manual therapy for or chronic non-cancer back and neck pain for adults.

The identified literature revealed mixed conclusions regarding the clinical effectiveness of manual therapies for the treatment of adults with chronic non-cancer back and neck pain. In the majority of included studies,[27-29,31,34-39,41-49,51,54-56] there were no statistically significant differences between participants who received manual therapies and those who received no treatment or sham therapy; however, some studies[27,29,32,37,43,45-48,50-54] suggested that treatment with manual therapies may improve back and neck pain, functional status, and health-related quality of life compared to no treatment or sham therapy. Overall, manual

therapies were well-tolerated, but both manual therapies and their comparators (sham treatment or no treatment) were associated with mild transient adverse events.

The findings of this report are similar to those from two previous 2017 CADTH reports that reviewed the evidence for manual therapies in treating neck[24] and lower back[23] pain separately. Similar to the current findings, the previous CADTH reports[23,24] identified inconsistent findings from studies that compared manual therapies versus no treatment or sham therapies. There were studies summarized in the previous reports[23,24] that demonstrated treatment with manual therapy improved outcomes compared to sham therapy or no treatment; however, there were also instances were there were no statistically significant differences between treatment with manual therapies and sham therapy or no treatment in adults with chronic neck or back pain. Taking the findings from the previous and current report together, there remains a high degree of uncertainty in the effectiveness of manual therapies due to the limitations of the available literature (e.g., heterogeneity of investigated interventions and populations, inconsistent results, the risk of performance bias due to a lack of blinding of participants, therapists, and outcome assessors). Further research investigating the clinical effectiveness of manual therapies, especially with large clinical trials that report long-term outcome data and incorporate measures to increase methodological quality, would help reduce this uncertainty.

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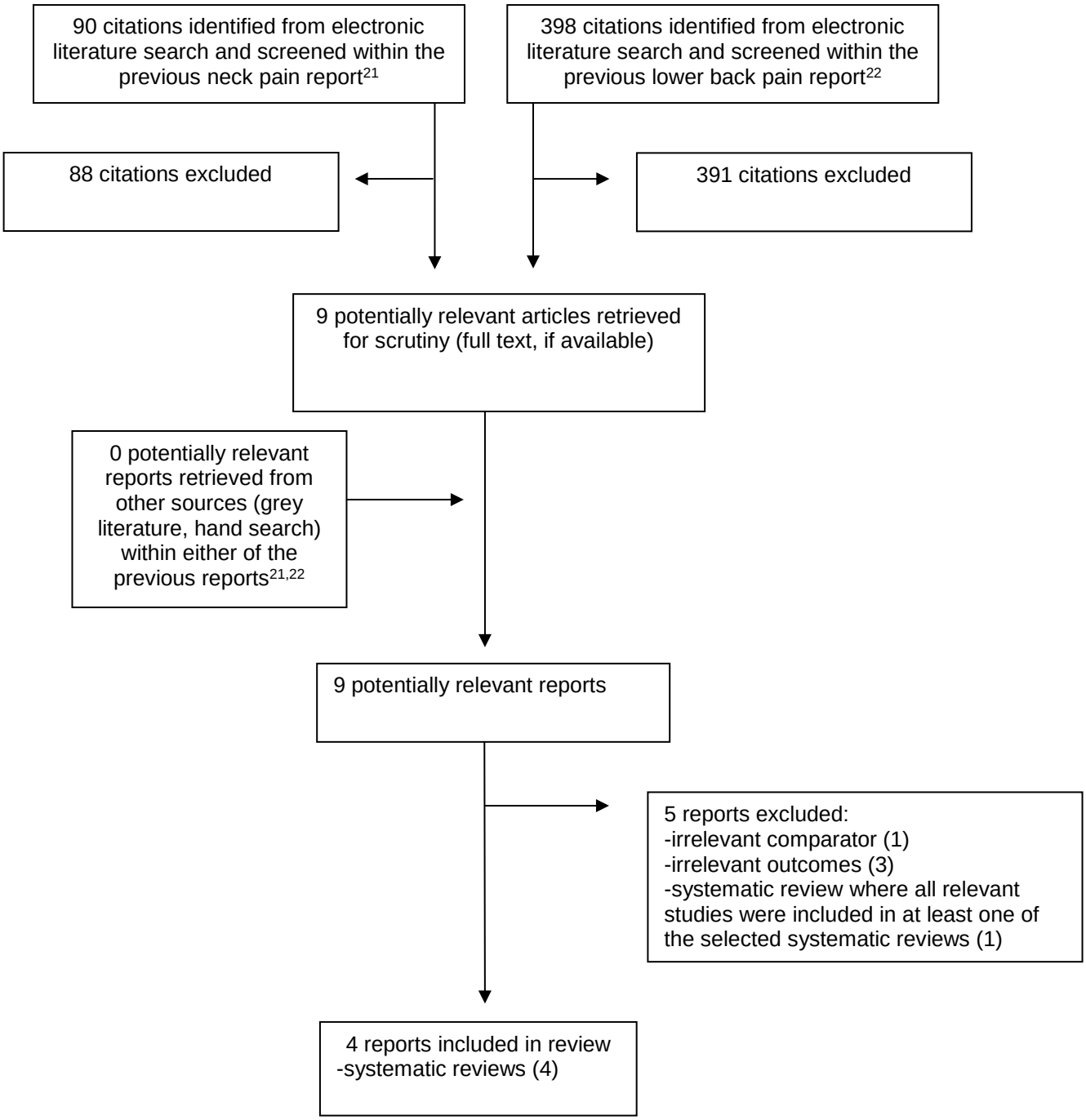
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Systematic Reviews

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Coulter et al., 2019[27] United States **Funding source**: Funding was received from the National Center for Complementary and Integrative Health (award #U19AT007912).	**Objective**: To determine the effectiveness and safety of mobilization and manipulation therapies for the treatment of adults with chronic non-specific neck pain. **Study design**: Systematic review and meta-analysis of RCTs. Additional primary study designs, such as controlled clinical trials and observational studies were identified and summarized to supplement the meta-analysis with additional information that may have more pragmatic "real world" implications. The additionally non-randomized studies were not formally included in the systematic review (i.e., they did not undergo quality assessment). **Literature search strategy**: Study authors search for literature published between January 2000 and September 20017 in PubMed/Medline, Cochrane, Embase, CINAHL, PsycINFO, and ICL. Additionally, reference lists were examined and experts were contacted to ensure comprehensiveness. **Number of studies included**: A total of 53 RCTs were included in the systematic review, six of which were pooled in the meta-analysis. Of these 53 RCTs, 11[31-41]	Adults (≥18 years of age) with chronic (pain symptoms lasting ≥12 weeks) and non-specific neck pain. Non-specific pain was defined as pain that was not attributable to specific conditions (e.g., cancer, rheumatoid arthritis, fibromyalgia, spondylolisthesis, spinal stenosis, temporomandibular disorders, ankylosing spondylitis, headaches as sole or principal condition). Studies on pain relating to osteoarthritis, whiplash, radiculopathy, vertigo, cervico-brachial pain syndrome, spondylosis, trauma, disc herniation, cervicobrachial, cervico-craniofacial pain, and neck pain of occupational or mechanical origin were eligible for inclusion.	**Intervention**: Manipulation and mobilization techniques in chiropractic settings. Interventions were categorized as thrust or non-thrust. **Comparators**: Sham treatment, no treatment, or other active therapies (e.g., acupuncture, message therapy, exercise). Only primary studies that used sham treatment or no treatment as comparators were relevant to the current report.	**Outcomes assessed in relevant studies**: - Pain - Disability - Health-related quality of life - Adverse events **Follow-up**: Varied by individual study. Relevant studies ranged from immediately post-treatment to 12 months post-treatment.

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	were relevant to the current report. Because all studies included in the meta-analysis were not relevant to the current report, the meta-analytic results were not extracted. **Quality assessment tool:** The SIGN 50 checklist and EVAT were used to assess risk of bias and external validity of the RCTs, respectively.			
Nascimento et al. 2019[28] Canada **Funding source**: The first author received support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (a Brazilian federal government agency).	**Objective**: To systematically review the literature regarding the clinical effectiveness of all interventions for the treatment of non-specific low back pain in older adults. **Study design**: Systematic review and meta-analysis of RCTs **Literature search strategy**: Electronic searches were conducted in Medline, EMBASE, CINAHL, LILACS, Physiotherapy Evidence Database, and Cochrane Central Register of Controlled Trials (CENTRAL) for RCTs published up to September 2018. **Number of studies included**: A total of 18 RCTs were identified and included in the qualitative synthesis. Eight of these studies were pooled in the meta-analysis. One primary study[42] was relevant to the current report. Because all studies included in the meta-analysis were not relevant to the current report, the meta-analytic results were not extracted.	Older adults (≥60 years of age) with non-specific low back pain. **Excluded**: Individuals with lower back pain resulting from problems beyond the lumbar spine (e.g., leaking aortic aneurysm) or pain that was attributed to specific disorders (e.g. epidural abscess, compression fracture, spondyloarthropathy, cancer, cauda equine syndrome, radicular pain, radiculopathy, or spinal canal stenosis).	**Intervention**: All available interventions to manage non-specific low back pain in older adults (e.g., manual therapy, exercise, acupuncture, thermotherapy, pharmacological agents, percutaneous neurostimulation). Studies relevant to the current report examined various spinal manipulative therapies. **Comparators**: All comparators were eligible for inclusion (e.g., sham treatment, usual care, minimal intervention).	**Outcomes assessed in relevant studies**: - Pain - Functional status or disability **Follow-up**: Results of primary studies analyzed at short-term (<6 weeks after randomization) and intermediate-term (>6 weeks and <12 months after randomization) follow-ups. No studies reported long-term (>12 months after randomization) follow-up data.

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Quality assessment tool: The risk of bias in eligible primary studies was assessed using the PEDro checklist.			
Rubinstein et al. 2019[29] Netherlands **Funding source**: No financial support was received for this research.	**Objective**: To investigate the benefits and harms of spinal manipulative therapy for the treatment of adults with chronic low back pain. **Study design**: Systematic review and meta-analysis of RCTs. **Literature search strategy**: Electronic searches were conducted in Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Medline In-Process and Other Non-Indexed Citations, Embase, CINAHL, Physiotherapy Evidence Database (PEDro), ICL, and PubMed for articles published up to May 4th, 2018. The electronic searches were supplemented by hand searching of reference lists of all included studies, trial registries (i.e., ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform), and by contacting trial authors and specialists in spinal manipulative therapies to identify any trials potentially missed. **Number of studies included**: A total of 47 RCTs were included in the qualitative synthesis (nine[43-51] of which were relevant to the current report). Of these studies, 41 RCTs were included in the quantitative synthesis (meta-analysis). Only	Adult (≥18 years of age) populations where at least 50% of individuals had chronic low back pain (pain symptoms lasting ≥3 months). **Excluded**: Individuals who had low back or pelvic pain relating to pregnancy, pain unrelated to the lower back, postoperative pain, and patients with serious pathology.	**Intervention**: Spinal manipulative therapies. Studies that were designed to test the immediate post-treatment effects of a single treatment were excluded. Additionally, if it was difficult to distinguish the effect of spinal manipulative therapy in combination intervention studies, the study was excluded. **Comparators**: Recommended therapies (e.g., exercise, non-steroidal anti-inflammatory drugs, analgesics), non-recommended therapies (e.g., light soft tissue massage, no treatment, waiting list control, electrotherapies), sham therapy (i.e., placebo), and spinal manipulative therapy as adjuvant therapy to any other therapy.	**Outcomes assessed in relevant studies**: - Pain - Back pain specific functional status - Adverse events **Follow-up**: Results of primary studies were presented at 1 month, 3 months, 6 months, and 12 months for each outcome (depending on data availability).

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	information from the relevant primary studies were extracted. **Quality assessment tool:** Risk of bias in primary studies was assessed using the 13 criteria recommended by the Cochrane Back and Neck Review Group.		Only primary studies that used sham treatment, no treatment, or waist list control as comparators were relevant to the current report.	
Coulter et al., 2018[30] United States **Funding source**: Funding was received from the National Center for Complementary and Integrative Health (award #U19AT007912).	**Objective**: To investigate the effectiveness and safety of mobilization and manipulation therapies for adults with chronic low back pain. **Study design**: Systematic review and meta-analysis of RCTs. Additional primary study designs, such as controlled clinical trials and observational studies were identified and summarized to supplement the meta-analysis with additional information that may have more pragmatic "real world" implications. The additionally non-randomized studies were not formally included in the systematic review (i.e., they did not undergo quality assessment). **Literature search strategy**: Authors searched PubMed/Medline, Cochrane, Embase, CINAHL, PsycINFO, and ICL for literature published between January 2000 and March 2017. In addition, reference lists were examined and experts were contacted to ensure comprehensiveness. **Number of studies included**: A total of 64 RCTs were included in the systematic review, nine of which were pooled in the	Adults (≥18 years of age) with chronic (pain symptoms lasting ≥12 weeks) and non-specific low back pain. Non-specific pain was defined as pain that was not attributable to specific conditions (e.g., cancer, rheumatoid arthritis, fibromyalgia, spondylolisthesis, spinal stenosis, ankylosing spondylitis) or pregnancy-related pain. Studies on pain relating to osteoarthritis, sciatica, radiculopathy, spondylosis, sacroiliac joint syndrome, trauma, disc herniation, pelvic anteversion, and low back pain of occupational or mechanical origin were eligible for inclusion.	**Intervention**: Manipulation and mobilization techniques in chiropractic settings. Interventions were categorized as thrust or non-thrust. **Comparators**: Sham treatment, no treatment, or other active therapies (e.g., exercise, physiotherapy, physical therapy). Only primary studies that used sham treatment or no treatment as comparators were relevant to the current report.	**Outcomes assessed in relevant studies**: - Pain - Disability - Health-related quality of life - Adverse events **Follow-up**: Varied by individual study. Relevant studies ranged from immediately post-treatment to 12 months post-treatment.

Study Citation, Country, Funding Source	Objective, Study Design, Search Strategy, Number of Primary Studies Included, Quality Assessment Tool	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	meta-analysis. Of these 64 RCTs, eight[46-48,52-56] were relevant to the current report. Because all studies included in the meta-analysis were not relevant to the current report, the meta-analytic results were not extracted. **Quality assessment tool**: The SIGN 50 checklist and EVAT were used to assess risk of bias and external validity of the RCTs, respectively.			

CINAHL = Cumulative Index of Nursing and Allied Health Literature; EVAT = External Validity Assessment Tool; ICL = Index to Chiropractic Literature; LILACS = Latin American and Caribbean Health Sciences Literature; NR = not reported; PEDro = Physiotherapy Evidence Database; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network.

Table 4: Description of Outcome Assessment Scales

Outcome Assessment Scale	Description
Pain	
Million Index	A 15-item questionnaire that assesses disability and pain intensity. Each question is scored between 0 (lowest level of pain) and 100 (highest level of pain). The total score is calculated by adding up the equally weighted scores from each item.[58,59]
Neck Pain and Disability Scale	A 20-item instrument that was developed to measure neck-specific pain. Subjects respond to each item by marking along a visual analogue scale that ranges between 0 (no pain) and 5 (maximal pain). Total scores are the sum of scores from each of the 20 items, ranging between 0 and 100.[60]
Northwick Park Pain Questionnaire	A 9-item questionnaire that evaluates the severity of neck pain. Subjects are asked to answer each of the 9 questions by selecting one of four options. Each answer is scored between 0 (no pain) and 4 (maximal pain), with total scores ranging between 0 and 36.[61]
Numeric Pain Rating Scale	A unidimensional measure of pain intensity where subjects select a whole number from 0 (no pain) to 10 (maximal pain) that best reflects the intensity of their pain.[62]
Visual Analogue Scale	A single-item continuous scale comprised of a horizonal or vertical line. Subjects select a point on this line between 0 (no pain) and 100 (maximal pain) that represents their level of pain.[63]
Disability or Functional Status	
Neck Disability Index	A 10-item instrument where each item is scored from 0 (no disability) to 5 (high disability). The total score (sum of the 10 items) classifies disability severity: 0 to 4 (no disability), 5 to 14 (mild disability), 15 to 24 (moderate disability), 25 to 34 (severe disability), and >34 (complete disability).[64]
Oswestry Disability Index	A self-administered questionnaire that includes 10 topics relating to pain, ability to care for oneself, ability to mobilize, sexual function, social life, and sleep quality. Each question is scored on a scale of 0 (minimal disability) to 5 (severe disability). Total scores are converted to a percentage and are interpreted as follows: 0% to 20% (minimal disability), 21% to 40% (moderate disability), 41% to 60% (severe disability), 61% to 80% (crippled), 81% to 100% (these patients are either bed-bound or have an exaggeration of their symptoms).[65,66]
Roland Morris Disability Questionnaire	A 24-item self-report questionnaire designed to assess physical disability caused by low back pain. Subjects are asked to put a checkmark in the box next to statements that apply to them. Each checkmark is scored as 1 point. Total scores range between 0 and 24, with a higher score indicating more serve disability.[67]
Health-Related Quality of Life	
12-Item Short Form Health Survey	A multipurpose, short form survey with 12 questions selected from the SF-36 that provide an assessment of physical functioning and health-related quality of life. Responses are weighted between 0 (lowest level of health) and 100 (highest level of health) and combined to yield a physical health composite score and a mental health composite score.[68]
36-Item Short Form Survey	A multipurpose survey consisting of 36 questions that is used to evaluate mental and physical functioning and overall health-related quality of life. Responses are weighted between 0 (lowest level of health) and 100 (highest level of health) and combined to yield a physical health composite score and a mental health composite score.[69]

SF-36 = 36-Item Short Form Survey.

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[25]

Strengths	Limitations
Coulter et al., 2019[27]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (PubMed/Medline, Cochrane, Embase, CINAHL, PsycINFO, and ICL). Additionally, reference lists of included studies were examined and experts in the field were consulted • Key search terms and publication restrictions were provided • Study selection and quality assessment processes were described and conducted in duplicate (disagreements were resolved through discussion and consensus) • A flow chart of study selection was provided • The review authors described the included primary studies in adequate detail • The risk of bias and external validity of included studies were assessed using the SIGN 50 checklist and the EVAT, respectively • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Publication bias was assessed using the Begg and Egger tests (none was detected) • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (the National Center for Complementary and Integrative Health) and was unlikely to have had an effect on the findings of the review	• It was unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • The authors did not explain their selection of study designs for inclusion in the review (i.e., only RCTs being formally included, with non-randomized designs for consideration in the discussion) • A grey literature search was not completed • It was unclear if data extraction was done in duplicate • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on sources of funding for the included primary studies • The countries in which relevant primary studies were conducted were not described; the generalizability to the Canadian setting was unclear
Nascimento et al. 2019[28]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • The review methods were established prior to conducting the review (a protocol was prospectively registered on PROSPERO) • Multiple databases were searched (Medline, EMBASE, CINAHL, LILACS, Physiotherapy Evidence Database, and Cochrane Central Register of Controlled Trials [CENTRAL] for RCTs). Additionally, reference lists of included studies were examined • Key search terms and publication restrictions were provided • The study selection process was described and conducted in duplicate (disagreements were resolved through discussion with a third reviewer) • A flow chart of study selection was provided	• The authors did not explain their selection of study designs for inclusion in the review (i.e., RCTs only) • A grey literature search was not completed • It was unclear if data extraction and quality assessment were conducted in duplicate • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on sources of funding for the included primary studies • The countries in which relevant primary studies were conducted were not described; the generalizability to the Canadian setting was unclear

Strengths	Limitations
• The review authors described the included primary studies in adequate detail • The risk of bias of included primary studies was assessed using the PEDro checklist • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Publication bias was assessed using an inspection of trial registries (no indicators of publication bias were identified) • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (The first author received support from Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) and was unlikely to have had an effect on the findings of the review	
Rubinstein et al. 2019[29]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • The review methods were established prior to conducting the review (a protocol was prospectively registered with the Cochrane Collaboration) • Multiple databases were searched (Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Medline In-Process and Other Non-Indexed Citations, Embase, CINAHL, Physiotherapy Evidence Database (PEDro), ICL, and PubMed). Additionally, reference lists of included studies were examined, trial registries were searched, and experts in the field were consulted • Key search terms and publication restrictions were provided • Study selection, data extraction, and quality assessment processes were described and conducted in duplicate • A flow chart of study selection was provided • The review authors described the included primary studies in adequate detail • The risk of bias of included studies was assessed using the 13 criteria recommended by the Cochrane Back and Neck Review Group • Review authors reported on the sources of funding for included studies • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Publication bias was assessed using funnel plots (none was detected; however, the authors stated it could not be ruled out) • Review authors stated that their potential conflicts of interest (various authors had received personal grants or funding from the European Chiropractors' Union, the European Centre for Chiropractic Research Excellence, the	• The authors did not explain their selection of study designs for inclusion in the review (i.e., RCTs only) • A grey literature search was not completed (grey literature was specifically excluded from the review) • A list of excluded studies was not provided (although the reasons for exclusion were) • The countries in which relevant primary studies were conducted were not described; the generalizability to the Canadian setting was unclear

Strengths	Limitations
Belgian Chiropractic Association, and the Netherlands Chiropractic Association)	
Coulter et al., 2018[30]	
• The objectives and inclusion criteria were clearly stated and included components of population, intervention, comparator, and outcomes • Multiple databases were searched (PubMed/Medline, Cochrane, Embase, CINAHL, PsycINFO, and ICL). Additionally, reference lists of included studies were examined and experts in the field were consulted • Key search terms and publication restrictions were provided • Study selection and quality assessment processes were described and conducted in duplicate (disagreements were resolved through discussion and consensus) • A flow chart of study selection was provided • The review authors described the included primary studies in adequate detail • The risk of bias and external validity of included studies were assessed using the SIGN 50 checklist and the EVAT, respectively • Appropriate methods for the statistical combination of results were used in the meta-analyses • Risk of bias and limitations of primary study methodology were considered when discussing the results • Publication bias was assessed using the Begg and Egger tests (none was detected) • Review authors stated that they had no conflicts of interest related to this review • Source of funding was disclosed (the National Center for Complementary and Integrative Health) and was unlikely to have had an effect on the findings of the review	• It was unclear whether the review methods were established prior to conducting the review (no mention of a protocol) • The authors did not explain their selection of study designs for inclusion in the review (i.e., only RCTs being formally included, with non-randomized designs for consideration in the discussion) • A grey literature search was not completed • It was unclear if data extraction was done in duplicate • A list of excluded studies was not provided (although the reasons for exclusion were) • Review authors did not report on sources of funding for the included primary studies • The countries in which relevant primary studies were conducted were not described; the generalizability to the Canadian setting was unclear

AMSTAR = A MeaSurement Tool to Assess systematic Reviews; CINAHL = Cumulative Index of Nursing and Allied Health Literature; EVAT = External Validity Assessment Tool; ICL = Index to Chiropractic Literature; LILACS = Latin American and Caribbean Health Sciences Literature; PEDro = Physiotherapy Evidence Database; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Coulter et al., 2019[27]	
Systematic review and meta-analysis that investigated the effectiveness and safety of mobilization and manipulation therapies for the treatment of adults (≥18 years of age) with chronic non-specific neck pain. Outcomes of interest were pain, disability, health-related quality of life, and adverse events. **Relevant primary studies**: The systematic review included 11 RCTs[31-41] that compared mobilization and manipulation therapies to sham treatment or no treatment. The systematic review included meta-analyses; however, not all of the studies pooled were relevant to the current report (i.e., the meta-analyses combined studies that compared mobilization and manipulation therapies to other active non-pharmacological interventions). Therefore, relevant results are summarized individually by primary study.	"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."[27] (*pE66*)

Primary study citation	Summary of relevant results	Statistical significance[a]
Outcome: Pain		
Pires et al., 2015[36] (N = 32)	- There were no significant differences between treatment with upper thoracic spine manipulation and sham manipulation with respect to neck pain (measured with the Visual Analogue Scale) post-treatment or at 2 to 3-day follow-up	NS
Snodgrass et al., 2014[39] (N = 64)	- Participants treated with high force mobilization reported increased neck pain (measured with the Visual Analogue Scale) immediately following treatment ($P < 0.001$) compared to those treated with sham therapy - There were no significant differences in neck pain at 4-day follow-up between the two groups	S NS
Klein et al., 2013[34] (N = 61)	- There were no significant differences between the strain-counterstrain and sham therapy groups with respect to neck pain (as measured with the German Version of the Neck Pain and Disability Scale) post-treatment	NS
Suvarnnato et al., 2013[40] (N = 39)	- There were no significant differences in neck pain (as measured with the Visual Analogue Scale) post-treatment or at 24-hour follow-up between the single thoracic manipulation or no treatment groups	NS
Vernon et al., 2012[41] (N = 67)	- Compared to sham cervical manipulation control, participants treated with cervical manipulation therapy had no significant improvements in neck pain (measured using the Numerical Rating Scale) post-treatment	NS
Martel et al., 2011[35] (N = 98)	- Compared to attention control (no treatment), participants treated with spinal manipulation therapy had no significant improvements in neck pain (measured using the Visual Analogue Scale) mid-trial or post-treatment	NS
Sillevis et al., 2010[38] (N = 101)	- Treatment with manipulative therapy did not result in significant improvements in neck pain (measured with the Visual Analogue Scale) post-treatment compared to sham treatment	NS
Schwerla et al., 2008[37] (N = 41)	- Compared to those who received sham ultrasound, participants who were treated with osteopathic treatment reported significant improvements in neck pain (measured with the Numeric Rating Scale and Northwick Park Pain	S

Main Study Findings			Authors' Conclusion
	Questionnaire) post-treatment (P = 0.02); SMD = −0.58 (95% CI: −1.24 to 0.09)		
Briem et al., 2007[31] (N = 40)	- There were no significant differences in neck pain (as measured with the Numeric Pain Rating Scale) post-treatment between individuals treated with inhibitive distraction or sham therapy	NS	
Cleland et al., 2005[32] (N = 36)	- Participants treated with thoracic manipulation had statistically significant improvements in neck pain post-treatment compared to those who received sham manipulation (measured with the Visual Analogue Scale); SMD = −0.95 (95% CI: −1.64 to −0.26)	S	
Hemmilä, 2005[33] (N = 42)	- Treatment with bone setting therapy improved neck pain (measured with the Million index) at 5 weeks (P = 0.002), 3 months (P = 0.01), and 6 months (P = 0.005), compared to the no treatment group - There were no differences in neck pain between the two groups at 12 months	S NS	
Outcome: Disability			
Snodgrass et al., 2014[39] (N = 64)	- There were no significant differences between participants treated with high force mobilization or sham therapy with respect to disability (measured with the Neck Disability Index)	NS	
Martel et al., 2011[35] (N = 98)	- Compared to attention control (no treatment), participants treated with spinal manipulation therapy had no significant improvements in disability mid-trial or post-treatment (measured using the Neck Pain Disability Index)	NS	
Outcome: Health-Related Quality of Life			
Martel et al., 2011[35] (N = 98)	- Compared to attention control (no treatment), participants treated with spinal manipulation therapy had no significant improvements in health-related quality of life mid-trial or post-treatment (measured using the SF-12)	NS	
Schwerla et al., 2008[37] (N = 41)	- Compared to those who received sham ultrasound, participants who were treated with osteopathic treatment reported significant improvements in health-related quality of life (measured with the SF-36) post-treatment (P = 0.019); SMD = −0.40 (95% CI: −1.06 to 0.26)	S	
Outcome: Adverse Events			
Snodgrass et al., 2014[39] (N = 64)	- No participants in either group reported any adverse events	NR	
Klein et al., 2013[34] (N = 61)	- Four participants who received strain-counterstrain therapy and one participant in the sham therapy group experienced mild transient adverse effects	NR	
Vernon et al., 2012[41] (N = 67)	- Participants in the cervical manipulation group experienced mild pain lasting less than 24 hours. The number of participants who were affected was not reported.	NR	
Martel et al., 2011[35] (N = 98)	- No participants in either group reported any adverse events	NR	
Schwerla et al., 2008[37] (N = 41)	- Some participants reported tiredness, although the number and distribution of these participants between groups was not reported in the systematic review	NR	
Cleland et al., 2005[32] (N = 36)	- No participants in either group reported any adverse events	NR	

[a]The threshold for statistical significance was set to $P < 0.05$.

Main Study Findings	Authors' Conclusion
CI = confidence interval; N = number of participants; NR = not reported; NS = non-significant; S = significant; SF-12 = 12-Item Short Form Health Survey; SF-36 = 36-Item Short Form Health Survey; SMD = standardized mean difference. Note: Studies are presented in reverse chronological and alphabetical order.	
Nascimento et al. 2019[28]	
Systematic review and meta-analysis regarding the clinical effectiveness of all interventions for the treatment of non-specific low back pain in older adults (≥60 years of age). **Relevant primary studies**: The systematic review included one RCT[42] that compared spinal manipulation therapies to sham treatment. Although the systematic review included meta-analyses, there was no meta-analysis specific to the primary studies or interventions relevant to the current report. Therefore, relevant results are summarized individually by primary study.	"To our knowledge, this is the most comprehensive systematic review investigating interventions for [non-specific low back pain] in older adults. However, this review does not allow to formulate definitive conclusions about the effectiveness of the interventions. Even though there are studies indicating some positive results, the evidence is weak and not clinically relevant. Future research is highly likely to change any recommendation we would make. Also, efforts to design trials with low risk of bias, provide a detailed description of the interventions applied in all groups, and have an appropriate estimation of the sample size are necessary."[28] (*p160*)

Primary study citation	Summary of relevant results	Statistical significance[a]
Outcome: Pain		
Dougherty et al., 2014[42] (N = 136)	- There were no significant differences in low back pain (measured with the Visual Analogue Scale) at short-term (MD = −2.48 [95% CI: −9.87 to 4.91]) or intermediate-term follow-ups (MD = −2.22 [95% CI: −9.96 to 5.52]) between individuals treated with spinal manipulative therapy or sham therapy	NS
Outcome: Function		
Dougherty et al., 2014[42] (N = 136)	- Compared to sham treatment, participants who received spinal manipulative therapy had no significant improvements in disability (measured using the Oswestry Disability Index) at short-term (MD = −0.90 [95% CI: −4.77 to 2.97]) or intermediate-term (MD = −4.10 [95% CI: −8.82 to 0.62]) follow-ups	NS

[a]The threshold for statistical significance was set to $P < 0.05$.
CI = confidence interval; N = number of participants; NS = non-significant; MD = mean difference.

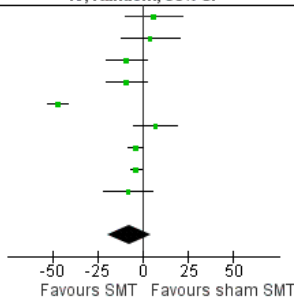
Rubinstein et al. 2019[29]	
Systematic review and meta-analysis that sought to assess the benefits and harms of spinal manipulative therapy for the treatment of adults (≥18 years of age) with chronic low back pain compared to recommended therapies (e.g., exercise, non-steroidal anti-inflammatory drugs, analgesics), non-recommended therapies (e.g., light soft tissue massage, no treatment, waiting list control, electrotherapies), sham therapy (i.e., placebo), and spinal manipulative therapy as adjuvant therapy to any other therapy. **Relevant primary studies**: The systematic review included nine RCTs[43-51] that compared spinal manipulative therapy to sham therapy or no treatment. The authors conducted several meta-analyses that pooled data from eight RCTs[43-49,51] relevant to the current report that could be extracted entirely. Two RCTs[43,50] were also pooled in additional meta-analyses; however, not all of the studies in these analyses were relevant to the current report (i.e., the meta-analyses combined studies that compared mobilization and manipulation therapies to other active non-pharmacological interventions). Therefore, these relevant results are summarized individually by primary study.	"[Spinal manipulative therapy] produces similar effects to recommended therapies for chronic low back pain but results in clinically better effects for short term improvement in function compared with non-recommended therapies, sham therapy, or when added as an adjuvant therapy. Clinicians should inform their patients of the potential risks of adverse events

Main Study Findings	Authors' Conclusion
Comparison of Spinal Manipulative Therapy and Sham Therapy with Respect to Pain	associated with [spinal manipulative therapy]."[29] (*p13*)

Outcome: Pain at 1 Month

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Mean Difference IV, Random, 95% CI
Bialosky 2014a	34	26	14	28	22	28	10.2%	6.00 [-9.87, 21.87]
Bialosky 2014b	34	26	14	30	23	27	10.1%	4.00 [-12.15, 20.15]
Ghroubi 2007	49.37	16.78	32	58.43	28.8	32	11.0%	-9.06 [-20.61, 2.49]
Hidalgo 2015	17	14	16	26	19	16	11.0%	-9.00 [-20.56, 2.56]
Krekoukiasa 2017	12	11	25	58.8	9.2	25	11.9%	-46.80 [-52.42, -41.18]
Licciardone 2003	37.7	26.2	42	30.7	21.9	23	11.0%	7.00 [-4.95, 18.95]
Licciardone 2013	34.97	23.8	230	38.8	21.89	225	12.0%	-3.83 [-8.03, 0.37]
Senna 2011	29.5	5.9	26	33.2	7.3	37	12.1%	-3.70 [-6.97, -0.43]
Waagen 1986	23	15	9	31	15	10	10.7%	-8.00 [-21.51, 5.51]
Total (95% CI)			**408**			**423**	**100.0%**	**-7.55 [-19.86, 4.76]**

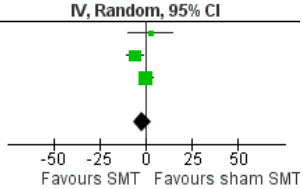
Heterogeneity: Tau² = 322.59; Chi² = 201.88, df = 8 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.20 (P = 0.23)



Outcome: Pain at 3 Months

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Mean Difference IV, Random, 95% CI
Licciardone 2003	31	24.5	36	28.5	20.3	19	12.5%	2.50 [-9.64, 14.64]
Licciardone 2013	26.91	24.22	230	32.78	24.39	225	40.5%	-5.87 [-10.34, -1.40]
Senna 2011	35.2	6.4	26	35.2	7.6	37	47.0%	0.00 [-3.47, 3.47]
Total (95% CI)			**292**			**281**	**100.0%**	**-2.06 [-6.87, 2.74]**

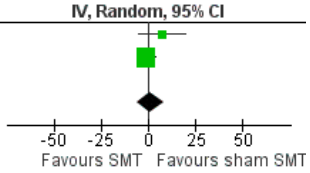
Heterogeneity: Tau² = 9.66; Chi² = 4.69, df = 2 (P = 0.10); I² = 57%
Test for overall effect: Z = 0.84 (P = 0.40)



Outcome: Pain at 6 Months

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Mean Difference IV, Random, 95% CI
Licciardone 2003	31.6	22.4	32	24.5	21.1	19	26.9%	7.10 [-5.16, 19.36]
Senna 2011	35.5	10.9	26	36.8	8.5	37	73.1%	-1.30 [-6.31, 3.71]
Total (95% CI)			**58**			**56**	**100.0%**	**0.96 [-6.34, 8.26]**

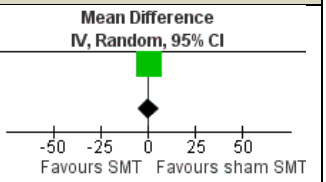
Heterogeneity: Tau² = 12.46; Chi² = 1.55, df = 1 (P = 0.21); I² = 35%
Test for overall effect: Z = 0.26 (P = 0.80)



Outcome: Pain at 12 Months

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Mean Difference IV, Random, 95% CI
Senna 2011	38.5	12.5	26	38.3	8.5	37	100.0%	0.20 [-5.33, 5.73]
Total (95% CI)			**26**			**37**	**100.0%**	**0.20 [-5.33, 5.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.07 (P = 0.94)



CI = confidence interval; IV = inverse variance; MD = mean difference; SMT = spinal manipulative therapy.
Source: Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. BMJ. 2019;364:l689.[29] *Used under Creative Commons License*: https://creativecommons.org/licenses/by-nc/4.0/
Used original material from Data Supplement:
https://www.bmj.com/content/bmj/suppl/2019/03/01/bmj.l689.DC1/rubs048232.ww1.pdf

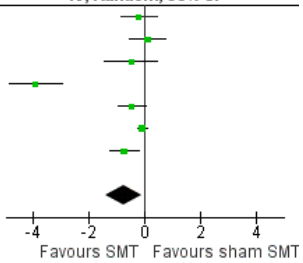
Main Study Findings	Authors' Conclusion

Comparison of Spinal Manipulative Therapy and Sham Therapy with Respect to Functional Status

Outcome: Functional Status at 1 Month

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Bialosky 2014a	12.5	9	14	15	13	28	14.4%	-0.21 [-0.85, 0.44]
Bialosky 2014b	12.5	9	14	11.5	9	27	14.4%	0.11 [-0.54, 0.75]
Hidalgo 2015	19	9	16	24	12	6	12.3%	-0.49 [-1.44, 0.46]
Krekoukiasa 2017	2.44	1.76	25	10.04	2.05	25	12.1%	-3.92 [-4.89, -2.94]
Licciardone 2003	5.7	4.1	42	7.7	4.8	23	15.2%	-0.45 [-0.97, 0.06]
Licciardone 2013	5.64	5.16	230	6.02	5.13	225	16.6%	-0.07 [-0.26, 0.11]
Senna 2011	24.1	9.3	26	32.5	12.5	37	15.1%	-0.73 [-1.25, -0.22]
Total (95% CI)			**367**			**371**	**100.0%**	**-0.74 [-1.39, -0.10]**

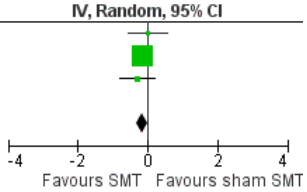
Heterogeneity: Tau² = 0.64; Chi² = 63.42, df = 6 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.26 (P = 0.02)



Outcome: Functional Status at 3 Months

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Licciardone 2003	6.1	4.5	36	6.1	4.1	19	8.8%	0.00 [-0.56, 0.56]
Licciardone 2013	4.27	4.87	230	5.03	5.22	225	80.5%	-0.15 [-0.33, 0.03]
Senna 2011	29.8	10.8	26	33.5	13	37	10.7%	-0.30 [-0.81, 0.20]
Total (95% CI)			**292**			**281**	**100.0%**	**-0.15 [-0.32, 0.01]**

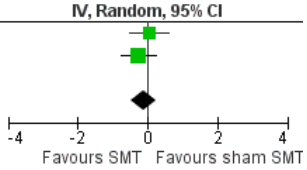
Heterogeneity: Tau² = 0.00; Chi² = 0.62, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.82 (P = 0.07)



Outcome: Functional Status at 6 Months

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Licciardone 2003	5.2	4.5	32	5	4.5	19	44.0%	0.04 [-0.52, 0.61]
Senna 2011	32.2	10.8	26	35.3	12.8	37	56.0%	-0.25 [-0.76, 0.25]
Total (95% CI)			**58**			**56**	**100.0%**	**-0.12 [-0.50, 0.25]**

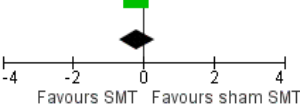
Heterogeneity: Tau² = 0.00; Chi² = 0.59, df = 1 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)



Outcome: Functional Status at 12 Months

Study or Subgroup	SMT Mean	SMT SD	SMT Total	Sham SMT Mean	Sham SMT SD	Sham SMT Total	Weight	Std. Mean Difference IV, Random, 95% CI
Senna 2011	34.9	12	26	37.4	13.4	37	100.0%	-0.19 [-0.69, 0.31]
Total (95% CI)			**26**			**37**	**100.0%**	**-0.19 [-0.69, 0.31]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



CI = confidence interval; IV = inverse variance; MD = mean difference; SMT = spinal manipulative therapy; Std. = standardized.
Source: Rubinstein SM, de Zoete A, van Middelkoop M, Assendelft WJJ, de Boer MR, van Tulder MW. Benefits and harms of spinal manipulative therapy for the treatment of chronic low back pain: systematic review and meta-analysis of randomised controlled trials. BMJ. 2019;364:l689.29[29] *Used under Creative Commons License*: https://creativecommons.org/licenses/by-nc/4.0/
Used original material from Data Supplement:
https://www.bmj.com/content/bmj/suppl/2019/03/01/bmj.l689.DC1/rubs048232.ww1.pdf

Summary of meta-analytic findings:

- Low quality evidence (as assessed by the authors of the systematic review using GRADE) suggested that there were no differences in participants treated with spinal manipulative therapy or sham therapy at one-month follow-up.
- Low quality evidence suggested that spinal manipulative therapy resulted in significant improvements in back specific functional status compared to sham therapy at one month.
- Very low quality evidence suggested that there were no statistically significant differences in treatment with spinal manipulative therapy and sham therapy with respect to pain or functional status at six months or 12 months.

Main Study Findings	Authors' Conclusion
In addition to the relevant studies in the meta-analysis, two additional RCTs[43,50] were included that compared spinal manipulative therapy to no treatment.	

Primary study citation	Summary of relevant results	Statistical significance[a]
Outcome: Pain		
Xia et al., 2016[50] (N = 150)	- Compared to no treatment, participants who received thrust (MD = −17.00 [95% CI: −25.54 to −8.46]) or non-thrust (MD = −12.80 [95% CI: −21.28 to −4.32]) spinal manipulative therapy both reported significant improvements in pain at 1 month	S
Bialosky et al., 2014[43] (N = 55)	- There were no significant differences in pain at 1 month (MD = 8.00 [95% CI: −5.74 to 21.74]) between individuals who received spinal manipulative therapy or no treatment	NS
Outcome: Functional Status		
Xia et al., 2016[50] (N =150)	- Compared to no treatment, participants who received thrust (SMD = −0.83 [95% CI: −1.34 to −0.32]) or non-thrust (SMD = −0.81 [95% CI: −1.31 to −0.30]) spinal manipulative therapy both reported significant improvements in functional status at 1 month	S
Bialosky et al., 2014[43] (N = 42)	- There were no significant differences in functional status at 1 month (SMD = −0.33 [95% CI: −0.98 to 0.32]) between individuals who received spinal manipulative therapy or no treatment	NS

[a]The threshold for statistical significance was set to $P < 0.05$.
CI = confidence interval; MD = mean difference; N = number of participants; NS = non-significant; S = significant; SMD = standardized mean difference.
Note: Studies are presented in reverse chronological and alphabetical order.

Coulter et al., 2018[30]

Systematic review and meta-analysis that investigated the effectiveness and safety of mobilization and manipulation therapies for adults (≥18 years of age) with chronic non-specific low back pain. Outcomes of interest were pain, disability, health-related quality of life, and adverse events.

Relevant primary studies: The systematic review included eight RCTs[46-48,52-56] that compared mobilization and manipulation therapies to sham treatment or no treatment. The systematic review included meta-analyses; however, not all of the studies pooled were relevant to the current report (i.e., the meta-analyses combined studies that compared mobilization and manipulation therapies to other active non-pharmacological interventions). Therefore, relevant results are summarized individually by primary study.

Primary study citation	Summary of relevant results	Statistical significance[a]
Outcome: Pain		
Licciardone et al., 2013[46] (N = 455)	- There were no significant differences in pain (as measured with the Visual Analogue Scale) post-treatment between participants who received osteopathic manipulative treatment or sham osteopathic manipulative treatment; ES = −0.40 (95% CI: −0.59 to 0.21) - Participants who received osteopathic manipulative treatment reported significant improvements in pain after 12 weeks (P = 0.02) compared to those who received sham therapy; ES = NR	NS S

"There is moderate-quality evidence that manipulation (ie, thrust) interventions may produce small-moderate reduction in pain intensity compared with other active comparators such as exercise. Thrust interventions are also likely to reduce disability for patients compared with these active comparator interventions. The effect seems to increase over time at 3 and 6 months follow-up. There is moderate-quality evidence that mobilization (ie, non-thrust) interventions are likely to have minimal effect compared with other active comparators

Main Study Findings			Authors' Conclusion
Senna and Machaly, 2011[48] (N = 60)	- Compared to sham therapy, participants who received spinal manipulation therapy reported significant improvements in pain (measured with the Visual Analogue Scale). The follow-up period for which this applied was unclear in the systematic review.	S	in terms of reducing pain intensity or disability. Multimodal programs may be promising options. More research is needed to assess other important patient reported outcomes in order to strengthen the evidence base regarding mobilization and manipulation for reducing disability and increasing [health-related quality of life] for patients with chronic low back pain. The research to date is still heterogeneous, and questions remain about optimal treatment duration, dose requirements, practitioners to be involved, and the kinds of patients who may benefit the most."[30] (*p876*)
Bicalho et al., 2010[52] (N = 40)	- Participants treated with high-velocity spinal manipulation had statistically significant improvements (*P* = 0.0379) in pain (measured with the Visual Analogue Scale) post-treatment compared to those who received sham manipulation	S	
Hondras et al., 2009[54] (N = 240)	- There were no significant differences in pain (as measured with the Visual Analogue Scale) post-treatment between participants who received high-velocity low amplitude spinal manipulation (group 1), low-velocity variable amplitude spinal mobilization (group 2), or no treatment (group 3); Group 1 vs. Group 3 (post-treatment) ES = −0.12 (95% CI: −0.49 to 0.25); Group 2 vs. Group 3 (post-treatment) ES = −0.12 (95% CI: −0.49 to 0.25)	NS	
Paatelma et al., 2008[56] (N = 134)	- There were no significant differences in pain (as measured with the Visual Analogue Scale) at 3-month follow-up, at 6-month follow-up, or at 12-month follow-up between participants who received osteopathic manipulative treatment or no treatment	NS	
Konstantinou et al., 2007[55] (N = 26)	- There were no significant differences in pain (as measured with the Visual Analogue Scale) post-treatment between the mobilization with movements and sham therapy groups; ES = −0.04 (95% CI: −0.82 to 0.74)	NS	
Licciardone et al., 2003[47] (N = 91)	- Compared to sham therapy, participants who received osteopathic manipulative treatment reported no significant difference in pain (measured with the Visual Analogue Scale) post-treatment, at 3-month follow-up, or at 6-month follow-up - Compared to no treatment, participants who received osteopathic manipulative treatment reported significant improvements in pain (measured with the Visual Analogue Scale) post-treatment (*P* = 0.01), at 3-month follow-up (*P* = 0.001), or at 6-month follow-up (*P* = 0.02)	NS S	
Goodsell et al., 2000[53] (N = 26)	- Compared to no treatment, participants who received central posteroanterior mobilization reported significant improvements (*P* < 0.05) in pain (measured with the Visual Analogue Scale) post-treatment	S	
Outcome: Disability			
Licciardone et al., 2013[46] (N = 455)	- There were no significant differences in disability (measured with the Roland Morris Disability Questionnaire) between individuals who received osteopathic manipulative treatment or sham therapy	NS	
Senna and Machaly, 2011[48] (N = 60)	- Compared to sham therapy, participants who received spinal manipulation therapy reported significant improvements in disability (measured with the Oswestry Disability Questionnaire). The follow-up period for which this applied was unclear in the systematic review.	S	
Hondras et al., 2009[54] (N = 240)	- There were no significant differences in disability (as measured with the Roland Morris Disability Questionnaire) post-treatment or at 24 week follow-up between participants who received high-velocity low amplitude spinal manipulation (group 1), low-velocity variable amplitude spinal mobilization (group 2), or no treatment (group 3); Group 1 vs. Group 3	NS	

Main Study Findings			Authors' Conclusion
	(post-treatment) ES = 0.02 (95% CI: −0.27 to 0.30); Group 2 vs. Group 3 (post-treatment) ES = −0.20 (95% CI: −0.57 to 0.17); Group 1 vs. Group 3 (24 weeks) ES = 0.17 (95% CI: −0.12 to 0.46); Group 2 vs. Group 3 (24 weeks) ES = −0.35 (95% CI: −0.72 to 0.02)		
Paatelma et al., 2008[56] (N = 134)	- There were no significant differences in disability (as measured with the Roland Morris Disability Questionnaire) at 3-month follow-up, at 6-month follow-up, or at 12-month follow-up between participants who received osteopathic manipulative treatment or no treatment	NS	
Licciardone et al., 2003[47] (N = 91)	- There were no significant differences in disability (as measured with the Roland Morris Disability Questionnaire) post-treatment, at 3-month follow-up, or at 6-month follow-up between participants who received osteopathic manipulative treatment, sham therapy, or no treatment	NS	
Outcome: Health-Related Quality of Life			
Licciardone et al., 2013[46] (N = 455)	- There were no significant differences in health-related quality of life (as measured with the SF-36) between individuals who received osteopathic manipulative treatment or sham therapy	NS	
Senna and Machaly, 2011[48] (N = 60)	- Compared to sham therapy, participants who received spinal manipulation therapy reported significant improvements in health-related quality of life (measured with the SF-36). The follow-up period for which this applied was unclear in the systematic review.	S	
Hondras et al., 2009[54] (N = 240)	- There were no significant differences in health-related quality of life (as measured with the SF-36) post-treatment between participants who received high-velocity low amplitude spinal manipulation (group 1), low-velocity variable amplitude spinal mobilization (group 2), or no treatment (group 3); Group 1 vs. Group 3 (post-treatment) ES = −0.12 (95% CI: −0.41 to 0.17); Group 2 vs. Group 3 (post-treatment) ES = 0.32 (95% CI: −0.05 to 0.69)	NS	
Licciardone et al., 2003[47] (N = 91)	- Compared to no treatment, participants who received osteopathic manipulative treatment reported significant improvements in health-related quality of life (measured with the SF-36) post-treatment (*P* = 0.04) - There were no significant differences in health-related quality of life (measured with the SF-36) at 3-month follow-up or at 6-month follow-up between participants who received osteopathic manipulative treatment, sham therapy, or no treatment	S NS	
Outcome: Adverse Events			
Licciardone et al., 2013[46] (N = 455)	- Adverse events were reported by 27 participants (nine of which were definitely or probably related to a therapy). The distribution of these participants between groups was not reported in the systematic review.	NR	
Senna and Machaly, 2011[48] (N = 60)	- Some participants reported local discomfort and tiredness, although the number and distribution of these participants between groups was not reported in the systematic review	NR	
Hondras et al., 2009[54] (N = 240)	- Twenty-two side effects were reported in 20 participants. All were resolved within six days. The distribution of these participants between groups was not reported in the systematic review	NR	

[a]The threshold for statistical significance was set to $P < 0.05$.

Main Study Findings	Authors' Conclusion
CI = confidence interval; ES = effect size; N = number of participants; NR = not reported; NS = non-significant; S = significant; SF-36 = 36-Item Short Form Health Survey. Note: Studies are presented in reverse chronological and alphabetical order.	

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial.

Appendix 5: Overlap between Included Systematic Reviews

Table 7: Relevant Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation			
	Coulter et al., 2019[27]	Nascimento et al. 2019[28]	Rubinstein et al., 2019[29]	Coulter et al., 2018[30]
Bialosky et al., 2014[43]			X	
Bicalho et al., 2010[52]				X
Briem et al., 2007[31]	X			
Cleland et al., 2005[32]	X			
Dougherty et al., 2014[42]		X		
Ghroubi et al., 2007[44]			X	
Goodsell et al., 2000[53]				X
Hemmilä, 2005[33]	X			
Hidalgo et al., 2015[45]			X	
Hondras et al., 2009[54]				X
Klein et al., 2013[34]	X			
Konstantinou et al., 2007[55]				X
Krekoukiasa et al., 2017[51]			X	
Licciardone et al., 2013[46]			X	X
Licciardone et al., 2003[47]			X	X
Martel et al., 2011[35]	X			
Paatelma et al., 2008[56]				X
Pires et al., 2015[36]	X			
Schwerla et al., 2008[37]	X			
Senna and Machaly, 2011[48]			X	X
Sillevis et al., 2010[38]	X			
Snodgrass et al., 2014[39]	X			
Suvarnnato et al., 2013[40]	X			
Vernon et al., 2012[41]	X			
Waagen et al., 1986[49]			X	
Xia et al., 2016[50]			X	

X = the primary study was included in the systematic review and relevant data were extracted for the current review.

Appendix 6: Additional References of Potential Interest

Previous CADTH Reports

Wells C, Ford C. Manual therapy for the treatment of cervicogenic headaches: clinical effectiveness. (*CADTH Rapid response report: reference list*). Ottawa (ON): CADTH; 2017 Jul: https://cadth.ca/sites/default/files/pdf/htis/2017/RA0914%20-%20Chiropractic%20Interventions%20for%20Headaches%20Final.pdf. Accessed 2020 Jan 30

Young C, Ford C. Manual therapy for the treatment of shoulder pain: clinical effectiveness. (*CADTH Rapid response report: reference list*). Ottawa (ON): CADTH; 2017 Jul: https://cadth.ca/sites/default/files/pdf/htis/2017/RA0915%20Chiropractic%20Interventions%20for%20Shoulder%20Pain%20Final.pdf. Accessed 2020 Jan 30

Review Articles

Cuenca-Martinez F, Cortes-Amador S, Espi-Lopez GV. Effectiveness of classic physical therapy proposals for chronic non-specific low back pain: a literature review. *Phys Ther Res*. 2018;21(1):16-22.
PubMed: PM30050749