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SUMMARY WITH CRITICAL APPRAISAL

Manual Therapy for Recent – Onset or Persistent Neck Pain: A Review of Clinical Effectiveness and Guidelines

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Context and Policy Issues

The lifetime prevalence of neck pain in the Canadian population is greater than 70%.[1] Neck pain is prevalent in both the adult and pediatric populations.[2] Poor psychological health, genetics, and exposure to tobacco have been previously identified as risk factors for neck pain.[2] Neck pain is a significant source of socioeconomic burden, arising from decreased health-related quality of life, decreased productivity and increased health care utilization.[3]

Neck pain and associated disorders (NAD), encompasses various neck pain syndromes[4] including but not limited to neck pain with no known cause and neck pain with or without radiculopathy.[5] NAD is categorized into grades I to IV, based on severity, impact on quality of life, and management implications.[4] Neck pain and associated disorders secondary to traffic collisions is referred to as whiplash-associated disorder (WAD).[3] Like NAD, WAD is also categorized into four grades from I to IV.[6] NAD and WAD grades I to III comprise of neck pain without signs and symptoms of major structural pathologies such as fractures, dislocations, tumours, etc.[3,6] NAD and WAD Grade IV includes some major structural pathologies such as fractures and dislocations,[3,6] which fall outside the scope of practice of chiropractors and other manual therapy practitioners.

The non-invasive treatment options for patients with NAD and WAD grades I to III include nonpharmacological treatments such as acupuncture, manual therapy, physical therapy modalities, and pharmacologic treatments such as nonsteroidal anti-inflammatory drugs(NSAIDs), and muscle relaxants.[3] There exists a paucity of evidence supporting the use of opioids for the treatment of NAD[7] and significant concerns exist for potential misuse/abuse.[8] Furthermore, the use of NSAIDs in the elderly population is limited due to potentially lethal side effects.[8]

Manual therapies for neck pain include manipulation, mobilization, soft tissue therapy, and traction.[9] During spinal manipulation, high-velocity low amplitude thrust to a joint in the spine, near or at the end of its physiological range of motion.[9] The application of a low-velocity force to a joint in the spine within its physiological range of motion is known as spinal mobilization.[9] Soft tissue therapy, such as Swedish massage, deep tissue massage and sports massage, delivered by the practitioners' hands or mechanical device is the therapeutic manipulation of muscles and other soft tissues.[10,11] Traction is the application of a continuous or intermittent force to increase the joint space between two adjacent bones.[12] Manual therapies, if proven safe and effective may be considered as an alternative intervention to pharmacologic treatments for neck pain. However, neck pain is not as extensively researched as low back pain.[1] Additionally, the effectiveness of only a limited number of interventions has been established.[9]

The purpose of this report is to examine the clinical effectiveness and evidence-based guidelines regarding the use of manual therapy for the treatment of neck pain in the adult and pediatric populations. For this report, acute neck pain will be used synonymously with recent-onset neck pain and chronic neck pain with persistent neck pain.

Research Question

1. What is the clinical effectiveness of using manual therapy for the treatment of adults or pediatric patients with recent-onset or persistent neck pain?
2. What are the evidence-based guidelines associated with the use of manual therapy for the treatment of adults or pediatric patients with recent-onset or persistent neck pain?

Key Findings

Evidence supports the use of manipulation and mobilization for the management of neck pain in the adult population. There is evidence that massage may be beneficial for neck pain. Evidence from a single systematic review found traction had a positive effect on pain after the completion of treatments, however, this evidence was of limited quality and the results should be interpreted with caution. Two evidence-based guidelines were identified that provided recommendations supporting the use of manual therapies for acute and chronic neck pain in adults. Both guidelines included recommendations for the use of manipulation, mobilization, multimodal manual therapy and massage. Additionally, they both offered recommendations to not use relaxation massage, strain-counterstrain therapy, and traction for neck pain. No systematic reviews or guidelines were identified concerning the management of neck pain in the pediatric population.

Methods

Literature Search Methods

Rapid Response reports are organized so that the evidence for each research question is presented separately.

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and guidelines. The search was limited to English language documents published between Jan 1, 2014 and Aug 11, 2017.

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 or pediatric patients with recent-onset or persistent neck pain from any cause (e.g., work related, trauma [whiplash], everyday use, etc.); including neck pain and associated disorders (NAD), and whiplash-associated disorders (WAD)
Intervention	Manual therapy, including manipulation, mobilization, traction, and soft tissue therapy

Comparator	Q1: Pharmacological interventions (including opioids); Non-pharmacological interventions (e.g., education, exercise, Other manual therapies, electrotherapy, etc.); Placebo/sham interventions; Wait list; No interventions Q2: No comparator
Outcomes	Q1: Clinical Effectiveness and safety, e.g.: • Self-rated recovery; • Functional recovery (e.g., disability, return to activities, work, or school); • Clinical outcomes (e.g., but not limited to, pain, health-related quality of life, depression, time to benefit, no change or worsening of pain, etc.); • Adverse events and harms Q2: Guidelines
Study Designs	Health Technology Assessments (HTAs), Systematic Reviews(SRs), meta-analyses(MAs), and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1 or if they were not published in English, were duplicate publications, or were published prior to 2014. HTAs, SRs and meta-analyses, and evidence-based guidelines not specific to chiropractic were excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised using the AMSTAR tool,[13] and guidelines were assessed with the AGREE II instrument.[14] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 60 citations were identified in the literature search. Following screening of titles and abstracts, 40 citations were excluded and 20 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, six publications were excluded for various reasons, while fourteen publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

The inclusion criteria for five of the included systematics reviews[9,10,15-17] was broader than the criteria outlined in Table 1. Therefore, only relevant studies included in the SRs are presented in this report.

Summary of Study Characteristics

The body of evidence included twelve SRs[5,9-11,15-22] with or without meta-analyses and two guidelines[3,23] addressing the treatment of acute or chronic neck pain with manual therapies.

There was a significant overlap in the included studies between SRs on manipulation and mobilization, which is summarized in Appendix 6.

Additional details regarding the characteristics of included SRs and evidence-based guidelines are presented below and in Appendix 2: Table A1 and A2 respectively.

Study Design

Five of the included SRs performed relevant meta-analyses.[5,11,19,20,22] The publication dates for the primary studies included in the reviews ranged from 1977[5] to 2016.[22] Seven of the SRs included only RCTs in their body of evidence.[9,11,15,18-20,22] In addition to RCTs, Gross et al.[5] included one quasi-RCT and one cross-over RCT. Young et al.[21] included one of each of the following: quasi-RCT, prospective cohort study, case-series and secondary analysis of a RCT. Three included studies were reviews of SRs.[10,16,17]

Two evidence-based guidelines[3,23] were identified regarding the management of neck pain. The guideline by Côté et al.[3] was informed by published SRs. Bussières et al.[23] included the same published SRs, but also performed an updated literature search to identify any additional studies. Clinical recommendations for both guidelines were consensus based.[3,23] The Bussières et al.[23] guideline provided ratings for the strength of the recommendations. Cote et al.[3] modified the National Institute for Health and Care Excellence methodology by wording the recommendations to reflect the strength of the recommendation (e.g., “offer”, “consider”, “do not offer”).

Country of Origin

The SRs were led by authors in Canada,[5,9,15,16] China,[11,17,20] Taiwan,[19] Norway,[22] and United States.[10,18,21]

The two evidence- based guidelines were developed in Canada.[3,23]

Patient Population

The patient population in Shekelle et al.[18] included adults with acute (less than 6 weeks) neck pain. The duration of neck pain was unclear in one SR.[17] Ten SRs included patients with pain of varying durations.[5,9-11,15,16,19-22] Southerst et al.,[15] Wong et al.,[9] and Wong et al.[16] defined the duration of pain as recent-onset (< 3 months) and persistent (≥3 months). Gross et al.[5] classified the duration into acute (<30 days), subacute (30 to 90 days) and chronic (>90 days).

Patients with cervical radiculopathy were the only population included in the SR by Wei et al.[17] Seven SRs included patients with or with radicular symptoms.[5,9,10,15,16,19,20] Fredin and Lorås[22] excluded patients with radicular signs. The inclusion criteria in Young et al.[21] was mechanical neck pain and therefore, patients with cervical radiculopathy and cervicogenic headache were excluded. In addition to patients with neck pain with or without cervical radiculopathy, Gross et al.[5] included patients with cervicogenic headaches. One of the included studies on cervicogenic headaches included patients with cervicogenic headache with temporomandibular joint dysfunction.[5]

The majority of the SRs[5,11,18-22] were concerned with the management of neck pain in adults (persons 18 years and older). Two SRs did not specify the age of the included population.[10,17] None of the included SRs investigated the effectiveness of manual therapies for the treatment of neck pain in the pediatric population. Children were included in the inclusion criteria for the SRs by Southerst et al.,[15] Wong et al.,[9] and Wong et al.,[16] but

none of the included studies relevant to manual therapy comprised of a pediatric population.

The clinical practice guideline by Bussières et al.[23] included adults and elderly patients with recent- onset (<3 months) and persistent (>3 months) NAD and WAD grades I-III. The guideline by Côté et al.[3] included adults with NAD grades I-III with neck pain of less than six months duration.

Interventions and Comparators

The interventions of interest in the SRs included manual therapy,[9,15-17,22] spinal manipulation and mobilization,[5,18,20,21] traction[19] and soft tissue therapy.[10,11] Comparators included control interventions (no treatment, usual therapy/standard care, waitlist, placebo, sham intervention or inactive control),[5,9,10,19-21] active interventions (exercise, physical therapy, physical therapy modalities, acupuncture, another manual therapy),[5,10,11,15,17,18,21,22] pharmacologic treatments,[16-18] and education.[10]

Interventions in the guideline by Bussières et al.[23] comprised of only conservative care interventions including exercise, multimodal care, education, work disability, manual therapy, and passive modalities. Côté et al.[3] included both pharmacologic and non-pharmacologic interventions. Relevant non-pharmacologic treatments included manual therapy, soft-tissue care and multimodal care.[3] Eligible comparators in the Bussières et al.[23] guideline included advice and education, strengthening exercise programs, wait list, massage, mobilization, medications and a clinic-based hardening program. Côté et al.[3] included other interventions, placebo/sham interventions, wait list or no intervention as comparators.

Outcomes

Pain was the primary outcome in all the twelve included SRs.[5,9-11,15-22] Ten of the included SRs included function/disability as an outcome.[5,9,11,15,16,18-22] Nine SRs reported on adverse events(AEs).[9,11,15-20,22] Quality of life (QoL) was reported in three SRs[5,15,22] and global perceived effect was reported in two SRs.[5,15] Wong et al.[9] and Young et al.[21] included self-rated recovery. Gross et al.[5] and Southerst et al.[15] included patient satisfaction.

The SRs and included primary studies used the following outcome measures:

Pain: visual analog scale,[17-22] numerical pain rating scale,[18,20,21] numerical rating scale,[15,16,19,22] Northwick Park Questionnaire,[5,21] functional pain scale,[21] McGill Pain Questionnaire[19]

Function/disability: Northwick Park Questionnaire,[18,20,22] Neck Disability Index[5,15,19-22]

QoL: 36-item Short Form Survey[5,15,22], 12-item Short Form Survey[5,22]
Global perceived effect: Global rating of change scale[5,21]

The length of follow-up varied from six weeks[18] to greater than a year.[11] Shekelle et al.[18] had the shortest follow-up interval at six weeks. A one year follow-up interval was included in four SRs.[15,19,21,22] Yao et al.,[20] Gross et al.,[5] Fredin and Lorås,[22] and Cheng et al.[11] classified their follow-ups into short-term, intermediate-term and long-term follow-ups, though time frame of each interval varied in all four SRs.

Pain and disability were the primary outcomes in the Bussières et al.[23] clinical practice guideline. Self-rated recovery, functional recovery, disability, pain intensity, health-related

QoL, psychological outcomes and adverse events were outcomes of interest in the second included guideline.[3]

Summary of Critical Appraisal

Additional details of the critical appraisal of the included SRs and evidence-based guidelines are provided in Appendix 3: Table A3 and A4

Systematic Reviews

A comprehensive literature search of at least two electronic databases was conducted in all the included SRs.[5,9-11,15-22] However, an appropriate search of the grey literature was conducted in two SRs.[5,20] Unpublished manuscripts were included in the exclusion criteria for three SRs.[9,15,16] Duplicate study selection and data extraction were adequately conducted in ten SRs.[5,9,10,15-20,22] However, the consensus procedure for discrepancies was not described in one SR.[22] It is unclear if duplicate study selection was performed in the reviews by Cheng and Huang[11] and Young et al.[21] Furthermore, it is unclear whether Young et al.[21] conducted duplicate data extraction. All the SRs provided a list of the included studies,[5,9-11,15-22] but only three SRs provided the list of excluded studies.[5,11,22] The mean age of participants was not adequately reported in seven SRs.[5,9,10,15,18,20,21] Additionally, seven SRs failed to include the breakdown of patients by sex.[5,9-11,15,18,21]

The scientific quality of included studies was assessed adequately in all SRs and was used to appropriately to formulate conclusions.[5,9-11,15-22] All five of the included reviews that performed a meta-analyses adequately assessed heterogeneity using appropriate statistical tests.[5,11,19,20,22] However, the I^2 statistic was not reported for all comparisons in two SR.[5,22] The pooling of data may not have been clinically appropriate in three of the reviews, as they included either varied patient populations, durations of neck pain or heterogeneous interventions and comparators.[11,19,20]

An assessment of publication bias was not undertaken in eight SRs.[9-11,15,18,19,21,22] The SRs by Yao et al.[20] and Gross et al.[5] partially assessed this criteria by only evaluating publication bias with graphical aids.

Young et al.[21] failed to declare any conflict of interest or sources of funding for the SR. The authors of two SRs failed to disclose the source of funding for the reviews.[11,20] None of the SRs reported conflict of interest or source of funding for the included studies.[5,9-11,15-22]

Guidelines

The two evidence-based guidelines included in the review were deemed to be of high quality.[3,23] The scope and purpose, stakeholder involvement, rigour of development, clarity of presentation and editorial independence were clearly defined. However, in the guideline by Côté et al.[3] the external review was conducted by the Government of Ontario and not the guideline development group. Additional details are not provided regarding the stakeholders invited to review the guideline.[3] The applicability domain was not adequately addressed in both guidelines.[3,23] The facilitators and barriers to application, resource implications and auditing criteria were not reported in either review.[3,23] However, Bussières et al.[23] do provide implementation tools to support guideline dissemination. Côté et al.[3] state that the applicability domain fell outside the scope of their guideline as it was developed for the Government of Ontario.

Summary of Findings

The overall findings of the body of evidence are summarized below. A detailed summary of the main findings and recommendations are available in Appendix 4: Table A5 and Table A6.

1. *What is the clinical effectiveness of using manual therapy for the treatment of adults or pediatric patients with recent-onset or persistent neck pain?*

Twelve SRs[5,9-11,15-21] were identified concerning the management of neck pain in the adult population.

Manual therapy

Fredin and Lorås[22] included seven RCTs concerning the effectiveness of combined exercise therapy and manual therapy in comparison to exercise alone. The relevant manual therapies in the included RCTs were manipulation, mobilization and soft tissue therapy.[22] The review reported no differences between combined manual therapy and exercise in comparison to exercise alone for pain at rest, disability and quality of life.[22] No serious adverse events were reported in the five studies included in the review that reported AEs.[22] Three RCTs reported mild AEs including muscle and joint soreness, headache, dizziness and nausea.

Wong et al.[16] conducted a review of SRs investigating the clinical effectiveness of NSAIDs. One SR in the body of evidence on neck pain and associated disorders included one RCT comparing manual therapy to intramuscular NSAID (ketorolac tromethamine).[16] A greater reduction in 10-point NRS score was reported in the osteopathic manipulation group, which received manipulation and soft tissue techniques (Mean difference between groups 1.1; 95% confidence interval [CI] 0.2 to 1.9).[16] This difference failed to meet the threshold for a minimal clinically important difference, which is 2 out of 10 on the numeric rating scale.[16] A greater percentage of patients in the NSAID group reported AEs.[16]

Fourteen RCTs on manual therapies including manipulation, mobilization, traction and massage were included in a review by Wong et al.[9] Authors of the review categorized the studies as exploratory or evaluation studies.[9] Exploratory studies can assess interventional efficacy but cannot provide evidence of effectiveness.[9] Evaluation studies can provide information on effectiveness or comparative effectiveness.[9] For patients with recent onset NAD I-II, exploratory evidence suggests that thoracic spine manipulative therapy (SMT) is beneficial.[9] No statistically significant differences between groups was found when thoracic SMT was compared to placebo for persistent NAD I-II.[9] The authors reported that that the type of cervical mobilization does not influence outcomes and strain-counterstrain, a type of soft tissue therapy is not efficacious for NAD.[9] One evaluation study reported traction conveys no additional benefit when added to a multimodal program for NAD grade III.[9] For NAD grades I-II, cervical manipulation and mobilization had comparable outcomes.[9] Clinical massage may provide benefits to patients with persistent NAD I-II.[9] No serious adverse events were reported in any of the trials on manipulation. [9] The authors concluded that mobilization, manipulation and clinical massage are effective manual therapies in the treatment of neck pain.[9]

Wei et al.[17] conducted a review of SRs evaluating the effectiveness of complementary and alternative medicine for the treatment of cervical radiculopathy. Four out of the eight included SRs were relevant to this report.[17] Three SRs were concerned with a combination of manipulation, massage and mobilization reported that manual therapy may be effective

for the treatment of CR. The fourth SR found that in comparison to cervical computer traction, spinal manipulation provided statistically significant pain relief in the immediate-term.

Manipulation and mobilization

The SR by Shekelle et al.[18] included five RCTs investigating the effect of spinal manipulation (including mobilization) on acute neck pain. A meta-analysis was not conducted and the results from the studies were reported separately.[18] One included RCT demonstrated a statistically significant effect on pain post treatment in the group receiving cervical SMT plus NSAIDs in comparison to NSAIDs alone. In the second RCT, no statistically significant effects were reported between groups receiving cervical collars alone, collars with physical therapy and collars with mobilization. The third RCT reported a statistically significant effect on immediate pain when cervical SMT was performed ipsilateral to the side of complaint. The last two RCTs reported statistically significant differences for pain and function in the groups receiving thoracic spine manipulation in conjunction with physical therapy (e.g., electro/thermal therapy and soft-tissue massage).

Yao et al.[20] evaluated the clinical effectiveness of manipulation in a SR that included 19 RCTs. For short-term pain (up to 12 weeks) , there was a statistically significant reduction in VAS scores (mean difference [MD] -1.14; 95% CI, -2.12 to -0.16; 7 RCTs, n=554) but not for trials reporting pain via NPRS scores.[20] For intermediate-term pain (six months), there were statistically significant reductions in NPRS score (MD -0.29; 95% CI, -0.53 to -0.05; 6 RCTs, n=916), but not for VAS scores.[20] There were no statistically significant differences in VAS and NPRS scores with respect to long-term pain.[20] For function, there were statistically significant reductions in NDI scores in the short-term (MD -2.10; 95% CI, -2.98 to -1.21; 8 RCTs, n=1,145) and intermediate-term (MD -1.45, 95% CI, -2.55 to -0.35; 7 RCTs, n= 987) but not in the long-term.[20] In one of in the included RCTs, a patient in the SMT group was withdrawn from the trial due to an unspecified serious adverse event.[20] Other reported adverse events included headache, fatigue and dizziness.[20]

Southerst et al.[15] included two RCTs relevant to manual therapy in their review on exercise. The first RCT found no statistically significant differences between home exercise advice (HEA) and SMT for pain, disability or function and health-related quality of life. Forty percent of the SMT group reported non-serious adverse events in comparison to 46% in the HEA group. The second RCT compared exercise therapy (ET), SMT plus ET and HEA.[15] In the short-term (12 weeks), a statistically significant difference was reported in favour of the ET plus SMT in comparison to HEA for pain, disability, and global perceived effect. [15] These effects were not statistically significant at 52 weeks. Satisfaction scores were significant at both follow-up intervals. ET plus SMT had a statistically significant difference in disability and physical component of SF-36 at 12 weeks. In the long-term (52 weeks), there were no statistically significant differences between the ET plus SMT and ET groups for any outcome.

Gross et al.[5] conducted an updated review on the effectiveness of manipulation and mobilization for neck pain including 51 publications. Three included RCTs demonstrated that in patients with subacute and chronic neck pain, a single session of cervical SMT in comparison to inactive control provided immediate pain relief, but not in the short-term. In comparison to mobilization; multiple sessions of SMT produced no statistically significant differences with respect to pain, function, quality of life, global perceived effect and patient satisfaction in patients with acute and chronic neck pain. Cervical SMT also had an effect on improving pain and function in the immediate-term and long-term follow-up when

compared to medication in patients with acute and subacute neck pain. For chronic cervicogenic headache, SMT is more effective than TENS for pain and massage for pain and function in the short-term and intermediate-term. In patients with acute neck pain, a course of SMT to the cervical spine is more effective than thoracic spine manipulation for pain and function. Thoracic spine manipulation was found to have a statistically significant effect on pain in patients with acute and subacute neck pain and function in patients with subacute and chronic neck pain. For patients with chronic neck pain, a single session of thoracic spine SMT was found to be comparable to thoracic mobilization for pain relief in the immediate-term.

In comparison to inactive controls, two of the included RCTs reported no differences in pain reduction with cervical mobilization.[5] In patients with acute and subacute neck pain, anterior-posterior mobilizations may provide benefit over rotary or transverse mobilizations in the immediate-term. In patients with chronic cervicogenic with temporomandibular joint (TMJ) dysfunction, manual therapy to the TMJ may be more effective than cervical mobilization for pain and function in the immediate- and intermediate-term. No statistically significant differences were found in pain, function, quality of life, and patient satisfaction when cervical mobilization as a stand-alone treatment was compared to ultrasound, TENS, acupuncture and massage in the immediate- and intermediate-term in patients with subacute and chronic neck.

Young et al.[21] included fourteen studies concerning thoracic manipulation and mobilization for mechanical neck pain. In comparison to thoracic mobilization, one RCT found thoracic manipulation has a statistically significant effect on pain, function and perceived recovery. Thoracic manipulation was found to be effective in the short-term for reduction in pain and disability The SR included one quasi-RCT, which the authors rated as poor quality, on thoracic mobilization for mechanical neck pain. The study found mobilization has statistically significant effects on pain, disability and muscle endurance in comparison to exercise.

Traction

Yang et al.[19] included seven RCTs evaluating the clinical effectiveness of intermittent cervical traction (ICT) in comparison to a placebo group. The placebo group comprised of manual therapy, physical therapy modalities, exercises and sham ICT.[19] In all the included studies, patients in both treatments arms received either exercises or manipulation.[19] The ICT group reported statistically significant reduction in pain scores after the completion of treatments (standardized mean difference [SMD] -0.26; 95% CI, -0.46 to -0.07; I^2 = 58%), but not at final follow-up.[19] No differences were observed in function scores between the two groups at either follow-up interval.[19] Mild increase in pain was the most commonly reported adverse event.[19]

Soft-tissue therapy

Miake-Lye et al.[10] conducted a review of SRs on the effectiveness of massage on pain. Six SRs were included in the body of evidence that concerned the effectiveness of massage on neck pain; three exclusively on neck pain.[10] Three of the six reviews reported some potential benefits for massage for the management of neck pain.[10] The other three SRs reported that the effect of massage on neck pain is unclear.[10]

The SR by Cheng and Huang[11] included fifteen RCTs concerning the effectiveness of massage for neck pain. The review found a statistically significant effect on immediate pain

relief in comparison with inactive therapies (SMD 1.30; 95% CI, 0.09 to 2.50) such as standard care and sham therapies, but not for active therapies.[11] In the short-term, acupuncture and exercises were found to have positive statistically significant effects on pain relief in comparison to massage.[11] Massage therapy did not have a positive statistically significant immediate effect on neck related dysfunction when compared to active or inactive therapies.[11] Two included RCTs reported adverse events; 21% experienced low blood pressure in one RCT and 28% reported mild adverse events such as pain, discomfort, and nausea.[11]

No relevant SRs were identified regarding the effectiveness of using manual therapy for the treatment of pediatric patients; therefore, no summary can be provided on this population.

2. *What are the evidence-based guidelines associated with the use of manual therapy for the treatment of adults or pediatric patients with recent-onset or persistent neck pain?*

Two guidelines were included in the body of evidence concerning the management of neck pain and its associated disorders (NAD) and whiplash-associated disorders (WAD) grades I-III.[3,23]

The evidence-based guideline by Bussières et al.[23] provided recommendations for adults and the elderly with recent-onset (<3 months) and persistent (>3 months) NAD and WAD grades I-III. For recent-NAD grades I-II, manipulation or mobilization, based on patient preference is recommended.[23] Multimodal manual therapy including varying combinations of manipulation, mobilization and soft tissue therapy are recommended for patients with recent onset NAD and WAD grades I-III and persistent NAD grades I-II.[23] For patients with persistent NAD grades I-II, high dosage of massage is recommended over no treatment.[23]

Côté et al.[3] recommends multimodal care including manipulation or mobilization for patients with recent-onset or persistent NAD grades I-II. Clinical massage may also be considered for patients with persistent NAD grades I-II.[3]

A few of the recommendations provided in Bussières et al.[23] were reproduced with permission from Côté et al.[3] The guidelines recommend that clinicians not offer relaxation massage and strain-counterstrain therapy for persistent NAD grades I-II.[3] Additionally, traction should not be offered for patients with recent-onset NAD grade III.[3]

No evidence-based guidelines were identified concerning manual therapy for the treatment of pediatric patients; therefore, no summary can be provided on this population.

Limitations

The main limitations of the body of evidence included in this review are significant clinical heterogeneity and lack of practitioner blinding.

Inclusion of patients with or without radiculopathy, varying durations of neck pain and diverse interventions and comparators were sources of clinical heterogeneity. Seven reviews included patients with or with radicular symptoms.[5,9,10,15,16,19,20] Two reviews excluded patients with radiculopathy[21,22] and one excluded patients with cervicogenic headaches.[21] One review included patients with or without cervical radiculopathy, cervicogenic headaches, and cervicogenic headaches with TMJ dysfunction.[5] Yang et al.[19] performed a SR evaluating the effectiveness of intermittent cervical traction for neck pain. However, the intervention and placebo groups in all the included studies also received either exercise or manipulation.[19] The intervention group in five of the included studies also

received physical therapy modalities.[19] Furthermore, the meta-analysis pooled patients with varying neck pain durations presenting with and without cervical radiculopathy [19] Yao et al.[20] pooled data from patients with and without cervical radiculopathy and mean neck pain durations ranging from a 18 days to 6.5 years.[20] Cheng and Huang[11] compared massage with inactive and active therapies. The pooled active therapies included acupuncture, traction, exercise and physical therapy.[20] The intent of delivering these therapies is not the same and pooling them may not be clinically appropriate.

Lack of practitioner blinding is a significant methodological flaw in all studies on manual therapy. In addition to lack of practitioner blinding, the majority of the included studies also failed to ensure adequate patient and outcome assessor blinding.

Two SRs in the body of evidence included study designs that are inadequate in ascertain the effectiveness of interventions.[5,21] Gross et al.[5] included a quasi-RCT and cross-over RCT. Young et al.[21] included a quasi-RCT, cohort study, case-series and secondary analysis of a RCT. Quasi-RCTs, cohort studies and case-series introduce a significant source of bias due to the lack of randomization.

The literature search conducted for this report did not identify any SRs concerned with the management of neck pain in the pediatric population. Therefore, the findings from the included SRs on the management of the adult population may not be generalizable to the pediatric population.

The process for the external peer review for the guideline by Côté et al. is unclear.[3] The applicability domain was inadequately completed in both guidelines.[3,23] The guidelines by Côté et al.[3] provides recommendations for patients with pain up to six months.[3] The recommendations may not be generalizable to patients with neck pain for greater than six months in duration.[3] The target population in both the guidelines are adults with neck pain, therefore, the recommendations may not be generalized to the pediatric population.

As a result of the strict inclusion criteria for this report, all SRs and evidence-based guidelines specifically targeted towards other healthcare professionals including osteopaths, physiotherapists, and registered massage therapists were excluded. Therefore, it is possible that some relevant publications were not included in the body of evidence.

The included SRs assessed the clinical effectiveness of manual therapy interventions including manipulation, mobilization, soft tissue therapy and traction. These interventions are used daily by North American chiropractors for the treatment of neck pain.[24] The two evidence based guidelines were developed in Canada. Therefore, the findings from the included SRs and evidence-based guidelines are generalizable to the Canadian adult population.

Conclusions and Implications for Decision or Policy Making

A total of fourteen publications were identified, including twelve SRs[5,9-11,15-22] and two guidelines.[3,23] No evidence was identified for the clinical effectiveness and guidelines concerned with the management of neck pain in the pediatric population.

Overall, the body of evidence supported the use of manual therapy interventions for neck pain. The evidence supports the use of cervical manipulation and mobilization, and thoracic manipulation. Evidence from a single systematic review found traction had a positive effect on pain after the completion of treatments, however, this evidence was of limited quality and the results should be interpreted with caution. Additionally, the evidence suggests that

soft tissue therapy may be effective for patients with neck pain. Seven of the included SRs reported on adverse events.[5,9,11,16,19-21] One SR reported that patient in the manipulation group was withdrawn due to a serious adverse event, but no specific details were provided.[20] A serious neurovascular event was not reported in any of the other trials.[5,9,11,16,19,21] Mild transient events were most commonly reported. In general, manual therapies appear to be safe in the treatment of neck pain.

Two evidence-based guidelines were identified concerning the management of neck pain.[3,23] Both guidelines recommend the use of manipulation and mobilization for recent onset NAD I-II. For persistent NAD I-II, massage is recommended. Multimodal manual therapy including varying combinations of manipulation, mobilization and massage were recommended by both guidelines for recent-onset NAD and WAD I-III and persistent NAD I-II. The guidelines recommended against the use of relaxation massage and strain-counterstrain therapy for persistent NAD I-II and traction for recent-onset NAD grade III.

Additional RCTs of high quality are needed to confirm the effectiveness and safety of manual therapies in the long-term. Authors should also strive to reduce clinical heterogeneity by providing additional details regarding the type of manual therapy procedure, frequency and duration of treatments. Furthermore, more RCTs concerning the effectiveness of manual therapy interventions in the pediatric population is required to bridge this identified gap in the research.

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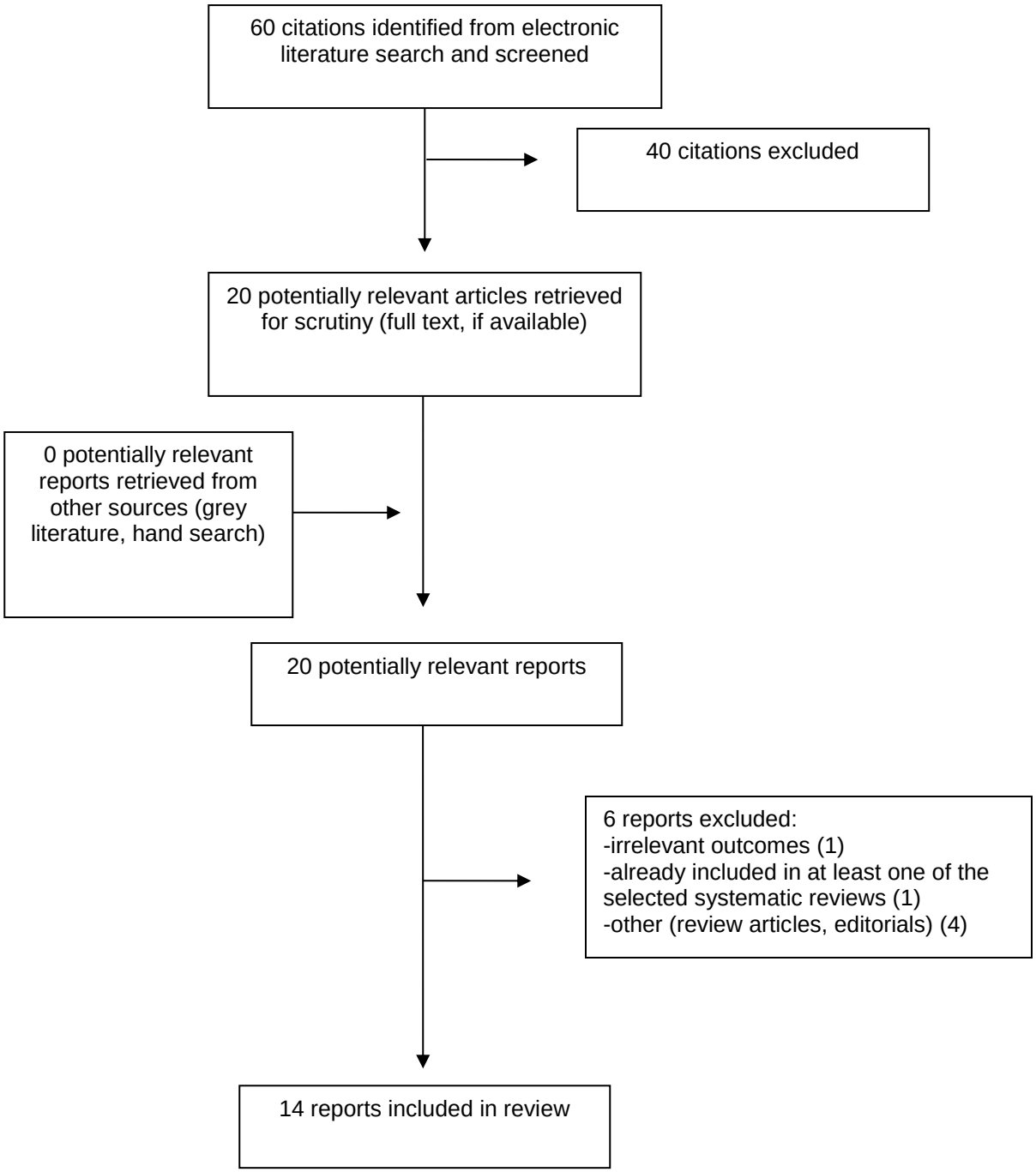
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Reviews

Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Fredin and Lorås 2017[22] **Norway**	7 RCTs	Adults (>18 years of age) with NAD grade I-II N = 936 Excluded : patients with unknown pathology or radicular signs	Exercise therapy with manual therapy	Exercise therapy	Primary outcome: pain (VAS, NRS), disability (NDI, NPQ), QoL (SF-36, SF-12), AEs Follow-up interval: immediate-term (2-12 weeks), intermediate-term (6 months), and long-term (12 months)
Shekelle et al. 2017[18] **United States**	5 RCTs	Adults, 18 years and older with acute (<6 weeks duration) neck pain N =198	Cervical and thoracic spine manipulation (including mobilization)	NSAIDs, Physical therapy, Cervical Collar	Primary outcome: pain (VAS, NPRS), function (NPQ), and AEs Follow up within 6 weeks
Yang et al. 2017[19] **Taiwan**	7 RCTs	Adults with neck pain with or without radicular pain of varying durations N=401	Intermittent Cervical Traction	Manual Therapy, exercise, physical therapy modalities (heat pack, infrared ultrasound, IFT, and TENS), sham ICT	Primary outcome : Pain (NRS, VAS,MPQ) Secondary outcomes: Function (NDI) and AEs Follow-up after completion of treatments and up to one year
Yao et al. 2017[20] **China**	19 RCTs	Neck pain with or without radicular pain including DJD/DDD of all durations N = 2,194 Excluded : patients with WAD, MFPS, spinal stenosis	Western and Chinese manipulation (Long's manipulation[manipulation and Chinese massage])	Control (self-exercise, waitlist/attention group and self-care book) and manipulation by sham findings	Primary outcome: Short-term pain (VAS, NPRS) Secondary outcomes: intermediate and long-term pain(VAS, NPRS), function(NDI, NPQ), safety

Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
					Length of follow up: Short-term: Up to 12 weeks Intermediate: 6 months Long-term: 1 year
Miake-Lye et al. 2016[10] **United States**	31 primary studies included on massage ; 6 SRs relevant to neck pain	Neck pain of varying durations	Massage	Comparators reported in two SRs : Standard care/no treatment, heat packs, exercises, acupuncture, sham laser, manual traction, mobilization and education	Primary outcome : pain Outcome measures: none specified
Southerst et al. 2016[15] **Canada and United States**	11 Primary studies included; 2 relevant RCTs on manual therapy	Adults or children with NAD Grades I-III or WAD Grades I-III N =542 (2 RCTs) Excluded patients with major structural pathology	Manual therapy (including SMT, mobilization, soft-tissue massage, assisted stretching, thermal packs, and advice) and manipulation plus exercise	HEA, exercises, medications, education, self-mobilization	Primary outcome: Pain (NRS) Secondary outcomes: disability (NDI), QoL (SF-36), satisfaction with care, global perceived effect and AEs Follow-up up to 52 weeks
Wong et al. 2016[16] **Canada**	8 primary studies included; 1 SR relevant to manual therapy	Adults or children with NAD Grades I-III or WAD Grades I-III	Osteopathic manipulative treatment (HVLA thrust, muscle energy and soft tissue techniques)	NSAID – intramuscular ketorolac tromethamine (30mg)	Primary outcome: pain (NRS)
Wong et al. 2016[9] **Canada and United States**	22 primary studies included; 14 RCTs relevant to manual therapy	Adults or children with NAD Grades I-III or WAD Grades I-III	Manual therapy (manipulation, mobilization, traction and soft tissue therapy)	Other interventions, waiting list, placebo, sham intervention or no treatment	Primary outcomes: *"self-rated or functional recovery, clinical outcomes (eg, pain, disability), psychological symptoms, administrative outcomes, or adverse events."*(p.1601)[9]

Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
					Outcome measures: Pain –NPRS, NPQ,NRS, VAS Function/disability - NDI Follow-up interval varied from post-treatment to up to 52 weeks
Gross et al.2015[5] **Canada, United States and Netherlands**	51 primary studies included; 45 RCTs ; 5 quasi-RCTs and 1 cross-over RCT 26 new trials added to previous update	Adults (≥ 18 years of age) with neck pain Including : neck pain with or without radicular findings, cervicogenic headache, myofascial pain syndrome N = 2,920	Manipulation and mobilization (cervical and thoracic)	Inactive control (placebo, sham or other active treatment), adjunct treatment (mobilization plus another active treatment), wait list, active treatments (e.g., exercise), different treatment techniques (e.g. rotary versus lateral break SMT) and different dosages	Primary outcome: Pain(VAS, NPRS) and disability (NDI,NPQ) Secondary outcome: GPE, patient satisfaction and QoL (SF-36, SF 12) Length of follow-up: Immediate: within 1 day Short-term: closest to 4 weeks Intermediate: up to 6 months Long-term: closest to 12 months
Wei et al. 2015[17] **China**	8 primary studies included; 4 SRs relevant to manual therapy	Neck pain due to cervical radiculopathy	Manipulation, mobilization, and massage	Cervical computer traction, acupuncture, medication, TCM	Primary outcomes: Pain (VAS, MPQ), adverse events
Cheng and Huang 2014[11] **China**	15 RCTs	Neck pain N= 1,062 Excluded: neck pain due to fractures, tumours, infections etc.	Massage (including Chinese traditional, Western, manual pressure release, strain/counterstrain technique, and myofascial band therapy)	Inactive therapies (standard care and sham therapies) and active therapies (including acupuncture, traction, physical therapy, exercise, bone setting, TCM, joint mobilization, and activator trigger point therapy)	Primary outcome: Pain (VAS, NPQ), neck-related dysfunction(NDI), AEs Length of follow-up: Immediate-term within one day Short-term: up to 3 months Intermediate-term: 3 to 12 months Long-term: greater than 1 year

Author, Publication Year, Country	Types and Numbers of Primary Studies Included	Population Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes, Length of Follow-up
Young et al. 2014[21] **United States**	14 primary studies included; 10 RCTs, 1 quasi-RCT, 1 prospective cohort; 1 case series; 1 secondary analysis of a RCT	Adults 18 to 60 years old with mechanical neck pain of varying duration Excluded whiplash, radiculopathy	Thoracic manipulation and mobilization	Exercises, physical therapy modalities, no intervention, placebo manipulation	Primary Outcomes: Pain (NPRS, NPQ, VAS, FPS) Disability (NDI), perceived recovery (GROC) Follow-up intervals ranged from post treatment to more than 12 months

AEs = adverse events; DJD/DDD = Degenerative joint disease/ degenerative disc disease; FPS = functional pain scale; GROC = global rating of change; GPE = global perceived effort; HEA = home exercise and advice; HVLA = high velocity low amplitude; ICT = intermittent cervical traction; IFT = interferential current treatment; MFPS = myofascial pain syndrome; MPQ = McGill Pain Questionnaire; NAD = neck pain and associated disorders; NDI = Neck Disability Index; NPQ = Northwick Park Pain Questionnaire; NRS/NPRS = Numerical rating scale/ numerical pain rating scale; NSAIDs = nonsteroidal anti-inflammatory drugs; QoL = quality of life; RCT = randomized controlled trial; SF-36 = 36-Item Short Form Health Survey; SRs= systematic reviews; TCM = traditional Chinese medicine; TENS = transcutaneous electrical nerve stimulation; WAD= whiplash associated disorder; VAS = visual analog scale

Table A2: Characteristics of Included Guidelines

Objectives			Methodology			
Target Population, Intended Users	Intervention and Practice Consideration	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Bussières et al.2016[23]						
Target population: Adults and elderly patients with recent onset or persistent NAD and WAD Grades I-III **Intended users:** Chiropractors, health care providers and policymakers	Exercise, multimodal care, education, work disability, manual therapy, and passive modalities	Pain and disability	Five published systematic reviews and updated searches of Medline and Cochrane Central in December 2015	Evidence evaluated using SIGN criteria	Recommendations developed using GRADE approach and consensus achieved using Modified Delphi technique	10 member external committee including stakeholders, end-users, and researchers
Côté et al. 2016[3]						
Target population: *"NAD grades I-III (including WAD)*	*"Non-invasive interventions included acupuncture,*	*"self-rated recovery, functional recovery,*	Evidence from eight published systematic	Evidence evaluated using SIGN criteria	Expert consensus based on evidence from systematic reviews	Stakeholders and public consultation; unclear if

Objectives			Methodology			
Target Population, Intended Users	Intervention and Practice Consideration	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
of less than 6 months duration"(p.2002) **Intended users:** *"clinicians (medical doctors, physiotherapists, nurse practitioners, chiropractors, kinesiologists, psychologists, and massage therapists) caring for patients with neck pain in primary, secondary, and tertiary health care settings"(p.2002)*	*exercise, manual therapy, passive physical modalities, psychological interventions, soft tissue therapy, structured patient education, multimodal care, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and muscle relaxants"* (p.2003)	*disability, pain intensity, health-related quality of life, psychological outcomes, or adverse events."(p.2003)*	reviews and qualitative research through experiences of persons treated for injuries from traffic collisions			stakeholders were internal or external

GRADE = Grading of Recommendations Assessment, Development and Evaluation; NAD = neck pain and associated disorders; NSAIDs = nonsteroidal anti-inflammatory drugs; SIGN = Scottish Intercollegiate Guidelines Network; WAD = whiplash-associated disorder.

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR[13]

Strengths	Limitations
Fredin and Lorås 2017[22]	
• Comprehensive literature search performed, including database searches and review of references • Keywords used in search strategy provided • Study selection by two independent reviewers • Data extraction by one reviewer, verified by second • List of included and excluded studies provided • Several key characteristics of included studies provided (e.g., age, sex, and disease duration) • Scientific quality of included studies assessed using PEDro scale and used appropriately when formulating conclusions • Review authors declared no conflict of interest and no source of funding	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • No formal grey literature search conducted, limited to review of references • Restriction by language (English only) • Consensus procedure for discrepancies in study selection and data extraction not specified • Heterogeneity assessed using I^2 statistic, but not for all comparisons • No assessment of publication bias • Conflict of interest and funding not reported for the included studies
Shekelle et al. 2017[18]	
• Systematic review registered on PROSPERO • Comprehensive literature search performed updating previously published systematic reviews • MeSH terms and keywords used in search strategy provided • No date or language restrictions in search strategy • List of included studies provided • Study selection and data extraction performed by two independent reviewers, disagreements resolved through discussion • Scientific quality of included studied assessed using Cochrane Back Group Risk of Bias tool and conclusions formulated adequately using GRADE approach • Review authors declared no conflict of interest and reported funding source	• No formal grey literature search conducted • List of excluded articles not provided • Several key characteristics of included studies not provided (e.g., age, race, sex, disease severity, disease duration, socioeconomic status, comorbidities) • No assessment of publication bias • Conflict of interest and funding not reported for the included studies
Yang et al. 2017[19]	
• Comprehensive literature search performed, including database searches and review of references • MeSH terms and keywords used in search strategy provided • No language restriction in search strategy • Study selection and data extraction performed by two independent reviewers, disagreements resolved through a third reviewer • List of included studies provided • Several key characteristics of included studies provided (e.g., age, disease severity, and disease duration) • Scientific quality of included studied assessed using Cochrane Collaboration risk of bias tool and used	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • No formal grey literature search conducted, limited to review of references • List of excluded articles not provided • Breakdown of patients by sex not provided for included studies • In all the included studies, patients in ICT or placebo group received exercises or manipulation • Meta-analyses pooled results from heterogeneous patients (neck pain with or without radicular pain) and varying

Strengths	Limitations
appropriately when formulating conclusions • Heterogeneity assessed using I^2 statistic for all comparisons • Review authors declared no conflict of interest and reported funding source	comparators (exercise, manual therapy and physical therapy modalities, sham ICT) which may not be clinically appropriate • No assessment of publication bias • Conflict of interest and funding not reported for the included studies
Yao et al. 2017[20]	
• Comprehensive literature search performed, including database searches and grey literature sources • No language restriction in search strategy • Keywords used in search strategy provided • Study selection and data extraction performed by two independent reviewers, disagreements resolved through a third reviewer • List of included studies provided • Several key characteristics of included studies provided (e.g., age, disease duration, interventions and outcomes) • Scientific quality of included studied assessed using Cochrane Back Group risk of bias tool and overall quality of evidence evaluated using GRADE approach • Scientific quality used appropriately when formulating conclusions • Heterogeneity assessed using Cochrane's χ^2 statistic • Review authors declare no conflict of interest	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • List of excluded studies not provided • Several key characteristics of included studies not provided (e.g., sex, disease severity, race, socioeconomic status) • Patients receiving manipulation also received other treatments (exercise, acupuncture, electro/thermal therapy and LLLT) • Meta-analyses pooled results from heterogeneous patients (neck pain with or without radicular pain) receiving multiple interventions, which may not be clinically appropriate • Publication bias assessed only with graphical aid and no statistical tests • Funding for the review not declared • Conflict of interest and funding not reported for the included studies
Miake-Lye et al. 2016[10]	
• Comprehensive literature search performed on electronic databases • MeSH terms and keywords used in search strategy provided • Study selection by two independent reviewers, discrepancies resolved by third reviewer • Data extraction by one reviewer, verified by second reviewer • Several characteristics of included SRs provided (e.g. description of massage, type of provider, duration, type of pain and main findings) • Scientific quality of included studied assessed using AMSTAR and GRADE approach used to assess the overall quality of evidence • Scientific quality used appropriately when formulating conclusions • Authors declared no conflict of interest and declared source of funding	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • Restriction by language (English only) • No formal grey literature search conducted • List of excluded articles not provided • Several key characteristics of included studies not provided (e.g., age, race, sex, disease severity, disease duration, socioeconomic status, comorbidities) • No assessment of publication bias • Conflict of interest and funding not reported for the included SRs
Southerst et al. 2016[15]	
• Protocol registered on PROSPERO prior to review • Comprehensive literature search of databases only • MeSH terms and keywords used in search strategy provided	• Restriction by language (English only) • Grey literature search not conducted, excluded unpublished manuscripts • List of excluded articles not provided

Strengths	Limitations
• Study selection by two independent reviewers, disagreements resolved by consensus or third reviewer if consensus not reached • Data extraction by lead author, verified by second reviewer • Scientific quality of included studies assessed using SIGN criteria and used appropriately when formulating conclusions • Several key characteristics of included studies provided (e.g., disease duration, interventions and outcomes) • Clinical appropriates of combining studies was taken into consideration • Authors declared conflicts of interest and declared source of funding	• Some key characteristics of included studies not provided (e.g., mean age, sex, race, socioeconomic status and comorbidities) • No assessment of publication bias • Conflict of interest and funding not reported for the included studies
Wong et al. 2016[16]	
• Protocol registered on PROSPERO prior to review • Comprehensive literature search of databases only • MeSH terms and keywords used in search strategy provided • Study selection by two independent reviewers, disagreements resolved by consensus or third reviewer if consensus not reached • Data extraction by lead author, verified by second reviewer • Several key characteristics of included SRs provided (e.g., population, disease duration, intervention, comparator and effect size) • List of included studies provided • Scientific quality of included studies assessed using SIGN criteria and used appropriately when formulating conclusions • Clinical appropriates of combining studies was taken into considerationAuthors declared conflicts of interest and declared source of funding	• Restriction by language (English only) • Grey literature search not conducted, excluded unpublished manuscripts • List of excluded articles not provided • Conflict of interest and funding not reported for the included studies • Some key characteristics of included studies not provided (e.g., mean age, sex, race, socioeconomic status and comorbidities)Discrepancy noted between results presented in evidence table and summary of evidence with respect to RCT on manual therapy
Wong et al. 2016[9]	
• Protocol registered on PROSPERO prior to review • Comprehensive literature search of databases only • MeSH terms and keywords used in search strategy provided • Study selection by two independent reviewers, disagreements resolved by consensus or third reviewer if consensus not reached • Data extraction by lead author, verified by second reviewer • Scientific quality of included studies assessed using SIGN criteria and used appropriately when formulating conclusions • List of included studies provided • Several key characteristics of included studies provided (e.g., disease severity and duration, interventions, outcomes and follow-up intervals) • Authors declared conflicts of interest and declared source of funding	• Restriction by language (English only) • Grey literature search not conducted, excluded unpublished manuscripts • List of excluded articles not provided • Some key characteristics of included studies not provided (e.g., mean age, sex, race, socioeconomic status and comorbidities) • No assessment of publication bias • Conflict of interest and funding not reported for the included studies

Strengths	Limitations
Gross et al. 2015[5]	
• Utilized 2002 protocol for update of previously published SR; deviations from protocol are reported • Study selection by two independent reviewers, disagreements resolved third reviewer • Comprehensive literature search performed, including database searches, grey literature sources and review of references • No language restriction in search strategy • MeSH terms and keywords used in search strategy provided • List of included and excluded studies provided • Scientific quality of included studies assessed using pre piloted forms and used appropriately when formulating conclusions • Authors declared conflict of interest and source of funding	• Included RCTs, quasi-RCTs and cross-over RCTs • Several key characteristics of included studies not provided (e.g., age, sex, race socioeconomic status and comorbidities) • Heterogeneity assessed using I^2, Tau^2,and Chi^2 statistic, but not for all comparisons • Publication bias assessed only with graphical aid and no statistical tests • Conflict of interest and funding not reported for the included studies
Wei et al. 2015[17]	
• Comprehensive literature search performed of electronic databases • No language restriction in search strategy • MeSH terms and keywords used in search strategy provided • Study selection and data extraction by two independent reviewers, disagreements resolved through by third reviewer • List of included SRs provided • Several key characteristics of included SRs provided (e.g., number of included studies, interventions, outcomes, conclusion) • Scientific quality of included studies assessed using R-AMSTAR and used appropriately when formulating conclusions • Authors declared no conflict of interest and sources of funding	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • No formal search of grey literature, hand searching of limited number of journals from China • Conflict of interest and funding not reported for the included SRs • List of excluded SRs not provided
Cheng and Huang 2014[11]	
• Comprehensive literature search performed of electronic databases • MeSH terms and keywords used in search strategy provided • Data extraction performed by two independent reviewers, disagreements resolved by discussion • List of included and excluded studies provided • Scientific quality of included studies assessed using PEDro scale and used appropriately when formulating conclusions • Heterogeneity assessed using I^2, Tau^2,and Chi^2 statistics • Authors declared no conflict of interest	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • No formal search of grey literature sources, limited to hand searching • Restriction by language Not specified whether study selection was performed by two independent reviewers • Several key characteristics of included studies not provided (e.g., sex, disease severity, race, socioeconomic status, and comorbidities) • No assessment of publication bias • Authors of the SR did not report source of funding • Conflict of interest and funding not reported for the included SRs

Strengths	Limitations
Young et al. 2014[21]	
• Comprehensive literature search performed of electronic databases • List of included studies provided • Keywords used in literature search provided • Scientific quality of included studies assessed using PEDro scale and used appropriately when formulating conclusions	• No reference to a protocol, ethics approval, or predetermined research objectives to indicate that the research question and inclusion criteria were established *a priori* • No formal search of grey literature sources • Restriction by language (English only) • Included quasi-RCTs, prospective cohorts, and case-series in the body evidence • Unclear if study selection and data extraction performed by two independent reviewers; procedure not specified • List of excluded studies not provided • Several key characteristics of included studies not provided (e.g., age, sex, disease severity and duration, race, socioeconomic status, and comorbidities) • Only P values reported in the SR, mean differences and confidence intervals not reported • No assessment of publication bias • Conflict of interest and source of funding not provided for SR or included studies

AMSTAR = A Measurement Tool to Assess Systematic Reviews; GRADE = Grading of Recommendations Assessment, Development and Evaluation; ICT = intermittent cervical tranction; LLT =low-level laser therapy; MeSH = medical subject heading; PEDro = physiotherapy evidence database; RCT = randomized controlled trial; SR/SRs = systematic reviews/systematic reviews; SIGN = Scottish Intercollegiate Guidelines Network

Table A4: Strengths and Limitations of Guidelines using AGREE II[14]

Item	Guideline	
	Bussières et al. 2016[23]	Côté et al.2016[3]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	✓	✓
6. The target users of the guideline are clearly defined.	✓	✓
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	✓	✓
8. The criteria for selecting the evidence are clearly described.	✓	✓

Item	Guideline	
	Bussières et al. 2016[23]	Côté et al.2016[3]
9. The strengths and limitations of the body of evidence are clearly described.	✓	✓
10. The methods for formulating the recommendations are clearly described.	✓	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	✓	✓
12. There is an explicit link between the recommendations and the supporting evidence.	✓	✓
13. The guideline has been externally reviewed by experts prior to its publication.	✓	x
14. A procedure for updating the guideline is provided.	✓	✓
Domain 4: Clarity of presentation		
15. The recommendations provided are specific and unambiguous.	✓	✓
16. The different options for management of the condition of health issue are clearly presented.	✓	✓
17. Key recommendations are easily identifiable.	✓	✓
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	x	x
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	✓	x
20. The potential resource implications of applying the recommendations have been considered.	x	x
21. The guideline presents monitoring and/or auditing criteria.	x	x
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	✓	✓
23. Competing interests of guideline development group members have been recorded and addressed.	✓	✓

✓ = yes; x = no or unclear

Appendix 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Fredin and Lorås 2017[22]	
<u>Combined Exercise + Manual therapy versus Exercise</u> Pain (VAS or NRS on a scale of 0 to 10) • No statistically significant differences found between groups at immediate post treatment (SMD -0.15; 95% CI, -0.30 to 0.00) , 6 months (SMD -0.05; 95% CI, -0.35 to 0.24) and 12 months (SMD 0.15; 95% CI, -0.17 to 0.46) Disability (NDI or NPQ on a scale of 0 to 100;) • No statistically significant differences found between groups immediate post-treatment (SMD 0.02; 95% CI, -0.26 to 0.30),6 months (SMD 0.01; 95% CI, -0.19 to 0.21), and 12 months (SMD -0.09; 95% CI, -0.41 to 0.22) QoL (physical component; SF 36 or SF 12 on a scale of 0 to 100) • No statistically significant differences were found between groups immediate post-treatment (SMD 0.14; 95% CI -0.20 to 0.48), 6 months (SMD 0.06; 95% CI, -0.14 to 0.26) and 12 months (SMD 0.17, 95% CI, -0.15 to 0.49) QoL (mental component; SF 36 or SF 12 on a scale of 0 to 100) • No statistically significant differences were found between groups immediate post-treatment (SMD 0.22; 95% CI -0.04 to 0.47), 6 months (SMD 0.05; 95% CI, -0.15 to 0.25) and 12 months (SMD 0.05, 95% CI, -0.27 to 0.37) AEs: Five of the included studies reported no serious adverse events occurred; mild AEs included muscle and joint soreness, headache, back pain, nausea, dizziness and upper extremity symptoms.	*"Based on the studies included in this review, it is concluded that combined treatment consisting of MT and ET does not seem to be more effective (moderate-to-low level of evidence), than ET alone in reducing neck pain at rest, neck disability, quality of life for adult patients with grade I and II neck pain"*(p.69)[22]
Shekelle et al. 2017[18]	

• No pooling of data was performed
• Five RCTs on SMT (including mobilization) for acute neck pain
  ○ SMT + NSAID **(**azapropazone) compared to NSAID alone in 1 RCT (n=52); 68% of patients in SMT+ NSAID group reported reduction in pain post-treatment, effect not statistically significant at one or three weeks
  ○ 1 RCT (n=30) compared mobilization + neck collar, TNS + neck collar and neck collar alone; at 1 week follow-up no significant differences between the three groups
  ○ 1 RCT (n=36) randomized patients to receive SMT ipsilateral to side of neck pain, contralateral to side of pain and placebo ultrasound; statistically significant improvement in VAS scores in group receiving ipsilateral SMT
	"We rated the evidence as low that SMT improves outcomes in patients with acute neck pain due to study quality concerns and imprecision of results (too few studies)."(p.6)[18]

Main Study Findings	Author's Conclusion
○ 1 RCT (n=45) patients allocated to physical therapy (TENS, superficial thermotherapy & STT) with or without thoracic spine manipulation; group receiving manipulation demonstrated statistically significant difference in NPRS and NPQ scores measured four weeks after baseline ○ 1 RCT (n=45) patients allocated to physical therapy (electro/thermal therapy) with or without thoracic spine manipulation; manipulation group reported statistically significant difference in VAS scores (at end of last treatment, two week, and four week follow-up) and NPQ (end of last treatment and two week follow-up) ○ No included RCT reported adverse events	
Yang et al. 2017[19]	
ICT vs. placebo group (exercise, manual therapy and physical therapy modalities, sham ICT) • Statistically significant reduction in pain scores after completion of treatments (SMD -0.26; 95% CI, -0.46 to -0.07; I^2 = 58%; 7 RCTs, n= 401), but not at final follow-up (SMD -0.57; 95% CI, -1.46 to 0.32; I^2 = 83%; 3 RCTs, n = 189) • No statistically significant reduction in NDI scores after completion of treatments (SMD -0.10; 95% CI, 95% -0.33 to 0.13; I^2=0%; 4 RCTs, n =298) or final follow-up (SMD -0.26; 95% CI, -1.08 to 0.55; I^2 = 76%; 2RCTs, n = 163) • Four RCTs reported adverse events; mild increase in pain most commonly reported; no serious adverse events (e.g., neurological deficit) reported	*" ICT was beneficial in reducing pain scores immediately after treatment; however, this effect had diminished by the final follow-up. In addition, ICT let to no functional improvement in the daily life of patients immediately after treatment or at the final follow-up."*(p.963)[19]
Yao et al. 2017[20]	
Pain Short-term pain: • SMT group had statistically significant reduction in VAS score(MD -1.14; 95% CI, -2.12 to -0.16; 7 RCTs, n=554) • SMT group had no statistical reduction in NPRS score (MD -0.30, 95% CI, -0.80 to 0.20; 10 RCTs, n= 1,502) Intermediate-term pain: • No statistical difference in VAS score (MD 0.26; 95% CI, -0.54 to 1.06; 2 RCTs, n=149) • SMT group had statistically significant reduction in NPRS score(MD -0.29; 95% CI, -0.53 to -0.05; 6 RCTs, n=916) Long-term pain: • No statistical difference in VAS score (MD -0.68; 95% CI, -1.63 to 0.27; 1 RCT, n=88) or NPRS score (MD =0.08; 95% CI, -0.24 to 0.40; 5 RCTs, n=670) Function Short-term function: • Statistically significant reduction in NDI score (MD -2.10; 95% CI, -2.98 to -1.21; 8 RCTs, n=1,145) Intermediate-term function: • Statistically significant reduction in NDI score (MD -1.45; 95% CI, -2.55 to -0.35; 7 RCTs, n=987)	*"The results do not support the existing evidences for the clinical value of Eastern or Western manipulative therapy for neck pain for short-term follow-up to MCIDS."*(p.543)[20]

Main Study Findings	Author's Conclusion
Long-term function: • No difference in NDI scores (MD -0.95; 95% CI, -2.42 to 0.51; 5 RCTs, n=758) Adverse Events • Ten RCTs included AEs as an outcome measure • Four out of ten RCTs reported no serious AEs occurred; six reported AEs occurred • One patient in the SMT group was withdrawn from the RCT due to an unspecified serious adverse event • Other reported AEs including headache, fatigue, nausea and dizziness	
Miake-Lye et al. 2016[10]	
6 SRs included on neck pain; 3 exclusively on neck pain and 3 which also included low back, headache or shoulder pain • For chronic neck pain, one SR reported a benefit on pain in comparison with inactive therapies but there is limited evidence for effectiveness over TCM • In one SR on acute and chronic neck and shoulder, statistically significant immediate effect reported for neck pain (SMD 1.79; 95% CI, 1.01 to 2.57) • In comparison to placebo, one SR reported reduction in pain intensity post treatment in patients with acute/subacute or unknown duration of nonspecific neck pain • Three SRs reported that effects of massage on neck pain are unclear	*"Findings from high-quality systematic reviews describe potential benefits of massage for pain indications including labor, shoulder, neck, back, cancer, fibromyalgia, and temporomandibular disorder."*(p.20)[10] *"These reviews all described the need for more research before any conclusions could be drawn for topics including tendinitis, labor, neck pain, headache, and other musculoskeletal conditions."*(p.16)[10]
Southerst et al. 2016[15]	

• Clinical appropriateness assessed and no pooling of data was performed
• 2 RCTs on manual therapy and exercise
• First RCT (n=272) compared HEA, SMT and medication
  ○ No statistically significant differences between HEA and SMT for pain (NRS), disability (NDI) and physical or mental quality of life(SF-36) at 12 week follow-up; satisfaction score statistically significant at 12 week follow-up
  ○ Forty percent of the SMT group and 46% in the HEA group reported nonserious AEs
• Second RCT (n=270), compared ET, ET+SMT and HEA
  ○ ET+SMT in comparison to HEA had statistically significant differences in pain, disability, global perceived effect and 12 weeks but not at 52 weeks; satisfaction scores statistically significant at 12 and 52 weeks
  ○ ET + SMT in comparison to ET had a statistically significant effect on disability and physical component of SF-36 at 12 week follow-up; no statistically significant differences reported for any outcome at 52 weeks
  ○ 98.9% of ET+SMT , 96.6% of ET group and 33.3% of HEA groups reported non-serious AEs
	"Our review suggests that patients with recent neck pain Grade I/II have similar outcomes whether they are managed with home exercises, multi-modal manual therapy, or medication (ie, NSAIDs or acetaminophen)."(p.1520)[15]

Main Study Findings	Author's Conclusion
Wong et al. 2016[16]	

• Clinical appropriateness assessed and no pooling of data was performed
• One included SR included 1 RCT on osteopathic manipulative treatment (HVLA thrust, MET, STT) in comparison to NSAIDs (30 mg intramuscular ketorolac tromethamine)
  ○ MD of 1.1(95 % CI, 0.2 to 1.9) on 10-point NRS favoured manual therapy
  ○ One patient in the OMT group reported AE in comparison to eight in NSAIDs group
 	
Note: Discrepancy noted between results presented in evidence table and summary of evidence with respect to the RCT on manual therapy. The results presented here are based on data from the evidence table.
	With regards to pain reduction, one RCT demonstrated that osteopathic manipulative treatment including a HVLA thrust and soft tissue technique has a statistically significant but clinically non-significant effect in comparison to intramuscular ketorolac tromethamine. A greater percentage of patients in the NSAID group reported adverse events.

Wong et al.2016[9]	

14 RCTs on manual therapy interventions classified as exploratory or evaluation studies; no pooling of data performed
<u>Exploratory Studies</u>
NAD Grades I-II of variable duration
• 1 RCT (n= 31) found no difference in pain intensity (Neck Pain Disability Scale) or self-perceived recovery between one session of strain-counterstrain and sham counterstrain
Recent-onset NAD Grades I-II
• 2 RCTs found evidence supporting thoracic spine manipulation
  ○ Thoracic manipulation vs. cervical mobilization and home exercise in 1 RCT (n= 66)
  ▪ SMT group had statistically significant between group difference (experimental minus comparison) on NRS (1.5; 95% CI, 1.06 to 1.94), NDI (8.8; 95% CI, 6.21 to 11.39) , and GROC (2.0; 95% CI, 1.0 to 3.0)
  ○ Thoracic spine thrust compared to non-thrust mobilization/manipulation in 1 RCT (n=60)
  ▪ Statistically significant mean differences between groups with respect to disability (NDI 10.03% on 0 to 100%; 95% CI, 5.3 to 14.7), pain (2.03% on 10-point NPRS; 95% CI, 1.4 to 2.7) and GROC(1.5 on scale from -7 to 7; 95% CI, 0.48 to 2.5); clinically significant effect on pain (>2/10 on NPRS) and disability(>10% on NDI); no serious AEs reported
Persistent NAD grades I-II
• 2 RCTs concluded that type of mobilization did not impact outcomes
  ○ First RCT (n=60); no difference in pain (VAS) or GPE between patients receiving one session of non-targeted mobilization of the cervical spine; no AEs reported
	"mobilization, manipulation, and clinical massage are effective interventions for the management of neck pain. It also suggests that electroacupuncture, strain-counterstrain, relaxation massage, and other passive physical modalities (heat, cold, diathermy, hydrotherapy, and ultrasound) are not effective and should not be used to manage neck pain."(p.1623)[9]

Main Study Findings	Author's Conclusion
○ Second RCT (n=60); statistically significant reduction in pain (VAS) in most painful movement in patients receiving central posterior-anterior cervical mobilization in comparison to randomly directed mobilization (9.2; 95% CI, 0.3 to 18.0) but not for global perceived recovery; no AEs reported • Efficacy of spinal manipulation is unclear from 2 RCTs ○ First RCT (n=80); no difference in pain (NPRS) or disability (NDI) in patients receiving cervical and cervico-thoracic SMT in comparison to kinesiotape; no serious adverse events reported; 7.5% of SMT group experienced minor increase in neck pain or fatigue ○ Second RCT (n=108); no statistically significant differences in VAS scores between patients receiving thoracic SMT in comparison to placebo thoracic SMT <u>Evaluation studies</u> Recent-onset NAD grades I-II • Cervical manipulation vs. mobilization; 1RCT (n=182); no statistically significant differences between groups with regards to pain(NRS), disability (NDI), time to recovery, health-related QoL(SF-12), GPE, and incidence of AEs; no serious neurovascular event reported; most common minor adverse events were increased neck pain (29.4%) and headache (22.0%) • Integrated neuromuscular inhibition technique (INIT) was compared to muscle energy technique (MET) in 1 RCT (n=60); statistically significant differences were reported with respect to pain (10cm VAS) and disability (NDI 0-50); ○ Mean difference at 2 weeks (INIT minus MET): pain (0.73; 95% CI, 0.52 to 0.93) and disability (4.72; 95% CI, 2.76 to 6.68) ○ Mean difference at 4 weeks (INIT minus MET): pain (0.98; 95% CI, 0.78 to 1.18) and disability(4.75; 95% CI, 2.82 to 6.68) Persistent NAD grades I-II • 1 RCT (n=270); no statistically significant differences in patients receiving SMT with or without exercise; with respect to pain (NRS), disability (NDI), satisfaction, quality of life (SF-36), global perceived effect, and medication use at 12 and 52 weeks; transient mild non-serious adverse events reported in 98.9% of patients in ET +SMT group • *Long's manipulation + Chinese massage vs. Chinese massage (1RCT; n=63); statistical significant difference between groups immediately post-treatment for pain and disability in patients with persistent ; no serious adverse events reported; 1 patient (3%) in Chinese massage group experienced increased pain • **1 RCT (n=64) compared massage (including Swedish and clinical massage and advice) to a self-care book; statistically significant effect favouring massage on symptom bothersomeness (MD 1.6 on 0-10 NRS; 95% CI, 0.7 to 2.5) and disability (0-50 NDI MD 2.1; 95% CI, 0.03 to 4.0) in the short-term (4 weeks) but not at 10 or 26 weeks; neck functional disability (Copenhagen Neck Functional	

Main Study Findings	Author's Conclusion
Disability Scale 0 - 30) and QoL(SF-36) were not statistically significant at any interval; medication use in self-care group increased by 14% from baseline; no serious adverse events reported; 9 patients reported mild adverse events from massage • 1 RCT (n=61); compared cupping massage (CM) to progressive muscle relaxation; statistically significant difference in disability (-2.18 on 0-50 NDI; 95% CI, -4.56 to -0.21) and pain pressure threshold at site of maximum pain (63.55 kPa/s ; 95% CI, 6.33 to 121.56) in favour of CM; no statistically significant differences with respect to pain(VAS), days of interference, interference in daily life, depression (HADS), and QoL; three patients reported adverse events in CM group (muscular tension and pain; pain in shoulder area and prolapsed intervertebral disc [serious but not related to the intervention]) • In 1 RCT (n=81), no statistically significant differences were reported for pain(NPRS), disability (NDI), patient satisfaction and GROC when manual therapy interventions were combined with or without cervical traction Adverse events • Manipulation, mobilization or traction – rate varied from 0% to 30%; majority were mild to moderate and transient; no serious neurovascular events reported • Soft tissue therapy – most AEs were mild and transient, one patient in cupping group suffered a prolapsed disc Note: * Long's manipulation + TCM massage demonstrated statistically significant effects on pain and disability; summary of evidence reports statistically significant effect on pain but not on disability ** Evidence table demonstrates symptom bothersomeness not statistically significant in the long-term, contradictory to statement in the summary of evidence	
Gross et al. 2015[5]	
<u>Cervical Spine Manipulation</u> *Manipulation vs. inactive control* • 3 RCTs on single session of manipulation; 1 RCT reported immediate pain relief; 2 RCTs reported no short-term benefit on chronic neck pain with radicular pain or headaches and patients with subacute or chronic neck disorders with associated cervical spondylosis • 2 RCTs reported conflicting evidence on the effectiveness of multiple sessions of SMT for subacute and chronic neck pain *Manipulation vs. oral medication* • Pain : 3 RCTs compared SMT with medications ○ 1 RCT; cervical SMT more effective than oral medication (NSAIDs, acetaminophen, opioids, and muscle relaxants) immediate post treatment (SMD -0.34; 95%CI, -0.64 to -0.05)	*"For individuals with acute/subacute neck pain, thoracic manipulation provided short-term neck pain relief, and for those with acute and chronic neck pain, it further improved function when contrasted with an inactive control." (p.34)*[5] *"For acute/ subacute neck pain, multiple sessions of cervical manipulation provided better pain relief and functional improvement than were attained with certain oral medications such as varied combinations of NSAIDs, analgesics, opioids and muscle relaxants at immediate-, intermediate- and long-term follow-up."(p.34)*[5] *"For individuals with acute and chronic neck pain, cervical manipulation versus mobilisation produced similar results in neck pain reduction, functional improvement, quality of life and global perceived effect at immediate-, short and intermediate-term follow-up. A similar pattern was observed*

Main Study Findings	Author's Conclusion
and long-term follow-up (SMD -0.32; 95% CI, -0.61 to -0.02), but not at intermediate-term follow-up(SMD -0.21; 95% CI -0.5 to 0.08) ○ 2 RCTs on chronic neck pain found no statistically significant differences between groups at immediate post treatment (first RCT; Tenoxicam with ranitidine) and long-term follow-up (second RCT; celaconxin, rofecoxib or paracetamol) • Function and Disability : ○ For patients with acute and subacute neck pain; 1 RCT demonstrated manipulation may have benefit in the short and intermediate-term (SMD -0.30; 95% CI -0.59 to 0.00), but not long-term follow-up (SMD -0.11; 95% CI, -0.40 to 0.18) in comparison to NSAIDs, acetaminophen, opioids, and muscle relaxants ○ 2 RCTs found no difference between oral medication and SMT post treatment (first RCT; Tenoxicam with ranitidine) and in the long term (second RCT; Celaconxin, rofecoxib or paracetamol) • Global perceived effect(GPE) and patient satisfaction : 1 RCT reported SMT may be superior to oral medications (NSAIDs, acetaminophen, opioids, and muscle relaxants) for GPE and patient satisfaction at the long-term follow-up • QoL : No significant differences between manipulation and oral medication (NSAIDs, acetaminophen, opioids, and muscle relaxants) groups at immediate-, intermediate-, and long-term follow-up *Cervical Manipulation vs. mobilization and other manual techniques* • Pain: ○ 2 RCTs on the effectiveness of a single session of SMT; one RCT reported immediate pain relief in comparison to MET and the other reported no significant difference with Activator instrument ○ Multiple sessions of SMT was found to be no more effective than mobilization ○ SMT was found to be more effective than massage in the short-term and intermediate-term follow-up ○ Cervical SMT more effective than thoracic manipulation and combined thoracic and sacroiliac manipulation in the short-term ○ No difference when comparing different number of sessions, different types of SMT or when comparing with instrument assisted SMT (Activator) • Function and disability: ○ SMT no more effective than mobilization at short-term and intermediate-term follow-up;	*when thoracic mobilisations were contrasted with thoracic manipulation techniques in chronic neck pain. (p.34)*[5]

Main Study Findings	Author's Conclusion
○ SMT more effective than massage and thoracic manipulation in the short-term and intermediate term ○ Twelve SMT sessions in comparison to three provides immediate functional improvement in patients with chronic CGH ○ SMT no more effective than activator SMT at any follow-up for patients with subacute and chronic neck pain • Global perceived effect: 2 RCTs showed no differences between SMT and or SMT and activator for GPE at any follow-up interval • Patient satisfaction: No differences between SMT and mobilization for patients with subacute and chronic neck pain • QoL: 2 RCTs demonstrated no significant differences between SMT and mobilization for subacute and chronic or SMT and activator for subacute neck pain *Manipulation vs. exercise or other physical therapy modalities* • Pain: ○ 1 RCT showed no difference in pain relief between a session of SMT vs. one single use kinesiotape application in patients with subacute or chronic neck pain ○ 5 RCTs assessed multiple sessions of SMT; ▪ SMT no more effective than exercise at any follow-up interval ▪ No more effective than low-level laser for subacute and chronic neck pain; but effective when paired with low-level laser ▪ No difference between low-voltage electrical acupuncture in immediate-term or acupuncture in the long-term ▪ SMT more effective than TENS for cervicogenic headache in the short-term • Function and disability: ○ 1 RCT ; single application of kinesiotape improved function (SMD 0.46; 95 % CI 0.01 to 0.92) post treatment in comparison to SMT ○ No differences found over exercise at any follow-up; low-voltage electrical acupuncture post treatment or acupuncture in the long-term ○ Combination of SMT and low-level laser more effective in the short-term • GPE: 1 RCT reported no differences between SMT and HEA at long-term follow-up • Patient satisfaction:1 RCT reported SMT superior to home exercise for patients with acute or subacute neck pain at the long-term follow-up • QoL: No difference between SMT and home exercise at intermediate- and long-term follow-up	

Main Study Findings	Author's Conclusion

Thoracic Spine Manipulation
Thoracic spine manipulation vs. inactive control
• Pain:
  ○ 1 RCT reported decreased pain in comparison to placebo SMT in patients with chronic neck pain; 2 RCTs reported no differences in comparison to inactive control and the same treatment in both arms
  ○ 7 RCTs assessed multiple sessions of thoracic SMT
  ▪ Immediate follow-up: 2 RCTs found positive effect on acute pain (SMT -3.45; 95% CI, -4.13 to -2.79); 2 RCTs found no effect on chronic pain (SMT -0.23; 95% CI -1.15 to 0.69, I^2=81%)
  ▪ Short-term follow-up: For acute and subacute neck pain , statistically significant effect (SMD -1.46; 95% CI -2.20 to -0.71; I^2 = 84%); similar effects on chronic neck pain
  ▪ Intermediate follow-up: 1 RCT reported benefits in favor of SMT group
• Function and disability:
  ○ 1 RCT reported single session of thoracic SMT significantly effects function in patients with chronic neck pain
  ○ 4 RCTs were concerned with multiple sessions of SMT
  ▪ Immediate follow-up: 2 RCTs reported statistically significant effects for SMT on function/disability (SMD -0.52; 95% CI, -0.85 to -0.18) for chronic neck pain
  ▪ Short-term follow-up: 4 RCTs reported statistically significant effects on function for neck pain of all durations (SMD -1.40; 95% CI, -2.24 to -0.55)
  ▪ Intermediate follow-up: 1 RCT favoured SMT for chronic neck pain
• QoL : 1 RCT favoured SMT for chronic neck pain
 	
Thoracic manipulation vs. mobilization
• Pain: 1 RCT; single session of thoracic manipulation comparable to mobilization for chronic non-specific neck pain
 	
Thoracic manipulation vs. exercise
• Pain: 1 RCT reported no difference between 4 sessions of thoracic SMT and instructed exercise at long-term follow-up
 	
Mobilization of Cervical Spine
Cervical mobilization vs. inactive control	

Main Study Findings	Author's Conclusion
• Pain: 1 RCT reported no difference in pain when mobilization added to SMT in patients with chronic CGH or degenerative changes post treatment period; 1 RCT favoured inactive control group for patients with subacute /chronic WAD–II *Cervical mobilization vs. medical injection* • For patients with neck pain with MFPS, 1 RCT reported mobilization using PNF was more effective than intramuscular lidocaine (SMD -1.05; 95% CI, -1.96 to -0.15) for pain relief, but no significant differences between groups for function <u>Mobilization of cervical spine vs. mobilization and other manual therapies</u> • Pain: ○ 3 RCTs comparing a single session of one mobilization technique versus other mobilization techniques demonstrated no significant differences between groups for chronic neck pain ○ 7 RCTs compared multiple sessions of mobilization; ▪ Mobilization was found to be more effective than a massage regimen for chronic CGH in 1 RCT, but another found no difference when using effleurage, stroking and pétrissage for chronic neck pain ▪ AP unilateral pressure was found to be more effective in the immediate relief in comparison with rotation or transverse; ▪ Mobilization was found to be no more effective than Activator for subacute neck pain at all follow-up intervals ▪ manual therapy to TMJ to in patients with TMJ and cervicogenic headache more effective than manual therapy to cervical spine; ▪ 2 RCTs found no differences when mobilization versus manipulation as an adjunct to physical therapy modalities for subacute or chronic neck pain or MET for chronic neck pain • Function and disability: ○ 4 RCTs evaluated multiple sessions of mobilization vs. various manual therapies: ▪ 3 RCTs reported no differences in comparison to massage or Activator ▪ One RCT reported manual therapy to TMJ was more effective than to cervical spine post treatment and intermediate-term in patients with	

Main Study Findings	Author's Conclusion
TMJ and cervicogenic headache • Global perceived effect: ○ 2 RCTs; No significant differences in results when comparing different mobilization techniques in patients with chronic neck pain <u>Mobilization of cervical spine vs. exercise and other physical therapy modalities</u> • Pain: ○ No statistically significant differences were reported between one session of neural dynamic mobilization and pulsed ultrasound ○ 5 RCTs assessed the effects of multiple sessions of mobilization: ▪ No difference was found over acupuncture for subacute or chronic neck pain including WAD at long-term follow-up ▪ No difference over exercise for cervical radiculopathy in the immediate-term; ▪ No difference over TENS for chronic neck pain ▪ Possible benefit over extracorporeal shockwave therapy post treatment ▪ Chuna manual therapy more effective than cervical traction post treatment for disc herniation • Function and disability: ○ No significant effect on function when compared to acupuncture, exercise, TENS, and shock wave therapy • Patient satisfaction : One RCT found no significant difference on TENS utilization at intermediate-term follow-up in patients with chronic neck pain • QoL: 1 RCT found no difference versus TENS utilization at immediate- and intermediate-term follow-up in patients with chronic neck and another found no difference in comparison to acupuncture at intermediate-term Adverse events • AEs reported for manipulation and mobilization were benign and transient; they included neck pain, soreness, headache, stiffness, fatigue, dizziness, paresthesia etc. • No severe AEs were reported in any of the trials	
Wei et al. 2015[17]	
• SR included 4 SRs relevant to cervical radiculopathy ○ One SR concluded that massage and manipulation may be safe and effective ○ The second SR concluded manipulation and massage in conjunction or separate may be	*" In conclusion, current systematic reviews showed potential advantages to CAM for CR in alleviating neck pain or related symptoms."*(p.7)[17]

Main Study Findings	Author's Conclusion
effective in treating cervical radiculopathy ○ The third SR concluded manual therapies including manipulation, massage, mobilization and acupressure have statistically significant effects on cervical radiculopathy in the short-term, but not in the long-term ○ Lastly, cervical SMT is more effective than cervical computer traction for pain in the immediate-term	
Cheng and Huang 2014[11]	

Pain
Immediate-Term:
• Massage demonstrated statistically significant immediate effect on pain relief in comparison to aggregated active and inactive therapies (SMD 0.49; 95 % CI, 0.07 to 0.92; 13 RCTS, n= 785)
  • Massage showed significant effect in comparison to inactive therapies (SMD 1.30; 95% CI, 0.09 to 2.50; n =785) but not active therapies (SMD 0.21; 95% CI -0.22 to 0.64; n=632)
  • Massage demonstrated statistically significant immediate effect over TCM (SMD 0.73; 95% CI, 0.13 to 1.33; n=125)
  • No statistically significant difference over traction (SMD 0.61; 95% CI, -0.09 to 1.30; n= 246)
  • Acupuncture (SMD -0.52; 95% CI, -0.82 to -0.21; n= 171) and other manual therapies (SMD -0.51; 95% CI -0.92 to -0.09; n=91) had statistically significant effects on pain relief over massage
Short-term:
• No differences were found when massage was compared to acupuncture (SMD -0.10; 95% CI, -0.47 to 0.28; n=111) at 12 weeks and exercise (SMD 0.71; 95% CI, -0.28 to 1.70; n=17) at 6 weeks
 	
Dysfunction
Immediate-term:
• No statistically significant difference in NDI scores when compared to inactive therapies (SMD 0.26; 95% CI, -0.09 to 0.62) or active therapies (SMD -0.7; 95% CI, -0.36 to 0.22)
Adverse Events
• 2 RCTs reported on AEs; low BP was experienced in 21% of participants in 1 RCT and 28% of participants in another reported mild AEs (discomfort, pain, soreness, and nausea)
 	
Note: This SR was included in Miake-Lye,[10] but only the outcome of pain was included in the evidence map. Additionally, further details on subgroup analyses were not reported.
	"this systematic review found moderate evidence of MT on improving pain in patients with neck pain compared with inactive therapies and limited evidence compared with traditional Chinese medicine due to few eligible studies. These are beneficial evidence of MT for neck pain. Assuming that MT is at least immediately effective and safe, it might be preliminarily recommended as a complementary and alternative treatment for patients with neck pain."(p.11)[11]

Young et al. 2014[21]	
<u>Thoracic manipulation vs. thoracic mobilization</u> 1 RCT (n=60); manipulation group had statistically significant effects on pain, disability and perceived recovery at 2-4 day	*"As a result of methodological concerns associated with the current research on the use of thoracic mobilization in the treatment of mechanical neck pain, there is no definitive*

Main Study Findings	Author's Conclusion

follow-up; no differences between groups with respect to number of side effects; AEs reported included muscle spasms, neck stiffness, headache and radiating symptoms.
 	
Thoracic manipulation
• 4 RCTs compared manipulation + modality vs. modality or modality/education group; thoracic manipulation was found to have statistically significant effects on pain reduction and range of motion
• 1 RCT comparing manipulation to a placebo intervention found statistically significant immediate pain relief in SMT group
• 2 studies examined exercise and manipulation
  ○ The first study found statistically significant reductions in pain and disability in the short-term; disability in the long-term; perceived recovery at 4 weeks and 6 months for the manipulation group
  ○ Second study reported only one of the ten patients reported statistically significant effects in function at 4 weeks and 6 months and 40% of patients had statistically significant pain reduction at 4 weeks
• One study compared thoracic manipulation to cervical manipulation, but the SR only reported results for the thoracic SMT group: thoracic manipulation group had statistically significant decrease in pain level post treatment
• 2 studies compared a single session of thoracic SMT with exercise; one RCT reported statistically significant effects on pain and bilateral cervical rotation post treatment and the case series reported patients experienced post treatment pain relief
• In comparison to exercise, the manipulation group in one RCT reported statistically significant reductions in pain at the one year follow-up
• The prospective cohort study was a clinical prediction rule derivation study to determine patients with mechanical neck pain who are most likely to benefit from thoracic SMT; probability of perceived recovery increased to 93% if four of the criteria were met
 	
Thoracic Mobilization
• 1 quasi-RCT demonstrated statistically significant effects on pain reduction, disability and muscle endurance in comparison to exercise
	evidence to support its clinical efficacy. In contrast, there is a significant amount of evidence, although of varied quality, that exists to support the use of thoracic manipulation in the treatment of mechanical neck pain for short-term improvements in neck pain, range of motion, and disability."(p.152)[21]

AE/AEs =adverse event/adverse events; AP = anterior –posterior; BP = blood pressure; CGH = cervicogenic headache; CI = confidence interval; ET= exercise therapy; GPE = global perceived effect; GROC = global rating of change scale; HADS = Hospital Anxiety and Depression Scale; HEA = home exercise and advice; HVLA = high-velocity low-amplitude; ICT = Intermittent Cervical Traction; INIT = integrated neuromuscular inhibition technique; MA = meta-analysis; MD = mean difference; MET = muscle energy technique; MFPS= myofascial pain syndrome; NAD = neck pain and associated disorders; NDI = Neck Disability Index; NRS = numeric rating scale; NPQ = Northwick Park Pain Questionnaire; NPRS = numerical pain rating scale; NSAID = nonsteroidal anti-inflammatory drug; OMT = osteopathic manipulative therapy; PNF = proprioceptive neuromuscular facilitation; QoL = quality of life; RCT = randomized controlled trial; ROM = range of motion; SF-12=12-Item Short Form Survey; SF -36 = 36-Item Short Form Survey; SMD = standardized mean difference; SMT = spinal manipulative therapy; SR/SRs = systematic review/systematic reviews; STT = soft tissue therapy; TCM = Traditional Chinese medicine; TENS transcutaneous electrical nerve stimulation; TMJ = temporomandibular joint dysfunction; WAD = whiplash-associated disorder; VAS = visual analog scale.

Table A6: Summary of Recommendations in Included Guidelines

Findings and Recommendations	Quality of Evidence, Strength of Recommendation
Bussières et al. 2016[23]	
Recent-onset (0-3 months) grades I to III NAD	
"For patients with recent (0-3months) grades I to II NAD, we suggest manipulation or mobilization based on patient preference." (p.537)[23]	Quality of Evidence: Low Strength of Recommendation: Weak ("Weak recommendations mean that patients' choices will vary according to their values and preferences, and clinicians must ensure that patients' care is in keeping with their values and preferences."(p564.e26)[23])
"For patients with recent (0-3months) neck pain grades I to II, we suggest either range-of-motion home exercises, medication, or multimodal manual therapy for reduction in pain and disability." (p.544)[23] "Multimodal manual therapy included manipulation and mobilization with limited light soft tissue massage, assisted stretching, hot and cold packs, and advice to stay active or modify activity as needed." (p.544)[23]	Quality of Evidence: Moderate Strength of Recommendation: Weak
Recent-onset (0-3 months) grades I to III WAD	
"For adult patients with recent (0-3 months) WAD grades I to III, we suggest multimodal care over education alone." (p.545)[23] "Remark: Multimodal care may consist of manual therapy (joint mobilization, other soft tissue techniques), education, and exercises." (p.545)[23]	Quality of Evidence: Moderate Strength of Recommendation: Weak
Persistent (>3 months) grades I to III NAD	
"For patients with persistent (>3 months) neck pain and associated disorders grades I to II, we suggest multimodal care* or stress self-management† based on patient preference, prior response to care, and resources available." (p.548)[23] "Remark: *Individualized multimodal care may include manual therapy (manipulation, mobilization, massage, traction), acupuncture, heat, transcutaneous electrical nerve stimulation, exercise, and/or ultrasound." (p.548)[23]	Quality of Evidence: Low Strength of Recommendation: Weak
"For patients with persistent grades I to II NAD, we suggest manipulation in conjunction with soft tissue therapy." (p.548)[23]	Quality of Evidence: Low Strength of Recommendation: Weak
"For patients with persistent (N3 months) grades I to II NAD, we suggest high-dose massage over no treatment (wait listing) based on patient preferences and resources available." (p.548)[23]	Quality of Evidence: Low Strength of Recommendation: Weak
"For patients presenting with persistent neck pain grades I to III, we suggest clinicians offer multimodal care* and/ or practitioner advice† based on patient preference." (p.549)[23]	Quality of Evidence: Low Strength of Recommendation: Weak

Findings and Recommendations	Quality of Evidence, Strength of Recommendation
"Remark: *Multimodal care and exercises may consist of thrust/nonthrust joint manipulation, muscle energy, stretching, and home exercises" (p.549)[23]	
Interventions that should not be offered	
Reproduced from Côté et al. 2016[3] • Relaxation massage and strain-counterstrain therapy for recent onset and persistent grades I-II NAD • Traction for recent-onset NAD grade III	
Côté et al. 2016[3]	
Recent NAD grades I-II	
"For patients with NAD grades I–II ≤3 months duration, clinicians may consider structured patient education in combination with: range of motion exercise, multimodal care (range of motion exercise with manipulation or mobilization), or a short course of muscle relaxants (as indicated)." (p.2011)[3]	Strength of Recommendation: Consider *("Recommendations for interventions providing similar effectiveness to other interventions (between group differences of the interventions were not statistically significant and/or clinically important"* (p2004)[3])
"In view of evidence of no effectiveness, clinicians should not offer structured patient education alone, strain-counterstrain therapy, relaxation massage, cervical collar, electroacupuncture, electrotherapy, or clinic-based heat." (p.2011-12)[3]	Strength of Recommendation: Should not offer *("Interventions that should not be offered because they provide no benefit beyond placebo/sham (i.e., statistically significant and clinical important between group differences favouring placebo/sham) or because they are harmful (i.e., serious adverse events or high frequency of minor adverse events)"(p2004)[3])*
Persistent NAD grades I-II	
"For patients with NAD grades I–II NAD >3 months duration, clinicians may consider structured patient education in combination with: range of motion and strengthening exercises, qigong, yoga, multimodal care (exercise with manipulation or mobilization), clinical massage, low-level laser therapy, or non-steroidal anti-inflammatory drugs." (p.2013)[3]	Strength of Recommendation: Consider
"In view of evidence of no effectiveness, clinicians should not offer strengthening exercises alone, strain-counterstrain therapy, relaxation massage, relaxation therapy for pain or disability, electrotherapy, shortwave diathermy, clinic-based heat, electroacupuncture, or botulinum toxin injections." (p.2013)[3]	Strength of Recommendation: Should not offer
Recent NAD grade III	
"In view of evidence of no effectiveness, clinicians should not offer structured patient education alone, cervical collar, low-level laser therapy, or traction." (p.2015)[3]	Strength of Recommendation: Should not offer

NAD = neck pain and associated disorders/ neck pain-associated disorders; WAD = whiplash-associated disorders.

Appendix 6: Overlap Between Included Publications

Table A7: Overlap in Included Studies between Systematic Reviews

Primary Study Author, Publication Year	Manipulation and Mobilization						
	Fredin and Loras 2017[22]	Shekelle et al.[18]	Yao et al.2017[20]	Southerst et al. 2016[15]	Wong et al.[9]	Gross et al.[5]	Young et al.[21]
Bronfort 2012			x	x		x	
Cheung Lau 2011			x			x	
Cleland 2005						x	x
Cleland 2007					x		x
Cleland 2010			x				x
Dziedzic 2005	x		x				
Egwy 2008						x	
Escortell-Mayor 2011					x	x	
Evans 2012			x	x	x		
Fernandez-de-las-Penas 2007							
Fernandez-de-las penas 2009			x				x
Gonzalez-Iglesias 2009		x	x			x	x
Gonzalez-Iglesias 2009		x	x			x	x
Howe 1983		x				x	
Hurwitz 2002						x	
Kanlayanaphotporn 2009					x	x	
Kanlayanaphotporn 2010					x	x	
Krauss 2008						x	x
Lau 2011			x				x
Leaver 2010					x	x	
Lin 2013					x	x	
Martinez-Segura 2006						x	x
Masaracchio 2013					x	x	

Primary Study Author, Publication Year	Manipulation and Mobilization						
	Fredin and Loras 2017[22]	Shekelle et al.[18]	Yao et al.2017[20]	Southerst et al. 2016[15]	Wong et al.[9]	Gross et al.[5]	Young et al.[21]
Puentedura 2011						x	x
Saavedra-Hernández 2012					x	x	
Saayman 2011			x			x	
Savolainen 2004						x	x
Sherman 2009			x		x		
Sillevis 2010			x		x	x	