

## Review Article

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# The efficacy of manual therapy and exercise for treating non-specific neck pain: A systematic review

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### Abstract.

**OBJECTIVE:** To review and update the evidence for different forms of manual therapy (MT) and exercise for patients with different stages of non-specific neck pain (NP). Data sources: MEDLINE, Cochrane-Register-of-Controlled-Trials, PEDro, EMBASE.

**METHOD:** A qualitative systematic review covering a period from January 2000 to December 2015 was conducted according to updated-guidelines. Specific inclusion criteria only on RCTs were used; including differentiation according to stages of NP (acute – subacute [ASNP] or chronic [CNP]), as well as sub-classification based on type of MT interventions: MT1 (HVLA manipulation); MT2 (mobilization and/or soft-tissue-techniques); MT3 (MT1 + MT2); and MT4 (Mobilization-with-Movement). In each sub-category, MT could be combined or not with exercise and/or usual medical care.

**RESULTS:** Initially 121 studies were identified for potential inclusion. Based on qualitative and quantitative evaluation criteria, 23 RCTs were identified for review. Evidence for ASNP: MODERATE-evidence: In favour of (i) MT1 to the cervical spine (Cx) combined with exercises when compared to MT1 to the thoracic spine (Tx) combined with exercises; (ii) MT3 to the Cx and Tx combined with exercise compared to MT2 to the Cx with exercise or compared to usual medical care for pain and satisfaction with care from short to long-term. Evidence for CNP: STRONG-evidence: Of no difference of efficacy between MT2 at the symptomatic Cx level(s) in comparison to MT2 on asymptomatic Cx level(s) for pain and function. MODERATE to STRONG-evidence: In favour of MT1 and MT3 on Cx and Tx with exercise in comparison to exercise or MT alone for pain, function, satisfaction with care and general-health from short to moderate-terms. MODERATE-evidence: In favour (i) of MT1 as compared to MT2 and MT4, all applied to the Cx, for neck mobility, and pain in the very short term; (ii) of MT2 using soft-tissue-techniques to the Cx and Tx or MT3 to the Cx and Tx in comparison to no-treatment in the short-term for pain and disability.

**CONCLUSION:** This systematic review updates the evidence for MT combined or not with exercise and/or usual medical care for different stages of NP and provides recommendations for future studies. Two major points could be highlighted, the first one is that combining different forms of MT with exercise is better than MT or exercise alone, and the second one is that mobilization need not be applied at the symptomatic level(s) for improvements of NP patients. These both points may have clinical implications for reducing the risk involved with some MT techniques applied to the cervical spine.

Keywords: Manual Therapy, musculoskeletal manipulation, exercise, neck pain, evidence based practice, systematic review

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## 1. Introduction

Non-specific neck pain (NP) is defined as pain in the posterior and lateral aspect of the neck between the superior nuchal line and the spinous process of the first thoracic vertebra with no signs or symptoms of major structural pathology and no or minor to major interference with activities of daily life as well as with the absence of neurological signs and specific pathologies; such as: traumatic sprain and fracture, tumour, infectious or inflammatory cervical spondylolysis, etc. [1–9]. It accounts for around 25% of all outpatient visits to physiotherapy [1–4] with a lifetime incidence rate of 12 to 70% among the general population [2,5–9], although men are less likely to be affected than women [8,10–13]. Most people with NP do not experience a complete resolution of symptoms with 50–85% reporting recurrence 1 to 5 years later [9]. Consequently, NP results in enormous health-costs in terms of treatment, lost wages and work absenteeism [7,10,13]. Despite its major prevalence and socioeconomic consequences, NP is the “poor cousin” to low back pain in terms of research investigation [6,7]. In most cases a specific diagnosis cannot be made and NP is labelled non-specific, because of the multifactorial etiology [9,10,14,15].

Within a “Bio-Psycho-Social” framework, a number of factors could be considered to contribute to NP. These include non-modifiable risk factors related to patho-anatomical features (e.g. history of trauma, age, gender and genetics) and adjustable risk factors, which are more related to psychosocial features (e.g. smoking, physical activity and sedentary life style, beliefs, coping style, expectations, and work satisfaction). These factors may also contribute to the transition from acute to chronic pain status [8–11,15,16].

Conservative treatments used to help manage NP are numerous and include usual medical care (UMC: i.e. face to face interview, education, reassurance, medication, ergonomic and stay active advice), various forms of exercise, massage, and acupuncture among others, but there is a lack of evidence regarding their relative efficacy [5,7,9]. Manual therapy (MT) is also an increasingly popular treatment available to people with NP and many countries include MT in national guidelines for treating musculoskeletal disorders [8, 17,18]. In general terms, these treatments are considered to be more useful than no intervention or placebo treatments [1,5,9–11,14,17]. MT includes both passive techniques (hands-on) and active techniques (hands-off) and should be used within a clinically reasoned

and evidence-based-practice framework [18–20]. The aim of MT in the context of NP is to decrease pain, improve movement, motor control, and function and thereby reduce disability [8,17–20].

A recent systematic review (SR) from Hidalgo et al. [20] examined the efficacy of different common forms of MT for low back pain which had been reported in the literature or used in clinical practice. In that review, three categories of MT were identified and their efficacy examined according to specific inclusion criteria (both qualitative and quantitative). These categories were MT1 comprising high velocity low amplitude thrust manipulation (HVLA), MT2 comprising a range of spinal mobilization and/or soft-tissue-techniques, MT3 being MT2 combined with MT1. All categories could be combined or not with exercise (general or specific) and/or with UMC [20]. In addition to these forms of MT, mobilization-with-movement (MWM; i.e. MT4) is an increasingly popular form of treatment used clinically for a range of musculoskeletal disorders and receiving increasing research attention [21,22].

This type of rigorous systematic review of different forms of MT combined or not with exercise and compared with UMC has not yet been reported for NP. For example, previous reviews have reported that MT is more effective than a placebo treatment or no treatment at all for NP, but failed to establish levels of evidence for other forms of treatment such as UMC or exercise in comparison to MT. Moreover, these studies have not adequately investigated which MT approach when combined with UMC or exercise, is more effective for NP [4,17,23]. However, the number of studies investigating MT for NP has recently increased, possibly in part due to its popularity and use in clinical practice. Hence, there are a number of recently published trials that have not been considered in previous SRs of NP [4,23,25–29]. Further, the SRs published to date on NP, are not up to date, rarely focus on NP in isolation (more often including headache, radiculopathy, and whiplash) have not considered low risk of bias studies (methodological quality  $\geq 7/11$  on the Cochrane checklist), and did not perform comprehensive analysis based on MT classification combined or not with UMC and/or exercise to establish the strength of the evidence. Thus, the aim of this SR is to inform clinicians, patients and policy makers of the best current evidence for a clinical-informed approach of the use of MT for NP, because there is a need for an updated and comprehensive SR on MT efficacy for NP.

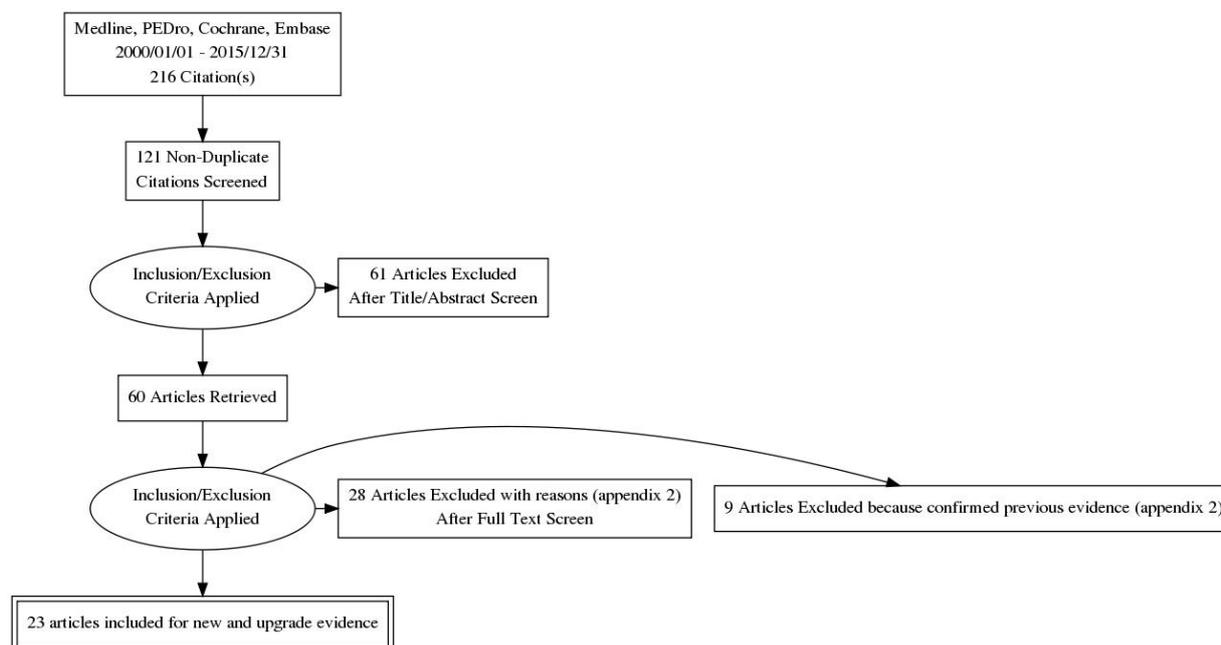


Fig. 1. PRISMA flowchart of inclusion.

## 2. Methods

This SR was conducted in accordance with the Cochrane Collaboration Back Review Group (CCBRG) and PRISMA updated guidelines for SR [24,30] and is based on the methodology and design of a previous qualitative-SR [20].

### 2.1. Search strategy

A literature search of randomized controlled trials (RCTs) published in English between 1<sup>st</sup> January 2000 and 31<sup>st</sup> December 2015, on the efficacy of MT in the treatment of NP was conducted by two reviewers in four electronic databases: MEDLINE (PUBMED), Cochrane-Register-of-Controlled-Trials (CRCT), Physiotherapy-Evidence-Database (P-EDro), EMBASE. The detailed search strategy in MEDLINE is presented in Appendix 1, and was adapted to search in the other databases. Based on information revealed in the titles and abstracts, a first selection of articles was performed using the inclusion criteria based on consensus between experts (i.e. authors). A final selection was conducted after critical appraisal of the quality of the studies. A consensus was reached at each step (Fig. 1) on the studies to be included.

### 2.2. Inclusion criteria

#### 2.2.1. Study design

RCTs were included only (i) if they presented a low-risk of bias, (ii) if subjects with NP were randomly allocated to receive either MT or a comparator group receiving “no-treatment”, a placebo procedure, or another usual conservative therapy for NP, (iii) if the randomization methods were appropriate and clearly reported, and (iv) if a single (assessors blinded) or double-blind design (assessors and patients blinded) was used.

#### 2.2.2. Patients

NP was differentiated on the basis of duration of the pain episode, with acute pain < 6 weeks, subacute pain 6–12 weeks, and chronic pain > 12 weeks. We also used a combination of duration, location, and signs/symptoms to determine the study population [9,20].

Studies were included if the patients were male or female aged between 18 and 60 years suffering from acute-subacute (0–12 weeks) or chronic (> 12 weeks) NP. Acute and subacute categories were combined because of their similarities in contrast to chronic NP category, where psychosocial factors appear more important. No mixed populations of combined acute-subacute and chronic NP were allowed. NP was re-

quired to be localized to the posterior neck between the superior nuchal line and the spinous process of the first thoracic vertebra [4,31]. NP is often associated with cervicogenic headache and/or tension type headache, or with peripheral neuropathic pain in the upper limbs; these clinical categories of patients were not included in the present SR.

With respect to severity, NP is also classified according to a 4-grade classification system of the Neck Pain Task Force [31], and for this SR, only RCTs with a population comprising NP grade I or II on this classification system were selected, i.e. no signs or symptoms of major structural pathology and no or minor (I) to major (II) interference with activities of daily life with the absence of neurological signs.

### 2.3. Interventions

As manual therapy (MT) interventions are broad by nature, we decided to use a clinical sub-classification system of MT in this SR with four major categories of MT techniques [20]. Moreover, this sub-classification was in accordance with a comprehensive evidence based search strategy and the MT treatment used and reported in the intervention group (IG) of included RCTs.

MT1 corresponds to spinal manipulation, where a HVLA thrust with “cavitation” is applied to the cervical spine (Cx) or thoracic spine (Tx) [32–34]. MT2 includes a range of mobilization techniques applied to the Cx or Tx which includes: low-velocity-mobilization such as physiological or accessory mobilization, articular muscle-energy-technique (MET, i.e. segmental analytic myotensive mobilization of Cx and Tx) and/or the soft-tissue techniques (STT) including “myofascial-release”, “trigger-points” “muscular-MET” (i.e. analytic myotensive techniques on specific muscles using “contract-relax” neurophysiological principles) of the neck region [11,20,32,35]. MT3 comprises the combination of MT2 and MT1 [32,34, 35]. MT4 corresponds to mobilization-with-movement (MWM) with cervical sustained-natural-apophyseal-glides (SNAGs) developed by Mulligan [36,37].

Furthermore, as modern MT include hands off approach, sub-categorization of groups MT1-4 was based on the addition or not of exercise either specific (for example based on directional-preference, strengthening/stabilization of specific deep-neck and scapular muscles, and motor control) or general (for example: range of motion exercises of the head and neck, sitting posture correction) or usual-medical-care (UMC; i.e. face to face interview, education, reassurance, medication, ergonomic and stay active advice) [20,23,33,38–41].

### 2.4. Control groups

The control groups received: “no treatment”, a placebo, or another usual conservative treatment for NP (e.g. UMC, exercise, electrotherapy, physiotherapy, or rehabilitation) [24,30,41].

### 2.5. Outcome measures of effectiveness

The outcome measures were classified according to the CCBRG recommendations: pain, function, overall-health and quality of life (Appendix 1). Timing of the follow-up measurements was defined as very-short-term (end of treatment/discharge to 1 month), short-term (1–3 months), intermediate-term (3 months–1 year), or long-term (1 year or more).

#### 2.5.1. Quality assessment

Two independent reviewers (JB and AD) assessed risk of bias, methodological quality, data extraction and clinical relevance of each trial.

Quantitative and qualitative criteria were assessed by applying the CCBRG criteria [24,30]. Quantitative risk of bias was assessed, using an 11-point check-list (see Appendix 1).

Qualitative assessments were made on the basis of the following criteria: a well determined distinction and separation between combined acute-subacute and chronic NP categories at baseline, a detailed description of MT intervention and the possibility that reviewers would be able to classify the MT techniques according to MT1-MT4 classification system, and a single-blind or double-blind RCT design.

Included studies were required to be low-risk of bias. We considered as “high-quality” those RCTs with single-blind (assessors blinded) or double-blind (patients and assessors blinded) designs that met at least 9/11 of CCBRG criteria indicated by an ‘A’. “Moderate quality” RCT status was assigned to studies of single-blind design with a minimum score of 7/11 indicated by a ‘B’ (Tables 1 and 2) [4,20]. To reduce the number of words and the number of studies included in this SR, only RCTs that present new findings or update/upgrade previous evidence from SRs with our methodology are fully described in the results section and Tables 1–3. However, all studies from our search strategy, as well as reason of exclusion are presented in the Appendix 2.

#### 2.5.2. Strength of evidence and clinical relevance

Strength of evidence was determined by grouping similar “Patients Interventions Comparisons Outcomes Study Design” to provide an overall level of evidence

Table 1  
Summary of articles for patients with acute-subacute neck pain

Authors sample size NP status	Methodological quality of studies	Intervention + Co intervention	Comparison group + co intervention	Outcomes measures of interest	Clinical relevance status on timing outcomes: between groups <i>P</i> value and effect sizes
Puentedura et al. [42] <i>n</i> = 24 ANP	Level A 9/11 No for patient and care provider blinded	IG: MT1 Cx + exercise 5 sessions over 2 weeks	CG: MT1 Tx + exercise 5 sessions over 2 weeks	Pain (NPRS) Functional disabilities (NDI) (FABQ)	Yes: From 1 week to 6 months ( <i>p</i> < 0.005; SMD = 2.2–2.7) Yes: From 1 week to 6 months ( <i>p</i> < 0.05; SMD > 1) Yes: At 6 months ( <i>p</i> = 0.04; SMD = 1.1)
Gonzalez-Iglesias et al. [1] <i>n</i> = 45 SNP	Level A 9/11 No for patient and care provider blinded	IG : MT1 Tx once a week over 3 weeks + Electro/thermal therapy 5 times over 3 weeks	CG: Electro/thermal therapy 5 times over 3 weeks	Pain (VAS) Functional disabilities (NPQ) (CROM) -Flex -Ext -R Rot -L Rot -R Lat Flex -L Lat Flex	Yes: From post treatment to 4 weeks ( <i>p</i> < 0.001; SMD > 2) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.001; SMD = 2.7–2.6) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.05; SMD = 2.5–1.6) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.05; SMD = 1.8–1.1) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.05; SMD = 1.9–2.0) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.05; SMD = 2.1–1.6) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.05; SMD = 2.2–1.9) Yes: At post treatment and 2 weeks ( <i>p</i> < 0.05; SMD = 2.5–1.4)
Gonzalez-Iglesias et al. [43] <i>n</i> = 45 SNP	Level A 9/11 No for patient and care provider blinded	IG : MT1 Tx once a week over 3 weeks + Electro/thermal therapy 6 times over 3 weeks	CG: Electro/thermal therapy 6 times over 3 weeks	Pain (NPRS) Functional disabilities (NPQ) (CROM) -Flex -Ext -L Lat Flex -R Lat Flex -L Rot -R Rot	Yes: At 1 week ( <i>p</i> < 0.001; SMD = 2.8) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 2.7) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 2.0) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.5) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.7) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.9) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.4) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.4)
Nagrале et al. [15] <i>n</i> = 60 ASNP	Level A 9/11 No for patient and care provider blinded	IG: MT2 (myotensive technique + trigger and tender points) 3 times/week over 4 weeks for all groups	CG: MT2 (myotensive technique)	Pain (VAS) Functional disabilities (NDI) (CROM) Lat flex	Yes: At 2 and 4 weeks ( <i>p</i> < 0.05; SMD = 1.2–1.7) Yes: At 2 and 4 weeks ( <i>p</i> < 0.05; SMD = 0.8–0.9) Yes: At 2 and 4 weeks ( <i>p</i> < 0.05; SMD = 2.0–3.8)
Blikstad and Gemmell [44] <i>n</i> = 45 ASNP	Level A 9/11 No for patient and care provider blinded	IG1: MT2 (Activator trigger point therapy) IG2:MT2 (myofascial band therapy) 1 time for all groups	CG: Sham Ultrasound (SUS)	Pain (NPRS) Functional disabilities (CROM)	No No
Gemmell et al. [45] <i>n</i> = 45 ASNP	Level A 9/11 No for patient and care provider blinded	IG1: MT2 (Ischaemic compression) IG2:MT2 (Trigger point pressure release) 1 time for all groups	CG: Sham Ultrasound (SUS)	Pain (VAS) Functional disabilities (CROM)	No No

Table 1, continued

Authors sample size NP status	Methodological quality of studies	Intervention + Co intervention	Comparison group + co intervention	Outcomes measures of interest	Clinical relevance status on timing outcomes: between groups <i>P</i> value and effect sizes
Bronfort et al. [46] and Leininger et al. [26] <i>n</i> = 272 ASNP	Level A 9/11 No for patient and care provider blinded	IG: MT3 Cx-Tx-STT  Number of sessions decided by therapist over 12 weeks	CG1: UMC (anti-inflam, acetaminophen/narcotic; Muscle relaxants) CG2: Home Exercise + advice 6 to 8 sessions per day	Pain (NPRS)  Functional disabilities (NDI) Satisfaction with care (information, general care) (CROM) Quality of life (SF-36)	IG vs CG1: Yes: At 12 and 52 weeks ( <i>p</i> < 0.005; SMD = 0.6–0.5) Yes: At 8 and 26 weeks ( <i>p</i> < 0.05; SMD = 0.5–0.4) Yes: At 12 and 52 weeks ( <i>p</i> < 0.005; MD = 11.6–16.4) No No  IG vs CG2: No difference on all outcome measures
Masaracchio et al. [48] <i>n</i> = 64 ASNP	Level A 9/11 No for patient and care provider blinded	IG: MT3 (MT1 Tx + MT2 Cx) + Exercise 2 times/1 week for all groups	CG : MT2 Cx + Exercises	Pain (NPRS) Functional disabilities (NDI)	Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.0) Yes: At 1 week ( <i>p</i> < 0.001; SMD = 1.1)
Ganesh et al. [25] <i>n</i> = 80 ASNP	Level B 7/11 No for patient and care provider blinded, ITT and dropouts (> 20%)	IG: MT2 Cx (PAIVMS) + Exercise 5 times/week for 2 weeks and for all groups	CG1: MT4 Cx (SNAGs) + Exercise CG2: Exercise alone	Pain (VAS) Disability (NDI) (CROM)	No No

ANP: acute neck pain/SNP: subacute neck pain/ASNP: acute-subacute neck pain/VAS: Visual Analogue Scale/NDI: Neck Disability Index/CROM: Active Cervical Range of Motion/PPT: Pressure Pain Threshold/US: ultrasound/NPRS: Numeric Pain Rating Scale/FABQ: Fear-Avoidance-Belief-Questionnaire/SF-36: Short-form-health-survey/NPQ: Northwick Pain Questionnaire/UMC: Usual Medical Care/Cx: cervical/Th: thoracic/MOB: Mobilization/SNAGs: Sustained Natural Apophyseal Glides/HVLA: high velocity low amplitude thrust/IG: Intervention Group/CG: Control Group/IRT: Infrared Radiation Therapy/PAIVMS: Passive Accessory Intervertebral Movements/STT: Soft-Tissues-Techniques/SUS: Sham Ultrasound/Yes: significant difference with moderate to large clinical effect size/No: no significant difference with small clinical effect size on all timing outcome measures.

(see Appendix 1 for the process of evidence) on the efficacy of the 4 categories of MT (MT1-MT4) combined or not with another intervention. Conclusions of evidence are summarized in Table 3.

The effect size was independently collected or calculated by two authors, and used to assess the clinical relevance of MT interventions in outcome measures. We reported the between groups means of difference ( $MD = \text{mean A} - \text{mean B}$ ) or Cohen's standardized means of difference ( $SMD = \text{mean A} - \text{mean B}/\text{mean SD}$ ). In this SR, the clinical relevance was determined by two conditions and scored by "YES" in favour of the intervention group; if there were (i) significant differences between groups ( $p < 0.05$ ) associated (ii) with between groups effect sizes equal or superior to the minimal clinically important difference for MD or moderate for SMD (from 0.4–0.8) to large SMD (from 0.8–1.2) and very large SMD (> 1.2) effects on specific outcome measures (Tables 1 and 2) [20,24].

### 3. Results

Two reviewers performed the selection of articles

(Fig. 1). A qualitative SR was undertaken on the 23 low-risk of bias RCTs, based on the qualitative and quantitative criteria described above; 21 studies were classified as level A and 2 as level B quality (Tables 1 and 2). Summary findings are shown in Table 3, which includes a presentation of the level of evidence drawn from the selected RCTs.

#### 3.1. Effects of interventions on acute-subacute NP

##### 3.1.1. MT1 to the cervical spine with exercise versus MT1 to the thoracic spine with exercise

Puentedura et al. [42] evaluated the efficacy of MT1 to the upper Cx in comparison to MT1 on the Tx. Both interventions were combined with the same exercise (ROM exercises of the head and shoulder, and upper limb exercise against moderate resistance elastic band's). The numbers of treatment sessions were similar in both groups ( $n = 5$ ). There were statistically significant and clinically relevant improvements for pain ( $p < 0.005$  and  $SMD > 2$ ) and disability ( $p < 0.05$ ;  $SMD > 1$ ) from 1 week to 6 months, and for quality of life at 6 months ( $p < 0.005$  and  $SMD$  of 1.14) for

Table 2  
Summary of articles for patients with chronic neck pain

Authors Sample size NP status	Methodological quality of studies	Intervention + Co intervention	Comparison group + co intervention	Outcomes measures of interest	Clinical relevance status on timing outcomes: between groups <i>P</i> value and effect sizes
Izquierdo- Pérez et al. [49] <i>n</i> = 61 CNP	Level A 9/11 care provider not blind and dropouts (> 20%)	IG: MT1 Cx 4 sessions over 2 weeks	CG1: MT2 Cx (PAIVMS) CG2: MT4 Cx (SNAGs) 4 sessions over 2 weeks	PAIN (VAS) Functional disabilities (NDI) (CROM) -Ext	NO NO IG vs CG2: YES: immediately after treatment up to 3 months ( <i>p</i> < 0.01; SMD ≥ 0.5)
Lopez et al. [50] <i>n</i> = 48 CNP	Level A 9/11 Care provider not blind Difference at baseline: CROM in Flexion/Extension	IG: MT1 Cx 1 single session	CG1: MT2 Cx (PAIVMS) CG2: MT4 Cx (SNAGs) 1 session	PAIN (VAS) (PPT) Functional disabilities (CROM)	IG and CG1 vs CG2: YES: immediately after treatment only for pain at rest ( <i>p</i> = 0.04) with SMD = 0.5–1.1) NO NO NO
Saavedra- Hernandez et al. [51] <i>n</i> = 80 CNP	Level A 9/11 No for patient and care provider blinded	IG: MT1 on Cx-Tx (1 sessions: 2 Cx-thrusts)	CG: Kinesio Taping (wearing during 1 week)	-Pain (NPRS) -Functional disabilities (NDI) (CROM) -flex, ext, latflex -Right rot  -Left rotation	NO NO  NO IG vs CG: YES: at 7 days ( <i>p</i> < 0.01; SMD = 0.6; MD = 6.8) IG vs CG: YES: at 7 days ( <i>p</i> < 0.01; SMD = 0.6; MD = 7.0)
Martinez- Segura et al. [52] <i>n</i> = 90 CNP	Level A 9/11 No for patient and care provider not blind	IG: MT1 on Cx (left) MT1 on Cx (right)	CG: MT1 on Tx	Pain (PPT) Functional disabilities (CROM)	NO NO
Sherman et al. [5] <i>n</i> = 64 CNP	Level A 9/11 No for patient and care provider blinded	IG : MT2 (STT) 10 times over 10 weeks	CG: no treatment:self- care-book	Pain (NPRS) Functional disabilities (NDI) Overall improvement (SF-36)	YES: at 4 weeks, ( <i>p</i> = 0,006; MD = 1,6) YES: at 4 weeks, ( <i>p</i> = 0,047; MD = 2,1) NO
Schwerla et al. [11] <i>n</i> = 41 CNP	Level A 9/11 No for care provider blinded and ITT	IG: MT3 Cx-Tx + SUS 9 times every 12 to 20 days	CG: no- treatment: SUS 9 times every 4 to 10 days	Pain (NPRS) -Average pain -Actual pain -Worst pain  Functional disabilities (NPQ) Overall improvement (SF-36)	YES: At 1 week ( <i>p</i> = 0.02; SMD = 0.9; MD = 1.7) at 3 months ( <i>p</i> = 0.009; MD = 1.5) at 3 months ( <i>p</i> = 0.03; MD = 1.6) at 3 months ( <i>p</i> = 0.05; MD = 1.2) YES: at 3 months ( <i>p</i> = 0.01; MD = 9) YES: at the end of treatment ( <i>p</i> = 0.02; MD = 13.3)
Lau et al. [8] <i>n</i> = 120 CNP	Level A 9/11 No for patient and care provider blinded	IG : MT1 Tx + IRT and exercise 8 times (/weeks) for all groups + home exercises	CG: IRT + exercise	Pain (NPRS)  Functional disabilities (NPQ) (CROM) -Ext  -Flex  -L Lat Flex  -R Lat Flex  Overall improvement (SF-36)	YES: at post treatment, at 3 months, and at 6 months ( <i>p</i> < 0.05; SMD > 0.6) YES: at post treatment and at 3 months ( <i>p</i> < 0.02 SMD = 0.5), at 6 months, ( <i>p</i> = 0.007, SMD = 0.4) YES: at 3 months ( <i>p</i> = 0.001; SMD = 0.8) at 6 months ( <i>p</i> = 0.001, SMD = 0.5; MD = 3.8) YES: at post treatment, at 3 months and at 6 months ( <i>p</i> < 0.05; SMD > 0.5) YES: at 3 months and at 6 months ( <i>p</i> < 0.005; SMD > 0.5) YES: at 3 months and at 6 months ( <i>p</i> < 0.05; SMD ≥ 0.6) YES: at post treatment, at 3 months and at 6 months ( <i>p</i> ≤ 0.002; SMD > 0.60)

Table 2, continued

Authors Sample size NP status	Methodological quality of studies	Intervention + Co intervention	Comparison group + co intervention	Outcomes measures of interest	Clinical relevance status on timing outcomes: between groups <i>P</i> value and effect sizes
Kanlayanaphotporn et al. [53] <i>n</i> = 60 CNP	Level A 10/11 No for care provider blinded	IG: MT2 on Cx symptomatic levels (PAIVMS) 1 time	CG: random MT2 Cx (PAIVMS) 1 time	Pain (VAS) Functional disabilities (CROM)	NO NO
Aquino et al. [19] <i>n</i> = 48 CNP	Level A 9/11 No for patient and care provider not blind	IG: MT2 Cx symptomatic levels (PAIVMS) 1 time	CG: random MT2 (PAIVMS), away from the concordant segment 1 time	Pain (NRS)	NO
Schomacher [54] <i>n</i> = 126 CNP	Level A 10/11 No for care provider blinded	IG: MT2 Cx symptomatic levels (PAIVMS) 1 time	CG: MT2 Cx (PAIVMS), 3 levels away from the concordant segment 1 time	Pain (NRS)	NO
Bronfort et al. [7] <i>n</i> = 191 CNP	Level A 9/11 No for patient and care provider blinded	IG1: MT3 on Cx-Tx (HVLA + STT) + exercise IG2: MT3 on CX-Tx (HVLA + STT) alone (sham microcurrent) 20 times (1h) over 11 weeks & home exercises for all groups	CG: MedX (Exercise with specific devices sessions)	Pain (NRS) Functional disabilities (NDI) (CROM) -Flex/Ext -Rot -Lat Flex Overall Improvement (SF-36)	NO NO YES: IG1 vs IG2: at 11 weeks ( <i>p</i> < 0.05; MD = 6.7) CG vs IG2: at 11 weeks ( <i>p</i> < 0.05; MD = 5.2) YES: IG1 vs IG2: at 11 weeks ( <i>p</i> < 0.05; MD = 6.7) YES: IG1 vs IG2: at 11 weeks ( <i>p</i> < 0.05; MD = 5.6) NO
Evans et al. [55] <i>n</i> = 270 CNP	Level A 9/11 No for patient and care provider not blind	IG1: MT1 Cx-Tx + Exercise IG2: High Exercise (High dose supervised strengthening exercise)	CG: HEA (Home Exercise and advice)	Pain (NPRS) Disability (NDI) Overall Improvement (SF-36)	IG1 vs CG: YES at 12 weeks ( <i>p</i> < 0.001; SMD = 0.9; MD = 1.4) IG2 vs CG: YES at 12 weeks ( <i>p</i> = 0.001, SMD = 0.7; MD = 1.2) IG1 vs CG: YES at 12 weeks ( <i>p</i> = 0.001; SMD = 0.5; MD = 4.3) IG1 vs CG: YES: at 12 weeks ( <i>p</i> < 0.001; MD = 1.3), at 52 weeks, <i>p</i> = 0.001; MD = 0.8) IG2 vs CG: YES: at 12 weeks ( <i>p</i> < 0.001; MD = 1.1), at 52 weeks ( <i>p</i> = 0.03, MD = 0.5)
Akhter et al. [27] <i>n</i> = 62 CNP	Level B 7/11 No for allocation concealed, No for patient and care provider blinded, dropouts, ITT	IG: MT1 Cx + exercise (6 sessions over 3 weeks for both groups)	CG: Supervised exercise alone	Pain (VAS) Functional disabilities (NDI)	NO NO

CNP: chronic neck pain/VAS: Visual Analogue Scale/NDI: Neck Disability Index/CROM: Active Cervical Range Of Motion/PPT: Pressure Pain Threshold/US: ultrasound/NPRS: Numeric Pain Rating Scale/FABQ: Fear-Avoidance-Belief-Questionnaire/SF-36: Short-form-health-survey/NPQ: Northwick Pain Questionnaire/UMC: Usual Medical Care/Cx: cervical/Th: thoracic/MOB: Mobilisation/SNAGs: Sustained Natural Apophyseal Glides/HVLA: high velocity low amplitude thrust/IG: Intervention Group/CG: Control Group/IRT: Infrared Radiation Therapy/PAIVMS: Passive Accessory Intervertebral Movements/STT: Soft-Tissues-Techniques/SUS: Sham Ultrasound/Yes: significant difference between groups with moderate to large clinical effect size/No: no significant difference between groups with small clinical effect size on all timing outcome measures.

patients who received MT1 to the Cx combined with exercise. However, in both groups (7% in the cervical group and 70% in the thoracic group) minor treatment side effects were reported such as increases in NP, headache and fatigue that resolved within 24 hours. The authors concluded that those patients might benefit more from MT1 to the Cx than Tx.

### 3.1.2. MT1 with electro/thermal-therapy versus electro/thermal-therapy alone

Gonzalez-Iglesias et al. [1,43] investigated in two studies the efficacy of MT1 (localized to the upper Tx) combined with electro/thermal-therapy as compared to electro/thermal-therapy alone for acute-subacute NP patients. The number of sessions was equivalent in both groups and both studies covered 5–6 sessions over 3 weeks. There were statistically significant improvements for pain ( $p < 0.001$  and  $SMD > 2$ ), disability ( $p < 0.001$  and  $SMD > 2.6$ ) and cervical range-of-motion (CROM). The authors concluded that the combined intervention provided clinically greater improvement on all outcome measures.

### 3.1.3. Comparison of two MT2 interventions

Nagrle et al. [15] evaluated comprehensive MT2 (STT) that combined muscular-MET, trigger (ischemic compression) and tender-points (strain-counterstrain) techniques on the trapezius in comparison to simple MT2 (STT) that included only the muscular-MET on the trapezius for acute-subacute NP patients. At 2 and 4 weeks follow-up, the results showed significant improvements in both groups on pain reduction, function and side-bending. However, there was a significant clinically relevant difference between groups with large effect sizes for pain and function ( $SMD$  for CROM lateral flexion  $> 2$ , for VAS  $> 1.1$ , and for NDI  $> 0.8$ ) at follow-up (2–4 weeks) in favour of the comprehensive MT2 intervention.

### 3.1.4. MT2 versus sham-Ultrasound (SUS)

Blikstad and Gemmell [44] and Gemmell et al. [45] compared the effect of MT2 (STT) consisting of trigger point techniques to the trapezius muscle (ischemic compression and trigger point release) to SUS for acute-subacute NP. The results demonstrate that MT2 had an immediate effect on pain compared to SUS. However, in both studies, no statistically significant differences were apparent for any outcome measures between the groups.

### 3.1.5. MT3 versus usual-medical-care and home exercise

Bronfort et al. [46] studied the efficacy of MT3 (on hypomobile Cx and Tx segments and on STT) as compared to UMC (private consultation and education combined with medication (AINS, narcotic drugs and/or muscle relaxants, and advice to stay active) and to home exercise ( $2 \times 1$  hours of education for flexibility and strengthening exercise of the head and shoulder) for acute-subacute NP. Short and long-terms analyses showed improvement for pain at 12 weeks and 52 weeks ( $p < 0.005$  and  $SMD > 0.5$ ) in favour of the MT3 as compared to UMC, but not for MT3 over home exercise or home exercise over UMC. No serious adverse events were reported in the study. However, 40% in the MT3 group and 46% in the home exercise group reported musculoskeletal pain, and 60% in the UMC group reported gastrointestinal symptoms and drowsiness. The authors concluded that MT3 and home exercise interventions led to similar short- and long-term outcomes, but participants who received UMC seemed to fare worse, with a consistently higher use of pain medication during the study period. Leininger et al. [26] in a secondary analysis of this study explored the relationship between satisfaction with care (information and general care, on 0–100 scale) using a multidimensional instrument [47], neck pain (VAS), and global satisfaction with care (scale). Differences in satisfaction with specific aspects of care were analyzed using a linear mixed model at 12 and 52 weeks. Individuals with acute/subacute NP were more satisfied with specific aspects of care received during spinal MT3 or home exercise interventions compared to UMC.

### 3.1.6. MT3 with exercise versus MT2 with exercise

Masaracchio et al. [48] compared the effect of MT3 during two sessions ( $2 \times$  HVLA targeted to T1–T3 and to T4–T7 combined with MT2 on the Cx in a supine position with accessory mobilization over the spinous processes from C2–C7) and home exercise (active Cx rotation ROM exercise), to MT2 (the same as above) and home exercise for acute-subacute NP patients. The results demonstrated significant differences in terms of pain ( $p < 0.001$  and  $SMD$  of 0.96) and disability ( $p < 0.001$  and  $SMD$  of 1.11) at one week in favour of the MT3 with exercise group. The authors concluded that the combination intervention led to better clinical short-term improvement in all outcome measures.

### 3.1.7. MT2 with exercise and MT4 with exercise versus exercise alone

Ganesh et al. [25] studied the effect of MT2 (accessory mobilization on the Cx for 10 sessions over 2 weeks) with exercise (flexibility and strengthening of cervical and scapular muscles, and cervical ROM exercises) in comparison to MT4 (SNAGs applied to the Cx in a sitting position) with exercise and exercise alone for patients with acute-subacute NP. All groups were instructed to continue the exercise at home for 4 weeks. The results demonstrated that all the groups improved overtime compared to baseline ( $p < 0.05$ ). However no significant differences between groups ( $p > 0.05$ ) were determined for all outcome measures (pain, disability, CROM) with very small effect size between groups (SMD = 0.2) after intervention and at follow-up. Any adverse events were reported in the study. The authors concluded that supervised exercises are as effective as both combined mobilizations and exercises on all outcome measures. However as 30–70% of acute NP patients improve spontaneously overtime; future studies should include a UMC group to analyse change with respect to the natural resolution of NP over time.

## 3.2. Effects of interventions on chronic NP

### 3.2.1. MT1 in comparison to MT2 and MT4

Izquierdo-Pérez et al. [49] compared three different treatments applied to the Cx. These were HVLA (MT1), accessory mobilization (MT2) and SNAGs (MT4). Each patient received 4 sessions within 2 weeks. All three groups showed similar improvements in pain, disability and ROM but there was no difference between interventions in any outcome measure apart from CROM in extension ( $p < 0.01$  and MD > 8.3) in favor of MT1 in comparison to MT4. No adverse events were reported for any intervention.

Lopez et al. [50] also studied the effect of the same three interventions applied to the Cx, i.e. HVLA (MT1), accessory mobilization (MT2) and SNAGs (MT4) and CROM. In comparison to Perez' investigation [49], each patient received only one single therapy session. All of the treatments groups demonstrated similar efficacy for the management of pain (at rest, flexion/extension, rotation, side bending, pressure pain thresholds on C2), and CROM (multidirectional). However, only one significant difference (two way; treatment x time interaction,  $p = 0.04$ ) between groups on all outcome measures was demonstrated with respect only for pain at rest in favor of MT1 and MT2 groups over the MT4 group with moderate to large ef-

fects size. There was also an interaction found between trait anxiety (all participants completed the State-Trait Anxiety Inventory; an introspective psychological self-report measure of anxiety affect), improvement in pain and technique applied, i.e. high anxiety levels expected better prognosis (prospect of recovery) outcome after MT2 application and low anxiety levels expected better prognosis after MT1 and MT4 application. Authors did not report adverse events.

Authors of both studies [49,50] concluded by saying that all 3 techniques applied to the Cx were effective in the management of chronic NP with no differences between them. However, MT1 appears marginally better than other forms of MT based on improved CROM in extension only and pain at rest [49,50].

### 3.2.2. MT1 to the cervical spine versus kinesio-Tape

Saavedra-Hernandez et al. [51] compared one group receiving MT1 (HVLA thrust to the mid-Cx and upper-Tx), to another group receiving only Kinesio-Tape applied to the neck for one week in patients with chronic NP. Both interventions demonstrated similar decreases in pain, disability and increases in CROM over the 1-week study period but the results showed that there were no statistically significant differences between both groups in all outcome measures except for the CROM in rotation at 7 days. Five patients reported minor adverse events with 3 (7.5%) in the manipulation group (minor increase in NP or fatigue) and two (5%) in the Kinesio-Tape group (cutaneous irritation related to the tape application). These minor post-treatment symptoms resolved within 24 hours. The authors concluded that the application of MT1 or Kinesio-Tape leads to similar reduction in pain and disability and increases in CROM, and that concerning CROM and disability, the changes were not clinically meaningful.

### 3.2.3. MT1 to the cervical spine versus MT1 to the thoracic spine

Martinez-Segura et al. [52] studied the relative efficacy of a single session of MT1 to the mid-Cx or to the upper-Tx for patients with chronic NP. All groups showed similar changes ( $p < 0.001$ ), but there were no significant differences between the 3 groups on all outcome measures (neck pain intensity with NPRS, CROM, pressure pain threshold with algometry). Two patients reported some minor side effects. The authors concluded that Cx and Tx spine MT1 induced similar changes in outcome measures.

### 3.2.4. MT versus «no-treatment»

Sherman et al. [5] investigated the effectiveness of MT2 (STT to the Cx and Tx region, i.e. connective tissue massage, ischemic compression, myofascial release) in comparison to “no treatment” with a self-care booklet for patients with chronic NP. Differences between both groups were statistically significant for pain ( $p < 0.005$ ) and disability ( $p < 0.05$ ) at 4-weeks of treatment. The authors concluded that MT2 is safe (i.e. no serious adverse effects were reported) and may have clinical benefits for treating chronic NP at least at short-term.

Schwerla et al. [11] compared MT3 to Cx and Tx combined with SUS to “no treatment” with SUS alone for chronic NP patients. The results showed clinical relevant differences in favour of the intervention group on pain reduction ( $p < 0.009$  and MD of 1.8), overall health-improvements ( $p < 0.019$  and MD of 14.6) and functional-status ( $p < 0.05$  and MD of 9) during the course and completion of treatment.

### 3.2.5. MT1 with infrared radiation therapy (IRT) and exercise versus IRT and exercise alone

Lau et al. [8] assessed the effectiveness of MT1 to the Tx combined with IRT (15 minutes over the painful site) and exercise (active neck mobilization, isometric neck muscle contraction for stabilization, and stretching of trapezius and scalene muscles) in comparison to a control group (IRT and exercise only) for chronic NP patients. This study showed that patients in the experimental group had clinically relevant improvements in NP ( $p < 0.001$  and SMD of 0.65) at 6 months and for function ( $p < 0.004$  and SMD of 0.5), overall health ( $p < 0.001$  and SMD of 0.83) and neck mobility ( $p < 0.05$ ) at 3 months when compared to the control group from the completion of treatment up to a 3 to 6 months follow-up.

### 3.2.6. MT2 on symptomatic spinal level(s) versus “sham” MT2 (random location)

Kanlayanaphotporn et al. [53] studied the immediate effects of MT2 (Cx accessory mobilization) on pain and active CROM. In the experimental group, the treatment details including the spinal level(s) to be treated, the grade of movement to be applied, and the most appropriate technique of mobilization were noted. In the control group, the patients received one of the following mobilization techniques that could be considered as a placebo procedure: a central PA, ipsilateral unilateral PA, or contralateral unilateral PA pressure. In both groups the MT2 intervention was applied for

1 minute repeated twice. Both group showed significant decrease in neck pain at rest and in pain at most painful movement. However, there were no statistically significant differences between the groups on pain and active CROM.

Aquino et al. [19] and Schomacher et al. [54] evaluated whether MT2, using the same techniques as described above for Aquino et al., and intermittent translatory traction in supine (accessory mobilization) between C2 and C7 for Schomacher et al., applied both to the symptomatic Cx level, was able to reduce pain compared to the same MT2 interventions but at an asymptomatic Cx level(s). Although all groups in both studies showed significant immediate pain relief, there was no significant difference between the groups.

These studies [19,53,54] demonstrate that identification of the symptomatic Cx segment is not important for the immediate effects of MT2 (accessory mobilization) on pain for chronic NP.

### 3.2.7. MT versus active rehabilitation

Bronfort et al. [7] compared MT3 alone (HVLA thrusts with STT) to the Cx and Tx for 20 sessions of 15–20 minutes), to MT3 with exercise (neck and upper body strengthening for 20 sessions of 1 hour), to MedX Exercise (high technology devices for strengthening of the neck and upper-body during 20 sessions of 1 hour). Although there was a tendency for greater improvement for the two exercise groups (MT3 with exercise and MedX exercise), the efficacy of these 3 interventions was not statistically different for pain, function and overall improvement during treatment. However, at 1-year follow-up, there were significant differences in favour of MT3 combined with exercise and MedX exercises groups as compared to MT3 alone on pain reduction ( $p < 0.05$  and SMD  $> 0.4$ ). The MT3 with exercise, however, showed greater gains in all measures of performance (strength, endurance, and CROM) than MT3 alone ( $p < 0.05$ ), as well as a greater satisfaction with care ( $p < 0.01$ ). After a 1-year follow-up, the authors concluded that MT3 with exercises and MedX exercise appeared to be more efficient than MT3 alone for chronic NP.

Evans et al. [55] investigated the efficacy of MT1 (to the Cx and Tx for 20 sessions of 15–20 minutes) combined with high dose (20 sessions of 1-hour) supervised strengthening exercise (neck and upper body strengthening), to high dose supervised strengthening exercise alone, and low dose home exercise and advice for chronic NP patients. There were clinically relevant improvements at 12 weeks for both high dose exercise

groups for pain and overall health improvement ( $p < 0.001$ ) in comparison to home exercise and a trend for disability for MT1 combined with exercise against home exercise. The authors concluded that high dose exercise combined or not with MT1 gained better outcomes than home exercise particularly in the medium-term (3 months).

Akhter et al. [27] investigated the role of MT1 (HVLA on the stiff Cx segments for around 6 sessions over 3 weeks) combined with supervised exercise (flexibility, strengthening of the cervical and scapular muscles and CROM exercise) in comparison to supervised exercise regime alone for chronic NP patients. At the end of 3 weeks interventions both groups were instructed to do the same exercise for a period of 3 months on a daily basis. Both groups made significant improvement in pain and functional outcome measures ( $p < 0.001$ ) over 3 and 12 weeks' time period in relation to baseline. However, between groups analysis showed no significant differences at all time points for both outcome measures ( $p > 0.05$ ). Adverse events were reported for one subject with episode of dizziness, he was excluded from the study. Authors concluded that both groups made significant improvements and that on closer inspection MT1 with exercise appeared as a favourable treatment preference (a better trend of improvements) compared to exercise alone.

The general trend of these three studies [7,27,55] was that combined MT1 and MT3 on the Cx and Tx with exercise demonstrated better results for pain, function, satisfaction with care and general health in comparison to exercise or MT alone for patients with chronic NP.

#### 4. Discussion

The goal of this SR was to assess and update the best evidence by including only low-risk of bias RCTs reporting on the effectiveness of different MT approaches, classified into 4 categories (MT1-MT4), in the management of NP without associated disorders such as cervicogenic headache or radiculopathy. Efficacy for MT1-4 interventions was assessed in isolation or when combined with exercise or UMC.

With respect to acute/sub-acute NP this review found moderate evidence in favour of (i) MT1 at the involved Cx level combined with exercise when compared to MT1 to the Tx combined with exercise [42]; (ii) MT3 (Tx HVLA + Cx accessory mobilization) combined with exercise compared to MT2 (Cx ac-

cessory mobilization) with exercise [49]; (iii) MT1 to the upper Tx combined with electro/thermal-therapy in comparison to electro/thermal-therapy alone, for pain relief and functional improvement in the very short to short-term; (iv) MT3 to the Cx and Tx or home exercise in comparison to UMC for pain and satisfaction with care from short to long-term [26,46]; (v) MT2 (STT) comprising muscular-MET, trigger-points (ischemic compression), and positional-release (tender-points) techniques to the trapezius compared to MT2 (STT) using only muscular-MET to the trapezius for pain, function and CROM in the very short-term [15].

This review found moderate evidence of no difference in efficacy between MT2, comparing trigger point therapy to SUS [44,45]. In addition there was limited evidence of no difference in efficacy between MT2 (Cx accessory mobilization) with exercise in comparison to MT4 (Cx SNAGs) combined with exercise in comparison to exercise alone on pain, disability and CROM [50].

With respect to chronic NP this review found strong evidence of no difference in efficacy for MT2 when comparing Cx accessory mobilization at the symptomatic level to the asymptomatic level for pain and function [19,53,54]. Moderate to strong evidence was found in favour of MT1 and MT3 at the Cx and Tx combined with exercise in comparison to exercise or MT alone for pain, function, satisfaction with care and general health at least in the short- to moderate-terms [7,27,55]. Moderate evidence was found in favour (i) of MT1 compared to MT2 (Cx accessory mobilization) and MT4 (Cx SNAGs), for CROM [49] and pain [50] in the very short-term; (ii) of MT2 (STT to the Cx and Tx) [5] and MT3 to the Cx and Tx [11] in comparison to no-treatment (self-care booklet or SUS), in the short-term for pain and disability [5]; (iii) of MT1 to the Tx with IRT and exercise as compared to IRT and exercises alone for pain, function, overall-health and CROM in the short to moderate-term [8]. Moderate evidence was found of no difference (i) between MT1 to the Cx and Cx-Tx in comparison to Kinésio-Tape applied to the neck region for pain, disability and CROM in the very short-term [51]; (ii) between MT1 to the Cx in comparison to MT1 to the Tx for pain, CROM and pressure pain threshold at the very short-term [52].

The evidence from this current SR is consistent with evidence provided from previous systematic reviews [4,23,56] reporting on the efficacy of MT for NP. However, the current review provides new evidence in this regard, as well as improves understanding of the

Table 3

Summary findings for MT1-4 combined or not with exercise and/or usual medical care for neck pain. Strength of new evidence is shown in italic text. Upgrade of previous evidence is shown in classical text [4,23,56]

For acute/subacute neck pain		
Categories of MT interventions vs comparison group	Quality of evidence (A high; B moderate)	Strength of evidence for interventions
MT1-upper Cx with Exercise vs MT1-Tx with Exercise	1 RCT, Level A, <i>n</i> = 24 Puentedura et al. [42]	<i>MODERATE evidence in favor of MT1-Cx with Exercise in comparison to MT1-Tx with Exercise</i> for pain and function at very short, short term and intermediate-term (6 months)
MT1-Tx with Electro/thermal therapy vs electro thermal therapy alone	2 RCT, Level A, <i>n</i> = 90 Gonzalez-Iglesias et al. [1,43]	MODERATE evidence in favor of MT1 combined with electro/thermal therapy in comparison to electro/thermal therapy alone for pain and function at very short- and short term
MT2 (STT: MET + trigger and tender points on trapezius) vs MT2 (only MET on trapezius)	1 RCT, Level A, <i>n</i> = 60 Nagrle et al. [15]	<i>MODERATE evidence in favor of MT2 using MET combined with trigger and tender points in comparison to MET alone</i> for pain and function at short term
MT2 (trigger points therapy) vs SUS	2 RCT, Level A, <i>n</i> = 90 Blikstad and Gemmell [44] Gemmell et al. [45]	MODERATE evidence of no difference between MT2 using trigger points and SUS for pain and function at very short term
MT3 (MT1-Tx and MT2-Cx) with Exercise vs MT2-Cx (accessory mobilization) with Exercise	1 RCT, level A, <i>n</i> = 64 Masaracchio et al. [48]	<i>MODERATE evidence in favor of MT3 with Exercise in comparison of MT2 (accessory mobilization) with Exercises alone</i> for pain and function at short term
MT3 on Cx-Tx and home Exercise vs UMC	2 RCT, level A, <i>n</i> = 272 Bronfort et al. [46] Leininger et al. [26]	MODERATE evidence in favor of MT3 and home Exercise groups in comparison of UMC for pain and satisfaction with care at post treatment, short and intermediate term
MT2-Cx (accessory mobilization) with Exercise vs MT4-Cx (SNAGs) with Exercise vs Exercise alone	1 RCT, level B, <i>n</i> = 80 Ganesh et al. [25]	<i>LIMITED evidence of no difference of efficacy between groups</i> on pain and function
For chronic neck pain		
Categories of MT interventions vs. comparison group	Quality of evidence (A high; B moderate)	Strength of evidence for interventions
MT1-Cx vs MT2-Cx (accessory mobilization) vs MT4-Cx (SNAGs)	1 RCT Level A, <i>n</i> = 61 Izquierdo-Pérez et al. [49]	<i>MODERATE evidence in favor of MT1 in comparison to MT4 for active CROM in extension</i> , immediately after treatment and during the 3 months follow-up <i>MODERATE evidence of no difference of efficacy</i> for all other outcome measures (pain, function) between groups
MT1-Cx vs MT2-Cx (accessory mobilization) vs MT4-Cx	1 RCT Level A, <i>n</i> = 48 Lopez et al. [50]	<i>MODERATE evidence in favor of MT1 and MT2 in comparison to MT4</i> only for pain at rest just after interventions <i>MODERATE evidence of no difference between groups</i> on all other outcome measures (pain and function)
MT1-Cx vs MT1-Tx	1 RCT Level A, <i>n</i> = 90 Martinez-Segura et al. [52]	<i>MODERATE evidence of no difference</i> between groups for pain, CROM and PPT
MT1 on Cx-Tx vs Kinésiotape	1 RCT Level A, <i>n</i> = 80 Saavedra-Hernandez et al. [51]	<i>MODERATE evidence in favor of MT1 only for CROM rotations</i> MODERATE evidence of no difference between groups on pain and function
MT3 on Cx-Tx with Sham electrotherapy vs MT3 with Exercise vs MedX (high dose of exercise with specific devices)	1 RCT Level A, <i>n</i> = 191 Bronfort et al. [7]	MODERATE evidence in favor of MT3 with Exercise and MedX groups in comparison to MT3 alone for pain and function at long term.
MT1-Tx with IRR and home Exercise vs IRR and home Exercise	1 RCT Level A, <i>n</i> = 120 Lau et al. [8]	MODERATE evidence in favor of MT1 with IRR and home Exercise for pain, disability, overall improvement and function for immediately post treatment which remained up to 6-months
MT1 on Cx-Tx with Exercise vs high dose of Exercise vs. HEA	1 RCT Level A, <i>n</i> = 270 Evans et al. [55]	MODERATE evidence in favor of MT1 with Exercise and high dose of Exercise groups in comparison to HEA group for pain, satisfaction and global perceived effect at 12 weeks
MT2-Cx (accessory mobilization) on symptomatic level(s) vs MT2-Cx (accessory mobilization) on random and/or asymptomatic level(s)	3 RCT level A, <i>n</i> = 234 Kanlayanaphotporn et al. [53]; Aquino et al. [19] and Schomacher et al. [54]	<i>STRONG evidence of no difference</i> between groups for pain and function

Table 3, continued

Categories of MT interventions vs comparison group	Quality of evidence (A high; B moderate)	Strength of evidence for interventions
MT3 with SUS vs “no treatment” (SUS only)	1 RCT Level A, <i>n</i> = 41 Schwerla et al. [11]	MODERATE evidence in favor of MT3 in comparison to “no treatment” for pain, overall improvement at the end of treatment and function at 3 months
MT2 with STT on the C-Tx vs “no treatment” (only self-care booklet)	1 RCT Level A, <i>n</i> = 64 Sherman et al. [5]	MODERATE evidence in favor of MT2 in comparison to “no treatment” for pain and function at 4 weeks of treatment
MT1-cx with Exercise vs. Exercise alone	1 RCT level B, <i>n</i> = 62 Akhter et al. [27]	LIMITED evidence of no difference between groups on all outcome measures (pain and function).

MT: manual therapy; MT1: HVLA thrust; MT2: accessory an physiological mobilization and/or soft-tissue-techniques (STT) and/or muscle energy technique (MET); MT3: MT1 + MT2; MT4: Mulligan's sustained natural apophyseal glides (SNAGs) to Cx. UMC: usual medical care; Cx: cervical spine; Tx: thoracic spine; SUS: sham ultrasound; IRR: infrared radiation; HEA: home exercise and advise; Exercise: specific and/or general exercise; PPT: pressure pain threshold.

levels of evidence for manual therapists. Due to the very large body of evidence regarding MT for NP, and the inability to present all this information in a single paper, we focused on RCT's with low-risk of bias that would update and improve on previous reviews. This new evidence and confirmation of previous reviews can be seen in summary in Table 3.

This review provides manual therapists with information about treatment efficacy covering a wide range of commonly used MT in everyday clinical practice. Rather than combining all MT into a single comparison group we sub-categorized MT into 4 distinct groups combined or not with exercise. This enables the reader to better understand the evidence for different forms of MT and whether the addition of exercise improves treatment efficacy.

#### 4.1. Adverse events

In addition to understanding the evidence for the efficacy of MT it is important to recognize any potential risks associated with MT intervention. This is particularly true for the cervical spine, which has a special vulnerability due to its unique anatomy and proximity to the brain. In the literature, MT to the cervical spine is often associated with adverse events particularly with regard to HVLA thrust techniques. Adverse events are important, not only from a morbidity/injury perspective, but also in terms of patient satisfaction and perception of improvement following treatment, which might be decreased in patients who experience adverse events [57]. In general however, there is a lack of consensus in reports of RCT's regarding the classification and definition of adverse events following interventions. When adverse events have been reported we have described these adverse events for each included study in the result section. Future studies

should follow more rigorous and standardized methods to allow more effective comparisons [58–65].

Clearly, a way to prevent adverse events is not to perform cervical manipulation, and perhaps manipulate the thoracic spine instead. It is suggested that thoracic manipulation may have some efficacy in the treatment of neck pain [4]. However, there is moderate evidence favouring cervical over thoracic manipulation for acute NP [42]. Combining cervical mobilization with thoracic manipulation may be one way to bypass the risks involved with certain cervical techniques and also improve treatment efficacy [48]. In chronic NP, although moderate evidence was found in favour of cervical manipulation when compared to accessory mobilization or SNAGs to the cervical spine [49,50], reported differences were marginal for Cx extension ROM only as well as pain at rest. Furthermore, there is moderate evidence of no difference between cervical and thoracic spinal manipulation at least in terms of immediate effects [52]. Hence, it is important to assess whether such small marginal improvements in outcome favouring Cx manipulation can be justified against the risks involved. Due to the rarity of serious adverse events following cervical MT techniques [66], it is virtually impossible to clearly identify the risk benefit analysis of Cx manipulation. Further investigation is required to compare a cervical and thoracic spine treatment approach against cervical manipulation alone, as well as the long-term effects. Meanwhile, we recommend the guidelines from a consensus of experts (<http://www.ifompt.org>) for cervical spine screening along with the evidence from this SR before applying HVLA thrust techniques to the Cx for patients with NP.

#### 4.2. NP classification

To our knowledge, and in contrast to LBP, there are no recommended or validated classification systems to

stratify NP and to target specific subgroups with OMT treatment formulated for each subgroup. Classification of patients with LBP into sub-groups and the application of specific OMT interventions for each matched sub-group has proved to be more effective than generic forms of treatment [67–71]. Consequently, stratified care for LBP is becoming a dominant topic in research and clinical practice [20,68,71].

Due to the lack of classification systems for NP, the treatment decision to apply a specific form of MT (MT1-4) and/or exercise is mainly based on clinical reasoning, which must include the subjective and physical examination. Firstly, the subjective examination should help to identify and exclude people with psychosocial issues (yellow flags) and serious spinal pathologies (red flags) [69]. Secondly, the dominant pain mechanism should be identified, and can be broadly divided into three categories. These categories are the “input mechanisms” corresponding to nociceptive pain and peripheral neuropathic pain; the “processing mechanism” defined as centrally maintained pain associated with central sensitization, and the cognitive-affective mechanisms of pain; the “output mechanisms” include the autonomic, motor, neuroendocrine and immune systems [69–71]. Thirdly, therapeutic goals and OMT treatment options can be determined from the integration of the subjective and physical examination [69–71].

## 5. Limitations

The results of our qualitative SR should be interpreted in the light of some limitations. First, although only low-risk of bias RCTs were included, there was much heterogeneity among trials; including the way the trial data was presented, the patients, comparison (control) groups (and co-interventions), outcomes measures, and studies’ design, as well as the report of adverse events. Secondly to identify which MT intervention should be evaluated, we used an original and comprehensive classification system in accordance with a comprehensive analysis of the literature as well as with clinical practice of MT. This classification system was used in a previous SR of MT for low back pain [20]. However, there is currently no ideal classification of MT techniques as MT is broad by nature. The MT2 category may be seen as the weakest category in this classification system, as it comprises a very wide range of mobilization techniques as well as articular MET and/or STT. For this reason we described throughout the text and tables the specific interventions

used in RCTs investigating MT2; attempting to improve understanding of the efficacy of this MT approach for NP. Due to the heterogeneity among trials, a meta-analysis enabling pooled statistics of effect was not possible. Thirdly, some studies used adjuvant therapy in both intervention and comparison groups which create difficulties to evaluate objectively the intrinsic efficacy of MT. Finally, only studies published in English from 1<sup>st</sup> January 2000 to 31<sup>st</sup> December 2015 were reviewed, leading to the possibility of relevant articles existing in other languages or before 2000.

## 6. Conclusion

This SR has confirmed previous evidence and increased levels of confidence regarding efficacy of MT for NP. The clinical implications of this evidence can be broadly summarized to a number of points. Firstly, in general it can be seen that combining different forms of MT with exercise is better than MT or exercise alone. Secondly, there is moderate to strong evidence in favor of MT1 or MT3 combined with exercise for improvement in pain, function, and satisfaction with care for patients with NP when compared to UMC, exercise alone, MT alone or to no treatment. Thirdly, there is strong evidence that for chronic NP mobilization need not be applied at the symptomatic level for improvement in pain and function. This may have implications for reducing the risk involved with some MT techniques applied to the Cx as well as to choose the level(s) of Cx treatment in function of the irritability state of the patient. Fourthly, there is moderate evidence that in general MT1, MT2 and MT4 have similar effects on NP. Since intuitively Cx manipulation carries greater risk than mobilization or MWM these interventions could be seen as a viable option to manage NP together with exercise and in combination with Tx MT1. Future RCTs should be more rigorous in their investigation by not mixing categories of patients as well as intervention types.

## Conflict of interest

None to report.

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## Appendix 1

Classification of outcome measures and Cochrane Collaboration Back Review Group (CCBRG) Levels of evidence for evaluating interventions [24,30]

Outcome measures	Validated assessment tools
Pain	Visual analogue scale (VAS) and numerical-pain-rating-scale (NPRS) pressure pain thresholds (PPT)
Functional disabilities	Neck-Disability-Index (NDI), Fear-Avoidance-Belief-Questionnaire (FABQ), the Northwick-Neck-Pain-Questionnaire (NPQ), the cervical-Range-Of-Motion (CROM)
Overall-health improvement	Short-form-health-survey (SF-36)
Quality of life	Adverse events
Overall level of evidence	Conditions description
Strong	Consistent findings from multiple high quality trials (level A) ( $n \geq 3$ )
Moderate	Consistent findings among multiple moderate quality (level B) and/or one level A
Limited	One level B
Conflicting	Inconsistent findings among multiple trials
No evidence	No trials
Search strategy in MEDLINE	"Manual-Therapy" was used as a free-term in MeSH (MEDLINE). "Musculoskeletal-Manipulations" was the result of the MeSH heading terms, we added "Neck-Pain" to the MEDLINE search box as follows: "Musculoskeletal-Manipulation" [Mesh] and "Neck-Pain" [Mesh] and ("human" [MeSH-Terms] and ("male" [MeSH-Terms] or "female" [MeSH-Terms]) and Randomized-Controlled-Trial [ptyp] and English [lang] and "adult" [MeSH-Terms] and "2000/01/01" [PDat]: "2015/12/31"[PDat])

## Risk of bias assessment

Criteria list for methodological quality assessment from Cochrane Collaboration Back Review Group

- A: Was the method of randomization adequate? Yes/ No/Don't know.
- B: Was the treatment allocation concealed? Yes/No/ Don't know.
- C: Were the groups similar at baseline regarding the most important prognostic indicators? Yes/No/ Don't know.
- D: Was the patient blinded to the intervention? Yes/No/Don't know.
- E: Was the care provider blinded to the intervention? Yes/No/Don't know.
- F: Was the outcome assessor blinded to the intervention? Yes/No/Don't know.
- G: Were cointerventions avoided or similar? Yes/ No/Don't know.
- H: Was the compliance acceptable in all groups? Yes/No/Don't know.
- I: Was the dropout rate described and acceptable? Yes/No/Don't know.
- J: Was the timing of the outcome assessment in all groups similar? Yes/No/Don't know.
- K: Did the analysis include an intention-to-treat analysis? Yes/No/Don't know.

## Operationalization of the criteria list

- A: A random (unpredictable) assignment sequence. Examples of adequate methods are computer generated random number table and use of sealed opaque envelopes. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.
- B: Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.
- C: In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurologic symptoms, and value of main outcome measure(s).
- D: The reviewer determines if enough information about the blinding is given in order to score a "yes".

- E: The reviewer determines if enough information about the blinding is given in order to score a “yes”.
- F: The reviewer determines if enough information about the blinding is given in order to score a “yes”.
- G: Cointerventions should either be avoided in the trial design or similar between the index and control groups.
- H: The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s).
- I: The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and dropouts does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a “yes” is scored. (N.B. these percentages are arbitrary, not supported by literature).
- J: Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.
- K: All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.

## Appendix 2

Studies that only confirmed previous evidence (not included in Table 3) (1) and studies that have been excluded from the SR (2)

(1) Authors, journals and quality score of included studies that confirmed previous evidences

Llamas-Ramos et al. 2014	Level B (7/11 cochrane-list)	Madson et al. 2012	Level B (8/11 cochrane-list)
Salom-Moreno et al. 2014	Level B (8/11 cochrane-list)	Leaver et al. 2010	Level B (8/11 cochrane-list)
Saavedra-Hernandez et al. 2013	Level A (9/11 cochrane-list)	Cleland et al. 2007	Level B (8/11 cochrane-list)
Suvarnato et al. 2013	Level B (8/11 cochrane-list)	Dziedzic et al. 2005	Level A (9/11 cochrane-list)
Saayman et al. 2011	Level B (8/11 cochrane-list)		

(2) Authors, journals and quantitative and/or qualitative criteria for reason of exclusion

Beltran-Alacreu et al. 2015	6/11 cochrane-list	Zaproudina et al. 2007	5/11 cochrane-list
Snodgrass et al. 2014	Mixed population	Ylinen et al. 2007	6/11 cochrane-list
Lluch et al. 2014	Mixed population	Martinez-Segura 2006	Mixed population
Vernon et al. 2013	Mixed population	Hoving et al. 2006	Mixed population
Dunning et al. 2012	Mixed population + mixed states	Palmgren et al. 2006	5/11 cochrane-list
Martel et al. 2011	Mixed states	Cleland et al. 2005	Mixed population
Escortell-Mayor et al. 2011	Mixed population	McReynolds et al. 2005	6/11 cochrane-list
Boyles et al. 2010	Mixed population	Evans et al. 2003	Mixed states
Groeneweg et al. 2010	Mixed population	Hurwitz et al. 2002	Mixed population
Kanlayana-photporn et al. 2010	Mixed population	Hoving et al. 2002	Mixed population
Mansilla-Ferragut et al. 2009	5/11 cochrane-list	Wood et al. 2001	Mixed population
Strunk et al. 2009	Mixed population	Van Schalkwyk et al. 2000	Mixed population
Walker et al. 2008	Mixed population + mixed states	Hanten et al. 2000	Mixed population
Häkkinen et al. 2007	Mixed population	Ali A et al. 2014	6/11 cochrane-list and mixed population

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