ULTRASOUND AS AN ADJUVANT TREATMENT FOR NON-SPECIFIC NECK PAIN

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Lay Abstract

Ultrasound therapy is widely used with exercise or manual therapy for the treatment of neck pain. Yet, its benefits are not clear. This review looked at the benefits of ultrasound added to exercise, manual therapy or both for the treatment of neck pain. The review contains six studies with 361 participants who suffered from neck pain. The results showed very low quality evidence. Applying capsaicin cream with ultrasound or continuous ultrasound in conjunction with exercise had some benefit for improving pain. The same treatment did not improve function as compared to exercise alone. There was no benefit in improving pain or function by adding continuous or high power ultrasound to manual therapy and exercise compared to manual therapy and exercise alone. Due to very low quality evidence, we are uncertain of whether there is a benefit to adding ultrasound to exercise or/and manual therapy for treatment of neck pain.

Abstract

Rationale: The use of ultrasound as an adjuvant to conservative treatment for neck pain is common, but the evidence of its benefit remains unclear.

Objective: To determine the effectiveness of ultrasound as an adjuvant to exercise or/and manual therapy for the improvement of patient-centered outcomes in adults with non-specific neck pain.

Methods: Electronic databases including MEDLINE, EMBASE, AMED, CINAHL, CENTRAL, PEDro and PubMed were searched from date of inception to March 2019 for controlled trials involving ultrasound or phonophoresis as an adjuvant to exercise or/and manual therapy in adults with non-specific neck pain. Review Manager 5.3 was used to calculate mean group differences.

Main results: Six studies (361 participants) examining ultrasound or phonophoresis as an adjuvant to exercise or/and manual therapy for sub-acute and chronic non-specific neck pain were included. The quality of evidence was of very low GRADE. Phonophoresis with capsaicin plus exercise improved pain immediately post-treatment (MD -3.30, 95% CI: -4.05 to -2.55) but not with diclofenac sodium plus exercise as compared to exercise alone. Continuous ultrasound plus exercise improved pain and Pressure Pain Threshold (PPT) at immediate post-treatment (pain: MD -3.42, 95% CI: -4.08 to -2.7; PPT: MD 0.91, 95% CI: 0.68 to 1.14) and at intermediate - term (pain: MD -2.70 95% CI: -3.62 to -1.78; PPT: MD 0.27 95% CI: 0.03 to 0.51) as compared to exercise alone. Continuous ultrasound or High Power Pain Threshold (HPPT) ultrasound plus manual therapy and exercise showed no benefit for pain reduction (MD -0.75, 95% CI: -2.08 to 0.58), increase in PPT (MD -1.15, 95% CI: -2.55 to 0.25) or improved function/disability

(MD -1.05, 95% CI: -4.27 to 2.17) at immediate or short-term as compared to manual therapy and exercise.

Conclusion: Based on very low quality evidence, there is insufficient data to support ultrasound or phonophoresis as an adjuvant treatment for non-specific neck pain.

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List of Abbreviations

NSNP:	Non-specific neck pain Neck pain
VAS:	Visual Analogue Scale
NRS:	Numerical Rating Scale
NPRS:	Numeric Pain Rating Scale
NDI:	Neck Disability Index
NPAD:	Neck Pain and Disability scale
QoL:	Quality of Life
PPT:	Pressure Pain Threshold
MPS:	Myofascial Pain Syndrome
HPPTUS:	High - power Pain Threshold Ultrasound
MT:	Manual Therapy
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
GRADE:	Grading of Recommendations, Assessment, Development and Evaluation
AMSTAR:	A MeaSurement Tool to Assess systematic Reviews
QTFC:	Quebec Task Force Classification
IFOMPT:	International Federation of Orthopedic Manipulative Physical Therapists
HVLA:	High Velocity and Low Amplitude Thrust Manipulation
ICF:	International Classification of Function, Disability and Health
COG:	Cervical Overview Group
CBNG:	Cochrane Back and Neck Group
PROSPERO:	International Prospective Register of Systematic Reviews

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Chapter 1

1 Introduction

Neck pain is a common musculoskeletal disorder in adults and a major cause of impairment and disability (Vitor et al., 2017). Neck pain had been identified as the fourth leading cause of disability worldwide and is considered a major public health issue, which affects physical, psychological, and overall well-being. (Cohen, 2015; Ehsani, Mosallanezhad, & Vahedi, 2017; Vitor et al., 2017; Vos et al., 2014). Neck pain also results in a substantial socioeconomic burden escalating the cost to society and contributing to loss of work productivity (Cohen, 2015; Ehsani et al., 2017; Vitor et al., 2017). Approximately two-thirds of the population will experience neck pain at some point in their lifetime (Binder, 2008). Several studies reported annual prevalence rates of neck pain ranging from 15% to 50% (Binder, 2008; Cohen, 2015; Hoy, Protani, De, & Buchbinder, 2010a; Kyvik & Hartvigsen, 2006). Furthermore, contrary to traditional beliefs, signs and symptoms of neck pain do not resolve on their own in a relatively high proportion of individuals. A study which followed neck pain participants over 12 months reported that 36.6% of individuals who experienced neck pain had a complete recovery from signs and symptoms of neck pain while 32.7% reported significant reduction in their symptoms. However, 37.3% reported having no change, and 9.9% had aggravated sign and symptoms (Côté, Cassidy, Carroll, & Kristman, 2004). Moreover, studies suggest that the prevalence of neck pain will grow significantly in the coming decades as sedentary work positions rise and the ageing population of low and medium income countries increase (Vitor et al., 2017).

Therefore, considering the burden of neck disorders to individuals and society, and the fact that the vast majority of neck pain is managed conservatively including physiotherapy, it is imperative that the intervention strategies for neck pain be based on evidence-based decisions

(Hall, McIntosh, Alleyne, & Cote, 2015). Thus, understanding how to effectively manage the impairment and disability associated with neck pain is an important area of study that could have an impact on individual and societal outcomes.

1.1 Diagnosis and classification of neck pain

Neck pain is an episodic disorder marked with remission and exacerbation (Côté et al., 2004). A specific underlying cause of neck pain can rarely be identified (Blanpied et al., 2017). Fortunately, neck pain does not usually involve the presence of serious pathology and a vast majority of neck pain is believed to be mechanical in nature (Hall et al., 2015). Mechanical neck pain is thought to arise from several anatomical structures in the cervical region including muscles, ligaments, vertebrae, intervertebral disc and neural structures (Blanpied et al., 2017; Hall et al., 2015). In addition, it is believed that the causes of neck pain are multifactorial, which makes neck pain a complex disorder to manage.

To address these complex neck disorders, researchers have proposed several neck pain diagnostic classification systems. Classifying neck pain can help to organize a large entity into similar subgroups of participants, guide the selection of the most effective interventions strategies and help determine the prognosis (Childs, Fritz, Piva, & Whitman, 2004). Furthermore, classification can also help organize and understand existing knowledge on neck pain (Guzman et al., 2009).

Neck pain classification systems involve both diagnostic and treatment specific classification. Some of the well-known proposed classifications include grade 0 to 4 proposed by The Quebec Task Force on Whiplash-Associated Disorders and grade I to IV proposed by the Task Force on Neck Pain and Its Associated Disorders (Guzman et al., 2009). Other proposed neck pain

classification systems include that of Fritz & Brennan (2007) who categorized neck pain into four categories linked to a treatment-based model. One of the widely used and recognized classifications is the Mechanical Diagnosis and Therapy (MDT) also known as the McKenzie approach which classifies participants into three categories; derangement, dysfunction or postural syndrome (Clare, Adams, & Maher, 2003).

Although some of the abovementioned classifications appear to be popular, the benefits of their use in clinical decision making may be limited. Studies that examined the efficacy of various neck pain classification systems failed to establish the clinical benefit of their use (Takasaki & May, 2014). A recent 2017 clinical practice guideline proposed a classification system that appears to offer some benefit in clinical decision making. The classification proposed a model for examination, diagnosis and management for neck pain which included four components that were based on medical screening, clinical evaluation of musculoskeletal impairments and pathology, determination of duration stage, and intervention strategies (Blanpied et al., 2017). However, there are no studies that have investigated the abovementioned classification system and its benefit in clinical decision making remains unclear. It is worth noting that there has been a constant shift and increased attempt to categorize and organize neck pain over the last two decades.

1.2 Risk factors

Understanding the risk factors for neck pain is not only the best means for reduction of neck pain burden but could be crucial in planning preventative measures. For example, when an individual working in a poor ergonomic workplace experiences neck pain, the intervention strategies might need to consider modifying the workplace. Risk factors can be categorized into two types, such as nonmodifiable and modifiable factors. While nonmodifiable risk factors cannot

be changed, modifiable factors can be reduced or eliminated. Studies have identified numerous nonmodifiable and modifiable risk factors for neck pain. Nonmodifiable risk factors include individual characteristics (genetics, female sex, age), while modifiable factors involve psychosocial (poor coping skills, catastrophizing, anxiety, low work satisfaction), occupation (poor physical work environment, repetitive movements, awkward body postures, work demand) and behavior (sedentary lifestyle, smoking) (Cohen, 2015; Langenfeld, Humphreys, Swanenburg, & Peterson, 2015; Vitor et al., 2017). Furthermore, neck pain is associated with comorbidities such as back pain, headache and arthralgias (Cohen, 2015). In the USA, the highest incidences of neck disorders are reported in office and computer workers (57%) (Hoy, Protani, De, & Buchbinder, 2010). Those in occupations involving the use of computers were identified at high-risk of developing neck pain with an annual prevalence rate of up to 45.8% and lifetime prevalence of 62.1% (Ehsani et al., 2017). Athletes are more likely to experience neck pain with a one-year prevalence rate of up to 73% and a lifetime prevalence of 48% (Noormohammadpour, Farahbakhsh, Farahbakhsh, & Kordil, 2018). Other important risk factors include low job satisfaction and poor workplace environment. (Cohen, 2015)

1.3 Prognosis of neck pain

Knowledge of prognostic factors associated with neck pain is vital for patient management and clinical decision making. Recognizing prognostic factors for neck pain can provide insight into the pathophysiology and natural course of the disease. For example, in individuals experiencing neck pain with positive prognostic factors, modest advice and patient education can be effective in resolving the signs and symptoms (Walton et al., 2013). However, for those presenting with poor prognostic factors, a detailed evaluation and intensive intervention may be

required (Walton et al., 2013). Furthermore, prognostic factors can guide appropriate intervention strategies for individuals experiencing neck pain. Understanding prognostic factors can be also useful in informing participants and families on the risk of reoccurrence of neck pain.

Several prognostic factors for development of persistent neck pain have been identified. Some of these factors include age, sex, prior history of neck pain, radiating pain into arms and coexisting psychosocial disorder (Cohen, 2015). Women are more likely to experience neck pain than men and have a higher incidence of persistent neck pain with a poorer rate of recovery than men (Côté et al., 2004). Being over the age of 46 years and having a prior history of neck pain is associated with poor prognosis and could be a valuable factor to predict a relapse of neck pain within one year (Côté et al., 2004; Langenfeld et al., 2015). Furthermore, chronic neck pain which presents as a "widespread sensation with hyperalgesia in the skin, ligaments and muscles on palpation and both passive and active movement" (Ylinen, 2007, p.119) lasting more than 90 days is associated with poor prognosis (Cohen, 2015). Several other factors including degenerative changes, genetic factors and workplace compensation policies, are believed to be associated with poor prognosis of neck pain (Carroll et al., 2010). Studies examining the natural history of neck pain and the transition from an acute to chronic condition are scarce. However, the role of psychological factors including stress, anxiety, emotions, mood and cognitive function have been identified as important variables in the onset of acute neck pain and critical to the transition of acute neck pain into chronic neck pain (Linton, 2000). Factors that predict better prognosis in neck pain include younger age, stable mental health, being optimistic, greater social support and better coping strategies (Carroll et al., 2010).

1.4 Current practice in the management of neck pain and clinical experience

Currently, there is no standardized intervention for management of neck pain although there are several clinical practice guidelines available (Bier et al., 2017; Blanpied et al., 2017). The current treatment strategies involve diverse practice. The nature and complexity of neck pain make the management of neck pain difficult and requires multifaceted intervention strategies to treat neck pain effectively.

Therapeutic ultrasound is a commonly used therapeutic modality to treat various conditions, including neck pain and other musculoskeletal disorders. Although ultrasound has been used for more than seven decades, there is no high level evidence to support its effectiveness. The mechanism on how ultrasound induces physiological and therapeutic effects has been studied only in animals and in-vitro and studies have reported that the effects observed may not occur in live individuals (Baker, Robertson, & Duck, 2001). Nevertheless, in Bhutan, a vast majority of the physiotherapy interventions for musculoskeletal disorders, including neck pain, involve use of some electrotherapy modalities, including ultrasound. Physiotherapy and rehabilitation services have grown significantly and expanded across the country since it was introduced in Bhutan at the Jigme Dorji Wangchuk National Referral Hospital (JDWNRH) by an expatriate physiotherapist in mid-1980s. Currently, there are more than a dozen qualified physiotherapists and eighty physiotherapy assistants working across the country. However, the lack of knowledge to critically appraise research studies and also lack of resources including latest edition textbooks and access to journals makes it challenging to navigate from clinical practice which is based on traditional beliefs rather than evidence.

In Bhutan, the leaders and educators in the physiotherapy profession have historically promoted the use of electrotherapy modalities, including ultrasound. For example, the students

pursuing physiotherapy assistant programs spend a significant amount of time learning about electrotherapy modalities. Moreover, the Royal Government of Bhutan, on the recommendation of the physiotherapy department, spends large sums of money in procuring and maintaining electrotherapy, including ultrasound machines. Modern health care practices emphasize evidence-based practice, and physiotherapy services in Bhutan should evolve towards evidence-based practice. Physiotherapy services in Bhutan are an essential part of the Bhutanese health care system and have a broad scope of practice. Therefore, it is imperative that clinical decisions be supported by high level evidence to maximize healthcare outcomes and reduce health care cost.

1.5 Study Objective

The unprecedented transformation in delivery of health care around the world, and emphasis on evidence-based practice to transform and equip health care professions to make better clinical decisions and improve patient outcomes, inspired and motivated me to conduct this systematic review.

The objective of this research was to conduct a systematic review to examine the effectiveness of ultrasound therapy as an adjuvant to exercise, manual therapy or exercise and manual therapy for the management of non-specific neck pain.

The results from this systematic review will provide important insight into the effectiveness of ultrasound as an adjuvant treatment for improving patient-related outcomes, including pain and function. Furthermore, the results of this systematic review might help persuade physiotherapists in Bhutan to reflect on their clinical decision making and incorporate evidence in their practice.

1.6 Thesis overview

This thesis is written in a traditional-format and has five chapters. The chapters include Chapter 1; Introduction, Chapter 2; Literature Review, Chapter 3; Research Methodology, Chapter 4; Results, Chapter 5; Discussion and Conclusion. Chapter 1 includes a brief background of neck pain, including the importance and challenges of managing neck pain. The chapter also reflects on my clinical experience and objectives of the research study. Chapter 2 provides a literature review on neck pain. The chapter contains critically reviewed studies including diagnostic classification of neck pain and benefits of ultrasound, manual therapy and exercise therapy in the management of neck pain. Chapter 3 describes the research methodology. It contains details on the inclusion and exclusion criteria of the studies, assessment of the quality of studies and methods of statistical analysis. Chapter 4 describes quantitative findings and provides a qualitative summary of the study. Chapter 5 discusses the study findings in relation to available literature that examined the effectiveness of ultrasound in the management of neck pain. The chapter also describes clinical and research implications along with challenges, limitations and strengths of the study. It concludes with knowledge translation intervention strategies and provides a conclusive summary of the study.

Chapter 2

2 Literature Review

A significant proportion of the population with neck pain is managed conservatively. In physiotherapy practice this usually involves utilization of a range of interventions such as exercise, manual therapy, ergonomics, and application of electrotherapy modalities and therapeutic ultrasound (Vos, Verhagen, Passchier, & Koes, 2007). Nevertheless, the evidence on the effectiveness of conservative treatments for neck pain is often conflicting and inconclusive (Hurwitz et al., 2009). This chapter critically appraises and synthesizes the research findings on conservative management for neck disorders. The aim of this literature review is to provide a comprehensive summary of current best practice of conservative management for neck pain focusing on manual therapy, exercise therapy and therapeutic ultrasound interventions.

2.1 Burden, Prevalence and Incidence of Disease

Inactivity, sedentary lifestyle, prolonged use of computers, performing repetitive tasks, high stress and awkward working positions are risk factors for developing neck pain (Côté et al., 2008; Jun, Zoe, Johnston, & O'Leary, 2017; Nunley et al., 2012). There is substantial evidence that shows a significant economic burden on both the individual with neck pain and their employer due to the costs associated with treatment, work absenteeism and reduced productivity (Côté et al., 2008; Hogg-Johnson et al., 2000; Hoy et al., 2010). The available study on the burden of neck pain in workers in Canada was published in July 2009, and reported the annual prevalence of neck pain in Quebec to be 47.8% (Côté et al., 2008). Studies have shown that office and computer workers have a higher prevalence (18-63%) and incidence (34-49%) rate of neck pain compared to other

occupations (Côté et al., 2004, 2008; Korhonen et al., 2003). A significant proportion of neck pain results from the complex association between individual and workplace risk factors with those from industrialized environments having increased risk (Côté et al., 2008). According to Côté et al. (2008), no prevention strategies have demonstrated reduction in the incidence of neck pain in workers and thus, one could hypothesize that the incidence of neck pain will increase as the world gets more industrialized.

Durmus et al. (2014) reported that approximately 70% of adults experience neck pain during their lifetime. The one-year prevalence of neck disorders in the general population is estimated to be between 4.8% to 79.5% with a mean value of 25.8%. The global age-adjusted point prevalence of neck pain in 2010 in men and women is estimated at 4.0% and 5.8% respectively (Hoy et al., 2014). The same study reported that the incidence of neck pain in a one-year period ranges between 10.4% and 21.3%, with a remission rate of 33% to 65%. The prevalence is higher in women, and peaks between 40 to 45 years of age (Hoy et al., 2010). As measured by years lived with disability, it is ranked as the fourth highest cause of disability and as the twenty first cause of overall burden among 291 conditions studied in a 2010 Global Burden of Disease study (Hoy et al., 2014, 2010). In those living with neck pain, the most recent Global Burden of Disease study reported an increased prevalence in those with pain of duration greater than 3 months from 2005 to 2015 of 21.1% (95% UI: 19.0 to 23.3) and an increase of 21% (95% UI: 18.9 to 13.2) in years lived with disability (Hurwitz, Randhawa, Yu, Côté, & Haldeman, 2018).

2.2 Definition and classification of neck pain

Neck pain is described as an unpleasant sensation perceived in the region from the superior nuchal line to the inferior level of the scapular spine and laterally to the margins of neck (Bier et

al., 2017; Bogduk, 2011; Hoy et al., 2014). The pain may occur with or without actual tissue damage (Jasper et al., 2017). However, this definition of neck pain is merely the description of the presence of pain around the neck and Hoy et al., (2010) reported over three hundred definitions of neck pain in a review of epidemiological literature.

The classification of neck pain into specific subgroups of participants with similar clinical presentation is imperative as it allows for the cataloguing of this heterogeneous disorder into more homogeneous subgroups where specific interventions could be targeted. Thus, as early as 1989, Rose proposed a classification of a diagnostic system in physiotherapy practice. He advocated that the classification systems provided healthcare workers with a way to label and categorize clusters of signs, symptoms and demographic data of similar individuals who had responded effectively to a specific intervention (Rose, 1989). Furthermore, he recognized that classifying and naming the disorder had a positive psychological impact and served as a source of comfort for both the patient and healthcare provider. Since Rose's proposal, many neck pain classification systems have been suggested including the Quebec Task Force classification of whiplash injuries (Spitzer et al., 1995) and classification based on hierarchical grades by the Task Force on Neck Pain and Its Associated Disorders (Guzman et al., 2009).

However, the presence of multiple definitions and classifications of neck pain across the literature demonstrates that researchers and clinicians do not have a common language and illustrates the diversity of intervention approaches in the management of neck pain (Hoy et al., 2010). The lack of uniformity among researchers and clinicians may have contributed to the broader inclusion criteria and recruitment of heterogeneous participants into available clinical trials, which could have potentially led to contradictory and inconsistent findings. Thus, it is

essential that clinicians and researchers be consistent with use of a single classification method and have the same understanding of neck pain nomenclature.

Several attempts have been made to develop an acceptable neck pain classification system. The initial categorization of neck pain was based on the biomedical model where neck pain was categorized by physiological and anatomical pathology (Jull & Sterling, 2009). The biomedical model assumed that the pain, impairment and disability resulting from the musculoskeletal system could be mitigated with the correction of underlying pathology (Minaire, 1992). However, classification of illness based on the biomedical model has several flaws. The pathoanatomical approach has limited utility as similar signs and symptoms can occur in different diagnoses and can lead to the mismatch between the treatment plan and diagnosis (Hoy et al., 2014). Some researchers have pointed out that the pathoanatomic approach may misdirect the intervention approach (Blanpied et al., 2017; Jull & Sterling, 2009; Ludewig, Lawrence, & Braman, 2013). Furthermore, a direct pathoanatomical cause of neck pain is rarely identified to support patient reports of neck pain and dysfunction. Studies examining the association between Magnetic Resonance Imaging of the cervical spine and pain or disability have reported poor correlations between pain and imaging results in patients with chronic neck pain and whiplash injuries (Cohen, 2015). In another study, no significant differences in pain or disability were found in participants with or without radiographic cervical spine degeneration (Rubin, 2007).Therefore, classification based on the biomedical approach was viewed as unproductive and did not resonate with researchers or healthcare professionals since it did not enhance the efficacy of management (Engel, 1997; Farre & Rapley, 2017).

Childs et al. (2004) proposed a classification system based on the overall goal of the treatment. They hypothesized that the most appropriate treatment approach can be matched to the

patient's signs and symptoms to maximize the benefits of intervention. A cluster of signs and symptoms were categorized into; mobility deficits, centralization of symptoms, tolerance to exercise and conditioning, level of pain control and headache. They presented a matched intervention to manage the above categories (mobility, centralization, conditioning and increased exercise tolerance, pain control and reduction of headache) and hypothesized that the classification allowed homogeneous design of a treatment approach. However, the underlying pathophysiology or etiology of neck pain may not be similar within the same category (Childs et al., 2004). The overview of classification categories with key examination findings and proposed matched interventions are provided in *Table 1* (Childs et al., 2004). This classification system was developed based on available evidence incorporating expert opinion and clinical experience (Childs et al., 2004).

Classification	Examination Findings	Proposed Matched Interventions
Mobility	Recent onset of symptoms No radicular/referred symptoms in the upper quarter Restricted range of motion with side-to-side rotation or discrepancy in lateral flexion range of motion No signs of nerve root compression or peripheralization of symptoms in the	Cervical and thoracic spine mobilization/manipulation Active range of motion exercises
Centralization	Radicular/referred symptoms in the upper quarter Peripheralization or centralization of symptoms with a range of motion Signs of nerve root compression present May have a pathoanatomic diagnosis of cervical radiculopathy	Mechanical/manual cervical traction Repeated movements to centralize symptoms
Conditioning and increased exercise tolerance	Lower pain and disability scores Longer duration of symptoms No signs of nerve root compression No peripheralization/centralization during a range of motion	Strengthening and endurance exercises for the muscles of the neck and upper quarter Aerobic conditioning exercises
Pain control	High pain and disability scores Very recent onset of symptoms Symptoms precipitated by trauma Referred or radiating symptoms extending into the upper quarter Poor tolerance for examination or most interventions	Gentle active range of motion within pain tolerance Range of motion exercises for adjacent regions Physical modalities as needed Activity modification to control pain
Reduce headache	Unilateral headache with onset preceded by neck pain Headache pain triggered by neck movement or positions Headache pain elicited by pressure on posterior neck	Cervical spine manipulation/mobilization Strengthening of neck and upper quarter muscles Postural education

Table 1. Overview of classification categories with key examination findings and proposed matched interventions. Adapted from "Proposal of a Classification System for Patients with Neck Pain," by J. Childs, J. Fritz, S. Piva, and J. Whitman, (2004). J. Orthop. Sport. Phys. Thearpy, vol. 34, no. 11, 686-700

The interrater reliability and effectiveness of Childs' classification to improve clinical outcomes was investigated by Fritz & Brennan (2007). They conducted a prospective longitudinal study over a period of one year and analyzed 274 participants with neck pain. A standardized form collected the variables at baseline, and an algorithm was created to place the participants into different categories of a classification system based on the baseline characteristics (*Figure 1*). The results found interrater reliability for classification high (kappa = 0.95, 95% CI: 0.87 to 1.0). The study reported that the 113 (41.2%) participants who received a proposed intervention for classification had a significant improvement in the Neck Disability Index (MD 5.6, 95% CI: 2.6 to 8.6) and Numeric Pain Rating Scale (MD 0.74, 95% CI: 0.21 to 1.3) compared to non-matched intervention (n=161, 58.8%) (Fritz & Brennan, 2007). This preliminary finding supported the interrater reliability, but conclusions on effectiveness of a classification system to improve clinical outcomes could not be established. The study had two major methodological limitations. First, there was a selection bias since the allocation of participants into a match or non-matched groups was not randomized. Second, there may have been a cross-over effect of interventions between the groups as there was no standardized protocol for the interventions. Physiotherapists chose their intervention which could have potentially led to differences in the intensity, dosage and techniques of intervention.

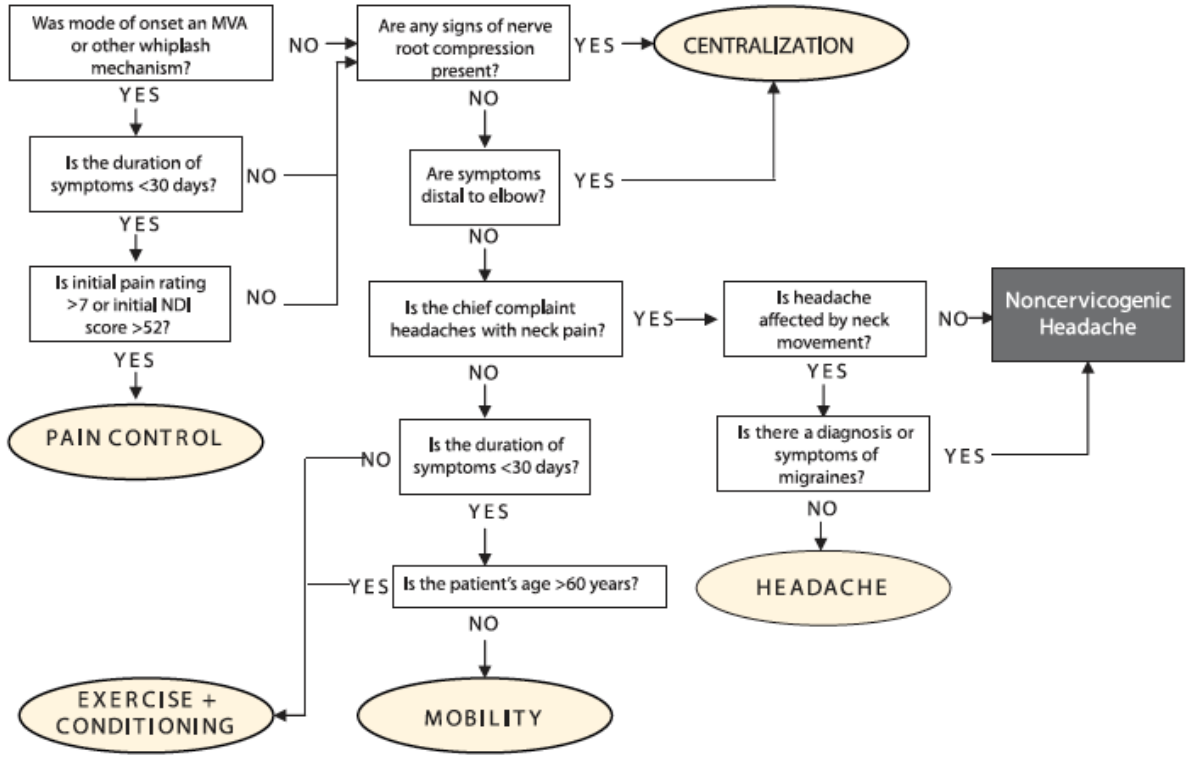

Figure 1. Classification decision-making algorithm. MVA = motor vehicle accident, NDI= Neck Disability Index. *Adapted from "Preliminary Examination of a Proposed Treatment-Based Classification System for Patients Receiving Physical Therapy Interventions for Neck Pain" by Fritz, J.M., & Brennan, G, P. (2007). Physical Therapy, 87(5), 513-525*

A clinical practice guideline (CPG) published by the American Physical Therapy Association (APTA) proposed the most recent classification (Blanpied et al., 2017). The authors reviewed 748 studies and classified neck pain into four categories; neck pain with mobility deficits, neck pain with movement coordination impairments, neck pain with a headache and neck pain with radiating pain. They presented a cluster of common signs and symptoms including expected patient examination findings for each of the above categories. They recommended intervention strategies which showed moderate to high level evidence. This classification considered four components for the categorization: (1) medical screening; (2) evaluation of musculoskeletal

pathophysiology (International Classification of Diseases (ICD)) and its association to impairment of body function (International Classification of Function, Disability and Health (ICF)); (3) timeline (acute, subacute and chronic) and (4) intervention. The classification system appears to be robust as it allows healthcare providers to assign appropriate and effective interventions primarily focused on pain management and it attempts to create common neck pain nomenclature amongst researchers. However, it does present with a few limitations. For example, the classification system ignores the biopsychosocial approach to pain management which acknowledges the biological, psychological, behavioural and social factors of illness (Jull & Sterling, 2009; Nielson & Weir, 2001). The efficacy and effectiveness of the biopsychosocial approach to pain management has been well established across the literature and should be considered when developing classification systems (Garcia & Saragiotto, 2016; Gatchel, Peng, Peters, Fuchs, & Turk, 2007; Gliedt, Schneider, Evans, King, & Eubanks, 2017).

The Neck Pain Task Force provided one of the most widely accepted classifications of neck pain and its associated disorders (Guzman et al., 2008). They classified neck pain into four grades; grade I, grade II, grade III and grade IV as presented in *Table 2* (Guzman et al., 2008). The classification can be applied to all neck pain and associated disorders including whiplash-associated disorders. Although the validity of the grading system has not been established the developers hypothesized that clinicians, researchers and policymakers could use the grading system to make decisions, describe and manage neck pain (Guzman et al., 2008; Nordin et al., 2008).

Grade Level	Symptoms
I	Neck pain and associated disorders with no signs or symptoms suggestive of major structural pathology and no or minor interference with activities of daily living
II	No signs or symptoms of major structural pathology but major interference with activities of daily living
III	No signs or symptoms of major structural pathology but the presence of neurologic signs, such as decreased deep tendon reflexes, weakness, or sensory deficits
IV	Signs or symptoms of major structural pathology; major structural pathologies include (but are not limited to) fracture, vertebral dislocation, injury to the spinal cord, infection, neoplasm, or systemic disease, including inflammatory arthropathies.

Table 2. Neck Pain Task Force Classification

2.3 Summary

There have been several attempts to classify neck disorders since Rose first proposed his classification in 1989. Researchers and clinicians have used a variety of theories and methodologies to classify neck disorders including medical and biopsychosocial models, as well as goals of treatment. However, classification systems based on the medical model have been severely criticized. There has been a considerable increase in adoption of the biopsychosocial model over the years. Medically unexplained signs and symptoms can be approached using this model as the biopsychosocial model considers three domains; biological, psychological and social to understand and manage illness (Engel, 1981). However, the model has been criticized as not having clear boundaries, not being testable, as having a lack of philosophical coherence, being insensitive to patients' subjective experience, and not being applicable in the routine clinical practice (Gritti, 2017; Ghaemi, 2009). Despite these criticisms, the biopsychosocial model had been seen as the heuristic approach in the management of chronic pain (Gatchel et al., 2007).

The most popular classification system was provided by Neck Pain Task Force which classified neck into four hierarchical grades which were based on the intensity of pain and level of impairments (Guzman et al., 2009). The classification system proposed by American Physical Therapy Association considered themes including the pathophysiology and its associated impairments, the timeline of the disorders and interventions (Blanpied et al., 2017). The grade-based classification system appears to be popular among researchers since it allows the researchers to perform data analysis more conveniently while the classification by Blanpied et al. (2017) appears to be more suitable for the clinicians as it provides more insight in to the clinical perspective and aids in making a clinical decision. Since the diagnosis or classification of neck disorders form the basis for the description of population or sample for studies, it is imperative that there should be homogeneity in the nomenclature used. Unfortunately, the lack of consensus on classification or definition of neck pain nomenclature exists contributing to heterogeneous samples, modest treatment effects and inconsistent study results across studies. Therefore, future research should focus on addressing the variability in nomenclature and classification systems as it is imperative for researchers and clinicians to be consistent in terminology, and to improve clinical decision making.

2.4 Approaches to neck pain management by healthcare practitioners

Neck pain is managed by a diverse array of health care professionals including physicians, osteopaths, orthopedic surgeons, chiropractors, massage therapist and physiotherapists. Among these healthcare practitioners, there are no standardized protocols for neck pain management nor consensus on the most appropriate intervention. Evidence based practice asserts making treatment choice based on the best available evidence, the experience and expertise of the practitioners, and

the clinical manifestation of the illness (Sackett, Straus, Richardson, Rosenberg,Haynes & Livingstone, 2000). However, lack of high level evidence on the effectiveness of conservative management of neck pain raises concern regarding evidence based neck pain management.

The international survey conducted by Carlesso et al. (2014) demonstrated this diversity of interventions for the management of neck pain. The survey analyzed 360 clinicians involved in neck pain management including physiotherapists, chiropractors, physicians, massage therapists, occupational therapists and medical specialists across 17 countries. The purpose of the survey was to describe the intervention methods utilized by clinicians for the management of neck pain. The results demonstrated that physiotherapists and chiropractors primarily used exercise and manual therapy, followed by ergonomic modification and work-related interventions. Clinicians used ultrasound primarily for enhancing tissue healing (40%) and pain relief (25%). Subgroup analyses revealed that physiotherapists used other additional interventions including patient education, relaxation and breathing techniques, referral to other clinicians and McKenzie techniques more frequently than chiropractors. There were also differences in exercise prescriptions. For example, physiotherapists used postural control, stretching, endurance, stabilization and motor control exercises more often than chiropractors. Laser, electrical muscle stimulation and acupuncture was more commonly used by the chiropractors. These differences in intervention strategies are not surprising since physiotherapists and chiropractors have a different scope of practice and educational background.

The survey also noted that the intervention pattern for neck pain amongst physiotherapists differed based on their clinical experience, educational background and scope of practice (Carlesso et al., 2014). Despite the differences in the approach to management of neck pain, a common approach by all practitioners was the use of a multimodal intervention. This approach is supported

in the literature and found to be superior to the use of a single intervention (Bier et al., 2017; Blanpied et al., 2017; Farooq, Mohseni-Bandpei, Gilani, Ashfaq, & Mahmood, 2018).

2.4.1 Manual Therapy

The International Federation of Orthopedic Manipulative Physical Therapists (IFOMPT) defines manual therapy as " Skilled hand movements intended to optimize any or all of the following effects: improve tissue extensibility; increase range of motion of the joint complex; mobilize or manipulate soft tissues and joints; induce relaxation; change muscle function; stabilize the joint complex; modulate pain; reduce soft tissue swelling, inflammation or movement restriction" (Rushton et al., 2016, p.31). Manipulation and mobilization are two types of manual therapy techniques. Manipulation is defined as a passive, high velocity, low amplitude thrust applied to a joint complex within its anatomical limit. Mobilization refers to a skilled passive movement performed to a joint complex or tissues at varying speed and amplitudes. Both techniques are applied with the intent to restore optimal motion, function or to reduce pain (International Federation of Orthopaedic Manipulative Physical Therapists, 2004). Myofascial release, soft tissue mobilization and massage are also forms of manual therapy that utilize hands on techniques on soft tissues, muscles, fascia and ligaments intended to reduce pain and improve function (Ajimsha, Al-Mudahka, & Al-Madzhar, 2015; Kennedy, Cambron, Sharpe, Travillian, & Saunders, 2016).

2.4.1.1 Evidence on manual therapy

Biomechanical and neurophysiological effects of manual therapy on the human body were described by Wise (2015). It is suggested that manual therapy provides neurophysiological effects

through the stimulation of the descending inhibitory pathways and excitability of alpha-motoneuron, influences brain function specific to the side of thrusts and alters Pressure Pain Thresholds leading to pain reduction and enhanced function (Wise, 2015). Additionally, it is suggested that the force applied during manual therapy produces mechanical effects on joints and tissues. The mechanical forces change the accessory joint movements which enhances physiological joint movements (wise, 2015). Finally, manual therapy has been demonstrated to provide significant pain relief and high patient satisfaction rates. The mechanisms on how manual therapy produces reduction in pain is unclear; however, Bishop et al. (2015) argued that it could be due to the modulation of biomechanical and neurophysiological mediators achieved immediately following manual therapy.

The evidence on the effectiveness of manual therapy in the management of neck pain is mixed. A systematic review by Wong et al. (2016) examined the effectiveness of manual therapy, therapeutic modalities utilized by physiotherapists and acupuncture used in the management of whiplash-associated disorders and neck pain and associated disorders. They screened 8551 citations and analyzed 38 studies (2261 participants). The inclusion criteria were restricted to children and adults with neck pain and associated disorders grade I-III and whiplash-associated disorders. The participants included in the studies had to fulfill the definition and classification of neck pain and associated disorders and whiplash-associated disorders provided by the Neck Pain Task Force and Quebec Task Force Classification (QTFC). The review assessed the following outcomes; function, pain intensity, quality of life, psychological outcomes and adverse effects. The review concluded that manipulation and mobilization were effective interventions in relieving pain and improving function for the management of acute and chronic neck pain, or associated disorders grades I-II and acute whiplash-associated disorders. The review reinforced the earlier

findings of the 2008 Neck Pain Task Force which suggested manual therapy, manipulation, and clinical massage as an effective intervention for the treatment of neck pain. The review was critically appraised using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) and found to be a high quality review. It included a clear definition of the terminologies used, predetermined inclusion and exclusion criteria and only studies with adequate sample size. It should be noted that the review did not report on types of mobilization techniques.

Another review on the effectiveness of manual therapy techniques by Hidalgo et al. (2017) supported the findings of Wong et al. (2016). They reported moderate quality evidence of benefit for reduction of pain, improving function and patient satisfaction in favour of manual therapy and exercise as compared to usual care, or exercise and manual therapy alone for subacute and chronic neck pain at short-term and intermediate-term follow-up. This was a qualitative systematic review including 23 randomized clinical trials (1941 participants) which were published from January 2000 to December 2015. The authors defined and classified manual therapy into four subgroups; (1) manual therapy 1 involving high velocity and low amplitude thrust manipulation (HVLA), (2) manual therapy 2 involving a range of soft tissue and spinal mobilization techniques, (3) manual therapy 3 involving a combination of manual therapy 1 and manual therapy 2, and (4) manual therapy 4 involving mobilization with movement. The analysis from the review was summarized into four points: First, combining manual therapy and exercise had a greater benefit in reducing pain and improving function and patient satisfaction as compared to manual therapy or exercise alone at short-term and intermediate-term. Second, manual therapy 1 or manual therapy 3 combined with exercise was more effective in pain management, improving function and achieved higher patient satisfaction compared to usual medical care at short-term and intermediate-term. Third, there is strong evidence that manual therapy need not to be applied on the symptomatic

level of the spine to reduce pain and improve function; manual therapy had the same effect even when applied at the asymptomatic level. Fourth, all categories of manual therapy may be equally useful in the management of neck pain. The review was critically appraised using AMSTAR and no serious flaws were found. Thus, the review could be considered high quality. It had a well-defined design and followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. However, it had the inherent limitations associated with systematic reviews including missing out on relevant studies.

A recent study by Rodríguez-Huguet et al. (2017) investigated the efficacy of myofascial release therapy for pain management and improving Pressure Pain Thresholds. A total of 41 participants were randomly assigned to either a physiotherapy group (21) or a myofascial release therapy group (20). Participants included individuals who had mechanical neck pain with or without radiation of pain into the upper extremity or head for at least one month. The physiotherapy group received a multimodal therapy comprised of transcutaneous electrical nerve stimulation, ultrasound, massage and relaxation techniques and the myofascial release therapy group received four techniques of mobilization including mobilization of cervical fascia, myofascial release of the suboccipital region, stretching of sternocleidomastoid muscle, and manipulation of the cervical spine. Both groups were treated for two weeks. The results demonstrated myofascial release therapy to be superior in the management of pain and improvement of Pressure Pain Thresholds for neck pain participants compared to multimodal physiotherapy. They found significant mean differences in Visual Analogue Scales at the end of treatment (MD -0.99, 95% CI: -1.82 to -0.16) and Pressure Pain Thresholds at suboccipital and right trapezius muscle (MD 0.38, 95% CI: 0.07 to 0.69).

A Cochrane review conducted by the cervical overview group (COG), in 2015 updated a review on the effects of manual therapy as a stand-alone intervention compared to inactive control or active treatment in the management of neck pain with or without radiation of pain into upper extremity or head (Gross et al., 2015). The review included 51 studies (2920 participants). They reported that a single cervical manipulation or mobilization did not improve pain when compared to inactive controls. However, they found moderate quality evidence that a single session of thoracic manipulation to be effective in improving pain, function and quality of life for acute and chronic neck pain at intermediate - term follow-up. This result supported the findings presented by Hidalgo et al. (2017) that manual therapy does not need to be applied at the symptomatic level to reduce pain and improve function. The same review reported that multiple sessions of cervical manipulation or mobilization were equally effective in reducing pain, improving function and quality of life, and had higher patient satisfaction rates when compared with other active treatments for acute and chronic neck pain. However, authors concluded that there is an uncertainty about the effectiveness of cervical manipulation and mobilization for the management of neck pain owing to a lack of high quality evidence. The review highlights the presence of publication bias and recommends further high quality research.

Similar conclusions were made by Fredin & Lorås (2017) in their recent systematic review. They screened 1169 citations and included seven studies (841 participants) in their review. The goal of the review was to assess the benefits of manual therapy or exercise therapy alone or in combination to manage pain and improve function in the participants with neck pain grade I-II. They found no significant between-group differences in pain, function and quality of life at the end of treatment, at six months and twelve months follow-up. Thus, they concluded manual therapy combined with exercise did not have superior effects on relieving pain and improving

function for adults with grade I-II neck pain when compared to exercise therapy alone. This finding is consistent with Wong et al. (2016) who concluded that cervical or thoracic manipulation did not provide additional benefit to high dose supervised exercise for acute neck pain. It should be noted that only one author did the data extraction, which could have increased the risk of errors in data compilation (Fredin & Loras, 2017).

The mechanism of how manual therapy helps to reduce pain and improve function is not fully established (Bialosky, Bishop, Price, Robinson, & George, 2010). The above reviews demonstrate a moderate quality of evidence in support of manual therapy to relieve pain and improve function for management of acute and chronic neck pain including neck pain and associated disorders grade I-II (Gross et al., 2015; Hidalgo et al., 2017; Wong et al., 2016). Studies also suggest that the manual therapy need not have to be applied at the symptomatic region to impact the outcome for chronic neck pain (Gross et al., 2015; Hidalgo et al., 2017; Wong et al., 2016). Moderate level evidence was found in favor of a single session of thoracic manipulation to relieve pain and improve function for acute and chronic neck pain, and across the studies, manual therapy was reported to be associated with high patient satisfaction (Gross et al., 2015; Hidalgo et al., 2017).

2.4.2 Exercise Therapy

Therapeutic exercise is defined as "systematic, planned performance of physical movements, postures, or activities intended to provide a patient with means to; remediate or prevent impairments of body functions and structure, improve, restore or enhance activities and participation, prevent or reduce health-related risk factors and optimize overall health, fitness or sense of well-being" (Kisner, Colby, & Borstad, 2018, p. 2).

The physiology of exercise therapy involves two stages; the acute response of the body to exercise in all its forms and the adaptation of the body's systems to repeated exercise. When performing an exercise, a series of complex interactions involving body systems occur including cellular and molecular levels (Kenney, Wilmore, & Costill, 2015). The impulses generated from the central nervous systems travel across the neuromuscular junction activating the protein molecules actin and myosin. Adenosine triphosphate (ATP) and phosphocreatine (PCR) provide energy which is necessary to fuel the contraction of muscle fibers. The skeletal system, cardiovascular system, respiratory system, integumentary system, nervous system and the endocrine system are all involved in support of the sustained and rhythmic muscular contraction and relaxation (Kenney, Wilmore & Costill, 2015). The overall benefits of exercise on different systems in the human body are well established (Taylor, Dodd, Shields, & Bruder, 2007).

2.4.2.1 Evidence on Exercise Therapy

Systematic reviews and meta-analyses examining the effectiveness of exercise therapy for the management of chronic non-specific neck pain found significant and medium effect size in favor of exercise therapy to improve pain at short-term (g -0.53, 95% CI: -0.86 to -0.20), and intermediate-term (g -0.45, CI: 95% -0.82 to -0.07) (Bertozzi et al., 2013). Bertozzi et al. (2013) reported medium effect size of exercise therapy to improve disability at short-term or intermediate post-treatment but this was not statistically significant. The review did not report on long-term effects of exercise due to the lack of studies. The review included 7 randomized controlled trials (889 participants) and the inclusion criteria included participants with chronic non-specific neck pain and trapezius myalgia. The intervention was limited to only exercise therapy, and studies with a multimodal approach were excluded. All the experimental arms in the included studies

performed exercise including neck and upper extremity strengthening, stretching and endurance exercises except for one study that did postural correction and stretching exercises. Outcomes assessed were pain intensity and disability (Bertozzi et al., 2013). The review appears to be high quality as evaluated by the AMSTAR. Strict inclusion criteria were followed which included only studies that had participants with chronic non-specific neck pain and interventions consisting of only therapeutic exercise. The strict inclusion criteria made the review more accurate in estimating the potential benefits of exercise therapy. However, the results should be interpreted with caution since a majority (6/7) of the included studies in the review were assessed as moderate to low quality.

Bertozzi et al. (2013) did not report on mediating factors such as; type, duration, intensity and frequency of exercise therapy due to the heterogeneity of included studies. O'Riordan et al. (2014) investigated these factors and examined the most effective frequency, intensity, time and type of exercise therapy used for the management of chronic neck pain. Their review included 16 randomized controlled trials (2479 participants) which were conducted between 2000 and 2012. They concluded with following recommendations; (1) exercise therapy should be performed for 30 to 60 minutes 3 times a week at an intensity reaching up to 80% of maximum voluntary contraction to achieve muscle strength and improve pain and disability, (2) resisted isometric strengthening of deep cervical flexor muscles should be performed to reduce pain and aerobic exercise to improve quality of life and global well-being, (3) exercise programs should be performed between 6 and 12 weeks and should be encouraged to continue life-long to alleviate pain and (4) a combination of group and home exercise program should be performed to increase adherence of exercise therapy.

A 2015 Cochrane review examined the effects of therapeutic exercise to relieve pain, improve function, patient satisfaction and quality of life for adults with neck pain (Gross et al., 2015). The review included 27 studies (3005 participants). The inclusion criteria included adults with mechanical neck disorders, whiplash-associated disorders grade I and II, myofascial pain syndrome, cervical degenerative disease, cervicogenic headache and cervical radiculopathy. The review found no evidence on the effectiveness of exercise for acute neck pain due to the lack of studies. Although no high quality evidence was found in favour of exercise for chronic neck pain, there was moderate quality evidence for cervical, scapulothoracic and upper extremity strengthening exercise to relieve pain and combined neck, scapulothoracic and shoulder strengthening and stretching exercise to improve pain and function immediately following the treatment (SMD -0.33 95% CI: -0.55 to -0.10). Low quality evidence was found for breathing exercise, general fitness exercise and stretching alone for chronic neck pain. The review concluded that there is moderate - quality evidence in favour of cervical and scapulothoracic strengthening and endurance exercise and pressure biofeedback in relieving pain, improving function and global perceived effect immediately following the treatment and at short-term for chronic neck pain. They also reported moderate - quality evidence in favour of the same intervention and outcomes at long-term follow-up for chronic cervicogenic headache. However, the review did not report on intermediate and long-term follow-up for participants with chronic neck pain.

The above findings are partially supported in a systematic review by Louw et al. (2017) who examined the effectiveness of exercise for non-specific neck pain among office workers. They included 8 randomized controlled trials (2075 participants). The results were consistent with the findings of Gross et al. (2015) that there was insufficient evidence on the benefits of stretching exercises to improve pain and quality of life for management of chronic neck pain. However, they

reported adequate evidence in favour of strengthening exercises to improve pain and recommended healthcare workers include strengthening exercises as a part of neck pain management (Louw et al., 2017). They noted findings should be interpreted with caution due to the lack of well-structured designs, high risk of bias and heterogeneity found across the included studies (Louw et al., 2017).

The studies discussed above demonstrate the effectiveness of exercise therapy intervention to relieve pain, improve function and quality of life for the management of chronic neck pain. Benefits of exercise therapy for acute neck pain cannot be established due to the lack of studies examining the effect (Gross et al., 2015). Although there is no high quality evidence found, there is a moderate level of evidence across the studies in favour of neck and upper extremity strengthening and endurance exercises to manage pain and improve function at short-term and intermediate-term follow-up for the management of chronic neck pain (Bertozzi et al., 2013; Gross et al., 2015; Louw et al., 2017; O'Riordan, Clifford, Van De Ven, & Nelson, 2014). It is recommended that the exercise therapy, including deep cervical flexor strengthening exercise, be performed between 30 to 60 minutes thrice a week for 6 to 12 weeks to achieve the best outcome for management of chronic neck pain (O'Riordan et al., 2014). However, only low quality evidence was found for stretching, breathing and aerobic exercise for the management of chronic neck pain (Gross, Kay, Paquin, Blanchette, Lalonde, Christie, Dupont, Graham, Burnie, et al., 2015; Louw et al., 2017).

2.4.3 Therapeutic ultrasound

Ultrasound therapy has been used by physiotherapists for decades and continues to be widely used to manage a variety of musculoskeletal conditions, wound care and fractures (Doan, Reher, Meghji, & Harris, 1999; Draper, Castel, & Castel, 1995). Ultrasound is defined as a "sound

wave or pressure wave with a frequency above the limit of the human hearing range (16 to 20 kHz)" (Doan et al., 1999, p.410). Therapeutic ultrasound used in rehabilitation treatments utilizes frequencies within 1 to 3 MHz with intensities of 0.1 to 2.0 W/cm^2 (Doan et al., 1999). Ultrasound at 1 MHz can penetrate deep into the tissues from 2 to 4 cm, while ultrasound at 3 MHz has been demonstrated to penetrate 1 to 2 cm (Byl, 1995).

The two theories explaining the biophysiological effect of ultrasound include thermal and a non-thermal effect theories (Baker et al., 2001). However, it is difficult to separate the therapeutic effects caused by ultrasound into thermal and non-thermal as these coexist as the application of ultrasound on tissues continually produces mechanical and thermal effects. Theoretically, a thermal effect is generated by an attenuation phenomenon which is caused by absorption, dispersion and reflection of the ultrasonic waves as it pass through the skin and tissues (Baker et al., 2001; Machet & Boucaud, 2002). Its physiological effects include increased blood flow, rise in metabolic activity, and analgesic effects. The thermal effects depend on the intensity of the ultrasonic waves and are significantly higher when applied in continuous mode compared to pulsating mode (Baker et al., 2001). Thermal effects are generally used to manage pain, muscle spasm and improve connective tissue disorders in sub-acute and chronic conditions (Doan et al., 1999; Draper et al., 1995).

Non-thermal effects of ultrasound are caused by the mechanical energy and shearing forces from the ultrasound waves which penetrates the cellular membrane and the molecular structures within the cell (Johns, 2002). The two main effects caused by non-thermal phenomenon are acoustic streaming and cavitation (Johns, 2002). Acoustic streaming is defined as the "physical forces of the sound waves that provide a driving force capable of displacing ions and small molecules" (Johns, 2002, p. 294). The acoustic steaming process causes movement of the free-

floating molecules and organelles at the cellular level around the stationary structures. Similarly, cavitation is defined as the "physical forces of the sound wave on microenvironmental gases with fluid" (Johns, 2002, p. 294). The movement of sound waves through the medium results in the formation of microscopic gas bubbles which contact and expand in the tissue fluids. The contraction and expansion of microscopic gas bubbles are thought to disrupt cellular activity, alter cellular function and damage the cells (Johns, 2002). Several in-vitro studies examining the effects of acoustic streaming and cavitation on cells have demonstrated growth retardation of cells, increased protein synthesis and membrane alterations (Dyson, Pond, Joseph, & Warwick, 1968; Loch, Fischer, & Kuwert, 1971; Maeda, Murao, Yoshiga, Yamauchi, & Tsuzaki, 1986; Pizzarello, Wolsky, Becker, & Keegan, 1975). Subsequently, the growth retardation and damage to cells initiate a cellular recovery process which is characterized by the increase in protein production (Dyson et al., 1968; Loch et al., 1971; Maeda et al., 1986; Pizzarello et al., 1975). Furthermore, other studies have reported that the non-thermal effects initiate facilitation of the immune system response by producing vasodilation of blood vessels and activation of adhesion molecules. Since the signal-transduction pathways regulate vasodilation and activation of adhesion molecules, it is suggested that these processes lead to changes in conformation and regulation of enzymatic activity of the protein (Johns, 2002). Non-thermal effects are typically used in acute conditions to manage pain, reduce edema and to stimulate tissue repair (Draper et al., 1995).

2.4.3.1 Evidence on Ultrasound Therapy

Randomized controlled trials (Dündar et al., 2010; Kavadar, Çağlar, Özen, Tütün, & Demircioğlu, 2015; Ökmen & Altan, 2018) examining the effectiveness of ultrasound therapy for neck disorders have found some evidence in favor of ultrasound therapy to manage pain and

improve functions for management of cervical myofascial pain and chronic cervical radiculopathy. Systematic reviews (Wong et al., 2016; Xia, Wang, Lin, Cheng, & Li, 2017) demonstrated statistically significant results in favor of ultrasound therapy to relieve pain and improve function for cervical myofascial pain, yet they concluded there is inadequate evidence to support use of ultrasound therapy due to the high heterogeneity and high risk of bias found across the included trials. The positive findings presented in the above clinical trials may have been the result of the limitations and biases exhibited in the studies. None of the clinical trials calculated the sample size or reported on intention to treat analysis, and it is most likely that the studies had selection bias. Furthermore, most of the clinical trials were multimodal interventions, including exercise and transcutaneous electrical nerve stimulations with ultrasound therapy as an adjuvant which may have made determining the efficacy of ultrasound therapy alone challenging.

Dündar et al. (2010) investigated the effects of ultrasound therapy in the management of cervical myofascial pain syndrome. Fifty-five participants with neck pain were randomly assigned to either an active ultrasound therapy group or a placebo group. The participants in the treatment group received ultrasound therapy applied on three trigger points for 8 minutes in continuous mode at the frequency of 1MHz and intensity of 1.5Watt/cm^2 for 15 sessions. The outcomes assessed were pain, function and disability. The results showed significant statistical differences in pain reduction as measured by Visual Analogue Scale in the ultrasound therapy group [mean (SD): -0.34 (0.10), p = 0.001] as compared to the placebo group [mean (SD): -0.25 (0.16), p = 0.001] at four weeks post-treatment. Similar results were reported in favor of ultrasound group [mean (SD): -0.38 (0.09), p = 0.001] at 12 week follow-up as compared to placebo group [mean (SD): -0.31 (0.14), p =0.001]. The ultrasound group also showed better improvement in the neck range of motions. Therefore, the authors concluded that ultrasound therapy was effective in the

management of neck pain. However, the study had substantial methodological flaws including unknown randomization, unknown allocation concealment, potential selective reporting and unknown compliance to intervention. Thus, it raises a serious concern regarding the validity of its findings.

Kavadar et al. (2015) concluded that continuous ultrasound therapy is an effective treatment for the management of myofascial pain syndrome. In their randomized controlled trial, they recruited 59 participants with upper trapezius myofascial pain syndrome and randomized the participants into active ultrasound therapy or placebo ultrasound therapy groups. The outcomes assessed were pain, Pressure Pain Threshold and depression. The analysis of the outcomes at immediate post-treatment demonstrated a significant decrease in pain as measured by the Visual Analogue Scale in the ultrasound group [mean (SD): 1.33 (1.69)] as compared to the placebo group [mean (SD): 5.10 (1.42)]. There was also a significant reduction in pain at three month follow-up in the ultrasound group [mean (SD): 2.47 (1.78)] as compared to the placebo group [mean (SD): 6.21 (1.47)]. The ultrasound group also showed an increase in Pressure Pain Threshold [mean (SD): 10.27 (0.94)] as compared to the placebo group [mean (SD): 8.62 (1.08)] at immediate post-treatment. Active ultrasound also lowered Beck's Depression Questionnaire (BDQ) scores compared to the placebo group ($p<0.001$). Although, the review concluded that ultrasound therapy is effective in the treatment of myofascial pain syndrome, the study had limitations including large dropouts (19.44%), no report of intention to treat analysis, unknown randomization and lack of study protocol.

All the above studies demonstrated the effectiveness of ultrasound therapy in the management of cervical myofascial pain syndrome. These findings were also supported by a recent prospective, controlled single-blinded study by Ökmen et al. (2018) who reported ultrasound

therapy to be an effective intervention for the management of chronic cervical radiculopathy. They recruited twenty-nine participants with a total of 42 affected cervical nerve roots (C5:18, C6:17, C7:7) and 42 unaffected cervical nerve roots (C5:18, C6:17, C7:7) confirmed by magnetic resonance imaging and consistent with electromyograph findings. The outcomes evaluated were pain intensity, neck disability, quality of life and cross-sectional area of nerve roots as measured by high-resolution ultrasound. The outcomes were assessed at baseline, at two weeks and six weeks. They found significant improvement in pain intensity [Visual Analogue Scale score (mean (SD): 5.00 (1.34)] and at 6-week follow-up [Visual Analogue Scale score mean (SD): 2.59 (1.24)] compare to pre-treatment [Visual Analogue Scale score mean (SD): 7.07 (1.36)]. Similar results were reported in favor of ultrasound to improve neck disability immediate post-treatment [Neck Disability Index mean (SD): 24.11 (11.07)] and at 6-week follow-up [Neck Disability Index score mean (SD): 14.21 (7.20)] compared to pretreatment [Neck Disability Index score mean (SD): 36.02 (15.66)]. The study also found a significant correlation in the positive direction between symptom duration and cross-sectional area of nerve roots in affected nerve roots (Spearman's R for C5: 0.707, $p = 0.001$, Spearman's R for C6: 0.842, $p < 0.001$, Spearman's R for C7: 0.777, $p = 0.040$). The limitation of the study includes a relatively small sample size and short-term follow-up period.

In contrast to the positive findings in support of ultrasound therapy, a few studies have reported no benefit or contradictory results for the use of ultrasound in the management of neck pain. A systematic review by Wong et al. (2016) found no evidence on the benefit of ultrasound therapy in the management of whiplash associated disorders or neck pain associated disorders. The review was to update the findings of the 2008 Neck Pain Task Force on the effectiveness of manual therapies and physical modalities for management of whiplash associated disorder and neck pain

associated disorders. The review included 38 studies (2261 participants) and recommended that ultrasound therapy not be used to manage neck pain including whiplash associated disorders. It is unclear how many of the included studies investigated the efficacy of ultrasound or what modes and parameters of ultrasound had been used.

Another review by Xia et al. (2017) evaluated the benefit of ultrasound therapy for management of myofascial pain syndrome across ten studies. Among the ten studies included in their review and meta-analysis, only three studies had utilized similar intensity and dosage of ultrasound therapy. The intensity and dosages of ultrasound included an application of ultrasound in continuous mode, at a frequency of 1MHz, and intensity of 1.5 Watt/cm^2 applied for ten sessions. These parameters were similar to that of the randomized controlled trials above which reported beneficial effects (Dündar et al., 2010; Kavadar et al., 2015; Ökmen & Altan, 2018). They included ten studies (428 participants) which utilized Visual Analogue Scale or Numerical Rating Scale to detect the change in pain intensity in the meta-analysis. The results revealed significant improvement and demonstrated clinically important minimal differences in pain at rest or on activity ((SMD -1.41 95% CI: -2.15 to -0.67), p=0.0002. However, there was a high heterogeneity (χ^2 =62.70, P<0.00001,I^2 =89%). Thus, the authors performed secondary analysis with only four studies which showed no heterogeneity (χ^2 =5.12, P<0.16, I^2 =41%). The results were still in favor of ultrasound (SMD -1.96, 95% CI: -2.50 to -1.43, p=0.00001). Similar findings were found for Pressure Pain Threshold in favour of ultrasound (SMD 0.71, 95% CI: 0.41 to 1.00, p=0.00001) immediately following the treatment. They found no evidence of benefit of ultrasound or combined ultrasound and exercise to improve cervical range of motion for myofascial pain syndrome. Although two included studies were assessed to have low risk of bias and another two were reported as unclear, the review concluded that findings were inconclusive due to the high

heterogeneity of included studies and the high risk of bias found across the trials. (Xia et al., 2017). This review appears to be a high quality review when critically appraised using AMSTAR.

It is evident from the above reviews that there is no standardized dosage and a lack of uniformity among healthcare workers on mode and parameters of ultrasound therapy. However, it should be noted that when the ultrasound is used in continuous mode for 5-10 minutes at the frequency of 1MHz and intensity of 1.5Watt/cm^2 for 10 sessions, all the studies observed ultrasound therapy to be effective in relieving pain and improving function and quality of life in neck pain (Dündar et al., 2010; Kavadar et al., 2015; Ökmen et al., 2018). Reviews presented above recommended further high quality randomized controlled trials with large sample sizes to confirm the efficacy of ultrasound on myofascial pain syndrome.

2.4.4 Phonophoresis

Phonophoresis, also referred to as ultrasonophoresis or sonophoresis is defined as a "migration of drug molecules, contained in a coupling agent, through the skin under the influence of ultrasound" (Tyle & Agrawala, 1989, p. 355). Local administration of topical medicines by ultrasound was demonstrated as early as 1954 when Fellinger & Schmid showed that hydrocortisone could be delivered across an avascular membrane by ultrasound in the treatment of polyarthritis of the hand (Byl, 1995; Tyle & Agrawala, 1989). Thermal, non-thermal and chemical effects generated by the ultrasound, drive the drug molecules into the tissues causing an enhanced penetration (Byl, 1995; Tyle & Agrawala, 1989). These effects exerted by the ultrasonic waves are thought to promote an influx of drug molecules by causing enlargement of intercellular space, alteration of structural keratin proteins in the stratum corneum and change in cell permeability (Byl, 1995; Machet & Boucaud, 2002). Furthermore, the use of ultrasonic waves to

induce topical medicine is considered painless, noninvasive and has fewer side effects as it is administered locally at the site of pain (Ustun, Arslan, & Mansuroglu, 2014). Commonly used drugs in phonophoresis for rehabilitation purposes are usually anesthetic or anti-inflammatory agents such as; lidocaine, salicylates, hydrocortisone and cortisone which are targeted locally at the pain (Byl, 1995; Machet & Boucaud, 2002).

2.4.4.1 Evidence of phonophoresis

A recent randomized control trial by Takla & Rezk-Allah Rezk (2017) investigated the effects of diclofenac phonophoresis, combined phonophoresis with transcutaneous electrical nerve stimulation and ultrasound to improve Pressure Pain Threshold and cervical range of motion for the acute mechanical neck pain with myofascial pain. A total of 100 participants were randomly assigned to four groups; 25 participants in each of the following groups; transcutaneous electrical nerve stimulation and phonophoresis, phonophoresis, ultrasound and sham ultrasound. The results showed there was significant improvement in Pressure Pain Threshold post-treatment in three groups compared to pre-treatment; mean difference with 95% confidence interval for Pressure Pain Threshold scores were as follows; in combined transcutaneous electrical stimulation and phonophoresis group: (MD 3.624, 95% CI: 3.7 to 3.4); phonophoresis group: (MD 2.241, 95% CI: 2.36 to 2.11) and ultrasound group: (MD 0.488, 95% CI: 0.61 to 0.36). Similar results were also found in cervical lateral flexion in favor of combined transcutaneous electrical nerve stimulation and phonophoresis, phonophoresis and ultrasound at immediate post-treatment; combined transcutaneous electrical stimulation and phonophoresis group: (MD 4.48, 95% CI: 4.88 to 4.07); phonophoresis group: (MD 3.12, 95% CI: 3.52 to 2.71) and ultrasound group: (MD 2.4, 95% CI: 2.8 to 1.99). No significant differences in cervical lateral flexion were found in the sham ultrasound

group immediately post-treatment compared to pre-treatment. The study appears to be high quality since the methodology was well described including randomization, allocation concealment, blinding and included intention to treat analysis. The results were also reported according to the recommendation by the Consolidated Standards of Reporting Trials. However, the study protocol was not registered, and only immediate effects were examined; therefore, the findings cannot be generalized to intermediate or long-term effect.

Durmus, Alayli, & Tufekci (2014) examined the effectiveness of capsaicin phonophoresis and exercise for the management of chronic neck pain. They recruited 61 female participants with chronic neck pain who were randomly assigned into three groups; 21 participants in capsaicin phonophoresis and exercise, 20 participants in placebo phonophoresis and exercise and 20 participants in exercise group. The outcomes were assessed pre and post-treatment, and included pain, disability, depression and quality of life. They found significant improvement in pain across all the groups at rest and on activity at immediate post-treatment. However, capsaicin phonophoresis and exercise group showed greater improvement [Visual Analogue Scale score post-treatment mean (SD): 1.65 (0.93) compared to pre-treatment mean (SD): 6.65 (1.42)]. Similar results were also found in Neck Pain and Disability scale scores in capsaicin phonophoresis and exercise group [post-treatment mean (SD): 11.70 (4.50) compared to pre-treatment mean (SD): 31.10 (1.09)]. There were significant changes in the other outcomes in all three groups although capsaicin phonophoresis and exercise group proved to be superior to the other two groups. The study recommended the use of phonophoresis combined with exercise for the management of chronic neck pain. Nevertheless, the study appears to be low quality as there was unclear selection bias, no blinding of participants or the assessors, no registration of study protocol and no intention

to treat analyses. Other limitations include recruitment of only female participants and outcomes that were assessed at only two-time points, pre-treatment and post-treatment.

No systematic reviews or meta-analyses which examined the effectiveness of phonophoresis for neck pain were found. The evidence is unclear on the use of different topical drugs for phonophoresis due to the lack of studies. However, the studies presented above showed phonophoresis could have potential benefits to reducing pain and improving function for cervical myofascial pain and chronic neck pain.

2.5 Summary

Evidence has shown neck pain is a highly prevalent musculoskeletal disorder and a leading cause of disability (Hoy et al., 2010). Neck pain is a complex disorder, and its management is challenging. Nevertheless, a significant proportion of neck pain is managed conservatively and includes manual therapy, exercise and ultrasound therapy with clinicians making the decisions based on their experience, the patient's choice and available evidence. However, there is a lack of high quality evidence on the conservative management of neck pain including manual therapy, exercise and ultrasound (Gross et al., 2015). There is a moderate level of evidence that indicates manual therapy can be an effective intervention for neck pain when it is provided in multiple sessions (Gross et al., 2015). The same level of evidence can be found for strengthening and endurance exercise (Louw et al., 2017). There is inconclusive evidence regarding the effectiveness of ultrasound therapy; although most of the randomized controlled trials reported positive findings, systematic reviews concluded with inconclusive results or no beneficial effects (Wong et al., 2016; Xia et al., 2017). The inconclusive findings in systematic reviews may be due to the poor quality of the primary studies including; high risk of bias, lack of intention to treat analysis, inconsistent outcomes assessed, and use of heterogeneous parameters of ultrasound therapy. The lack of

common neck pain nomenclature amongst researchers and clinicians may have led to the heterogeneous recruitment of participants in clinical trials eventually leading to mixed results. The small number of participants also may have contributed to the inconclusive and contradictory findings. Furthermore, at present, we are not aware of any review that examined the effectiveness of ultrasound therapy as an adjuvant to manual therapy, exercise or combined with manual therapy and exercise for the management of neck pain. Therefore, this review aims to bridge the gap of inconsistent and conflicting evidence concerning conservative management of neck pain including ultrasound therapy, manual therapy and exercise.

Chapter 3

3 Methods

The protocol for this systematic review was registered in the International Prospective Register of Systematic Reviews (CRD42018095521).

3.1 Search Methods for identification of studies

3.1.1 Electronic search

This review included randomized controlled trials published in English. A comprehensive systematic literature search was conducted and completed on March 10, 2019. The search strategy contained terms that were related to five main domains; 1) neck pain; 2) ultrasound therapy; 3) phonophoresis; 4) manual therapy and 5) exercise. The following electronic bibliographic databases were searched, and specific search strategies are presented in Appendix A:

1. Medline; 1946 to March 2019 (via Ovid);
2. Embase; 1974 to March 2019 (via Ovid);
3. Allied and Complementary Medicine Database (AMED); 1985 to March 2019 (via Ovid);
4. Cumulative Index to Nursing and Allied Health Literature (CINAHL); 1981 to March 2019;
5. Cochrane Central Register of Controlled Trials (CENTRAL); inception to March 2019;
6. Physiotherapy Evidence Database (PEDro); inception to March 2019;
7. PubMed; inception to March 2019.

3.1.2 Other sources

Additional literature searches were done up to March 2019 in the following databases:

1) clinicaltrials.gov;
2) who.org;
3) International Clinical Trials Registry Platform (ITRP);
4) Scopus (peer reviewed research literature).

A Cervical Overview Group (COG) database for conservative management of neck pain was also screened for eligible studies.

3.2 Selection of Studies

Two reviewers (KD and JG) independently screened the titles and abstracts for relevant studies. Full text papers were used to determine eligibility and data extraction was conducted using a pre-determined standardized data abstraction form (Appendix B). Disagreements between the two reviewers were resolved through discussion or by a third reviewer (NG).

3.2.1 Types of studies

Studies included were published reports of completed randomized controlled trials and quasi-randomized controlled trials.

3.2.2 Types of participants

Studies with participants who were adults 18 years of age and older, presenting with acute, subacute or chronic non-specific neck pain without cervicogenic headache and radiculopathy were considered for this systematic review (Carette, Phil, & Fehlings, 2005; Jull, 2008). Non-specific neck pain included mechanical neck pain, sprain and strain, whiplash associated disorders

grade I and II, neck pain associated with occupation and neck pain associated with myofascial pain. Time lines for neck pain were acute (less than six weeks), subacute (six to twelve weeks) or chronic (twelve weeks or longer) (Balagué et al., 2006).

3.2.3 Types of intervention

Studies with a multimodal intervention approach that included ultrasound therapy, phonophoresis, manual therapy and exercise were included in this review. Ultrasound therapy included any mode of treatment; pulsed, continuous and High-Power Pain Threshold (HPPT). Phonophoresis included topical ointments including analgesics and non-steroid anti-inflammatory drugs. Exercises included muscle strengthening, flexibility, stretching, mobility, postural correction and proprioception exercises. Maneuvers performed by the practitioner such as joint manipulation and mobilization, and myofascial release techniques, were considered as manual therapy.

3.2.4 Types of outcome measures

Studies that reported patient-centered outcomes were considered for this review.

3.2.5 Primary Outcomes

The following were considered as the primary outcomes of interest:

1. Change in pain intensity: Studies measuring pain intensity related to neck pain using valid pain scales (e.g. Numeric Pain Rating Scale (NPRS): Visual Analogue Scale (VAS)) (Williamson & Hoggart, 2005).
2. Function/disability: Studies that included reliable and valid condition specific disability

measures and general disability measures. (e.g. Neck Disability Index (NDI) and Neck Pain and Disability score (NPAD)) (Cleland, Childs, & Whitman, 2008).

3.2.6 Secondary outcomes

The secondary outcomes were patient satisfaction, Quality of Life (e.g. SF36), Global Perceived Effect (Global Perceived Effect scale) and Return to Work (e.g. Readiness to Return-To-Work (RRTW) scale.

3.3 Data extraction and management

Two reviewers independently extracted relevant data from the included studies using the forms developed by the COG (Appendix C and Appendix D). The following data were extracted:

1. Characteristics of included studies: methodology, number analyzed, power analysis, intention to treat, settings, location of study and funding source;
2. Characteristics of participants: type of neck pain, gender, age, severity of pain, duration of complaint;
3. Characteristics of intervention: Ultrasound; (application technique, dose, frequency, mode, duration and timing). Phonophoresis; (topical ointment used, ultrasound application technique, dose, frequency, mode, duration and timing). Manual therapy; (technique, number of sessions, site, protocol and Exercise: (number of sessions, types of exercise, protocol);
4. Comparison; manual therapy, exercise, manual therapy plus exercise;
5. Outcome measures; type of outcome, measures used, baseline mean, end of the study mean, absolute benefit, timing of outcome, lost to follow-up;
6. Intervention results: significant, not significant, inconclusive;

7. Reported adverse events; and
8. Cost of care.

3.4 Assessment of risk of bias of included studies

The risk of bias of included studies was assessed using the risk of bias assessment tool, recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* and the Cochrane Back and Neck (CBN) group (Furlan et al., 2015; Sterne, Egger, Moher, Higgins, & Green, 2011). The risk of bias assessment was independently assessed by two reviewers (KD and JG) and disagreement between the reviewers was resolved by discussion or by a third reviewer (NG). Each included study was rated as 'Low Risk,' 'High Risk', or 'Unclear' according to the criteria of risk of bias assessment tool. A detailed operational definition of criteria for the risk of bias assessment can be found in Appendix E.

3.5 Measurement of treatment effect

The outcomes recorded as continuous data (e.g., pain: VAS, NPRS) were reported as Mean Differences (MD) or Standardized Mean Differences (SMDs) with 95% confidence intervals (CIs). Mean differences were used for studies reporting the same outcome measure, and when studies used different outcome measures to report the same outcome standardized mean differences were used to pool the results of studies. Risk Ratios (RRs) were calculated for the dichotomous outcomes. The Minimum Clinically Important Difference (MCIDs) for pain, function/disability was based on Cochrane Back and Neck group recommendations (Furlan et al., 2015). The minimum clinically important difference for Numeric Pain Rating Scale (NPRS) with a 100 point scale was set at 10 points (Farrar, Polomano, Berlin, & Strom, 2010; Salaffi, Stancati, Silvestri,

Ciapetti, & Grassi, 2004). For the Neck Disability Index (NDI), MCID of 7 Neck Disability Index units was considered (MacDermid et al., 2009). When there were no clear guidance on the size of clinically important effect size for outcomes, a Cohen's interpretation of effect size; small (0.20), medium (0.50) and large (0.80) was used (Cohen, 1988).

3.6 Dealing with missing data

The primary authors were contacted to provide further information whenever there was missing data from a publication. A mean and standard deviation was estimated when possible using methods suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* when the data were not available (Sterne et al., 2011).

3.7 Assessment of heterogeneity

Assessment of heterogeneity of included studies was done according to the recommendation provided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne et al., 2011). Chi-square test with a level of significance of 0.1 was used to determine the heterogeneity of studies. Studies with an I^2 more than 40 % were pooled together and the grade of evidence was downgraded due to the inconsistencies. An I^2 less than 40% was considered as an indication of homogeneity.

3.8 Assessment of reporting biases

To reduce the probability of reporting bias in our study, searches for the study protocols were performed. Published study protocols were identified to confirm whether all the pre-specified outcomes were reported. Studies were categorized as 1) unclear; when the protocol was not found,

2) low; when all the pre-specified outcomes had been adequately reported in a published report and 3) high; when one or more pre-specified outcomes in protocol were not measured, reported incompletely or not reported in the published report. The Cochrane Reporting Bias Methods Group describes the following types of reporting bias and definitions:

- Publication bias: publication or non-publication of research findings, depending on the nature and direction of results;
- Time lag bias: rapid or delayed publication of research findings, depending on the nature and direction of results;
- Language bias: publication of research findings, depending on how results align with the aspirations of the funding body;
- Outcome variable selection bias: selective reporting of some outcomes but not others, depending on the nature and direction of research findings; and
- Developed country biases: non-publication or no-indication of findings, depending on whether study authors were based in developed or developing countries

3.9 Data synthesis

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach endorsed by the *Cochrane Handbook for Systematic Reviews of Interventions* and CBNG guideline methods was utilized to analyze the overall quality of evidence for each outcome measure (Furlan et al., 2015; Sterne et al., 2011). The quality of the evidence on a specific outcome is based on performance against four domains:

1. Risk of bias; quality of evidence was not downgraded when all the studies were judged as having a low risk of bias in the earlier category. The evidence was downgraded when there

were categories within the studies that were considered to have either high or unclear risk of bias.

2. Consistency; magnitude to which outcomes for a specified comparison are reliable in terms of direction and significance. This domain was downgraded when meta-analysis was performed, and the heterogeneity test indicated $I^2 > 40\%$. The domain was also downgraded when the studies did not show statistically significant results or non-significant effects in the same direction.
3. Directness; magnitude of similarities between population, intervention and comparator, for the intervention and outcome of interest. This domain was downgraded if there was inclusion of other outcomes that were not pre-specified in our protocol (e.g. proportion of participants who improved and percentage improved in Pressure Pain Threshold). However, we considered the inclusion of outcomes (pain, function/disability, participants satisfaction, global perceived effect, return to work and quality of life) as direct evidence.
4. Precision; degree of confidence in the effect estimate. A quality of evidence was downgraded when there were fewer than 70 participants included per study arm in a comparison.

Chapter 4

4 Results

4.1 Description of studies

4.1.1 Results of the search

An electronic database search and hand search through the Cervical Overview Group database identified 224 studies after removal of duplicates. We examined 26 studies at the full-text level and included 6 studies (358 analyzed/ 361 randomized participants) for this review (*Figure 2*). The agreement for study selection at the full-text stage was 96%.

4.1.2 Included studies

The included studies involved ultrasound or phonophoresis as an adjuvant to exercise, manual therapy or combined exercise and manual therapy for treatment of neck pain. Four studies examined ultrasound including phonophoresis as an adjuvant to exercise compared to exercise alone (Durmus, Alayli, & Tufekci, 2014; Esenyel, Aldemir, & Esra, 2007; Esenyel, Caglar, & Aldemir, 2000; Mohamed, 2016). Two studies evaluated ultrasound as an adjuvant to exercise and manual therapy compared to exercise and manual therapy (Dibai-filho et al., 2017; Haran & Singh, 2013). All studies had a small sample size that ranged from 15 to 36 participants per randomized arm, and all studies were in English. Five studies included participants with chronic myofascial pain associated with neck pain (Dibai-filho et al., 2017; Durmus, Alayli, Tufekci, & Kuru, 2014; Haran & Singh, 2013; Esenyel et al., 2007, 2000), and one study included participants with subacute mechanical neck dysfunction (Mohamed, 2016).

The participants included were 18 to 60 years old. The duration of treatment was from 4 to 6 weeks in 4 studies (Dibai-filho et al., 2017; Durmus, Alayli, Tufekci, & Kuru, 2014; Haran &

Singh, 2013; Mohamed, 2016), and 10 days to 2 weeks in 2 studies (Esenyel et al., 2007, 2000). The most commonly reported outcomes were pain and function/disability. None of the included studies assessed the quality of life, global perceived effect, patient satisfaction or return to work. Detailed characteristics of individual studies are shown in the 'characteristics of included studies' (Appendix F) including treatment characteristics, co-interventions, baseline values, absolute benefits, mean differences (MD) and side effects.

4.1.3 Excluded studies

Twenty studies were excluded after full-text screening. The reasons for exclusions includes irrelevant population (n = 4; i.e. neck pain with back pain, cervical radiculopathy and temporomandibular joint disorders) ; inappropriate intervention (n = 13; i.e. multimodal therapy or ultrasound was compared to sham ultrasound) and irrelevant comparison (n = 3: i.e. ultrasound as adjuvant to exercise or manual therapy was compared to sham ultrasound plus exercise or manual therapy). Multimodal therapy refers to the intervention in which ultrasound was added to other therapies including infrared therapy, transcutaneous electrical nerve stimulation or a heat packs (Farooq et al., 2018; Kaur & Kapila, 2006; Waschl, Morrissey, & Rugelj, 2015; Yıldırım et al., 2016). See 'characteristics of excluded studies' (Appendix G) for details.

4.2 Risk of bias in included studies

The internal validity of included studies was assessed using twelve criteria in the guidelines recommended by the Cochrane Back and Neck Group (CBNG) (Furlan et al., 2015). Each risk of bias criteria is presented as a percentage across all included studies in *Figure 3*. Manual therapies and exercise therapy interventions presented with specific challenges, in which blinding of patients

and care providers was not possible. Thus, blinding of care provider and patient were rated at high risk. Similarly blinding of outcome assessor was rated high risk of bias as all of the studies involved self-reported outcomes.

4.2.1 Allocation (selection bias)

Adequate concealment had to be ensured for the study to be rated as "low risk." Common concealment methods include sequentially numbered opaque, sealed envelopes and central allocation including computer-generated randomization. One study Dibai-filho et al. (2017) was rated "low risk"; four studies were rated " unclear risk" due to inadequate reporting (Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2000; Haran & Singh, 2013; Mohamed, 2016). One study Esenyel et al. (2007) was rated " high risk." This was due to the study design which involved the consecutive assignment of participants which does not guarantee allocation concealment.

4.2.2 Blinding (performance bias and detection bias)

Three criteria including blinding of patients, care providers and outcome assessors were assessed under blinding. All six studies were rated "high risk" for patient and care provider blinding criteria. This was due to the nature of the study design involving manual therapies and exercise therapy intervention, making the treatment distinguishable. Thus, blinding was not possible for the patients and care providers. All six studies were rated either "high risk" (n = 3) or "unclear risk" (n = 3) for outcome assessor blinding. Most of the studies involved self-reported outcome measures including the Numerical Rating Scale, Visual Analogue Scale and Neck Disability Index; therefore, blinding of assessor was not possible.

4.2.3 Incomplete outcome data (attrition bias)

Two studies adequately described drop-outs with the use of tables or flow charts and were rated as "low risk" (Dibai-Filho, de Oliveira, Girasol, Dias, & Guirro, 2017; Esenyel et al., 2007). Two studies (Haran & Singh, 2013; Mohamed, 2016) were rated "high risk" due to inadequate reporting and the other two (Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2000) were rated "unclear risk" as they did not reported drop-outs.

4.2.4 Selective reporting (reporting bias)

For a study to be rated as "low risk" all the specified outcomes included in the published study protocol had to be reported apriori. This prevents selectively reporting outcome measures that favoured the hypothesis while disregarding the outcomes that dispute the hypothesis. Additionally, an intention to treat analysis was required and had to be reported. All the randomized participants in each group had to be analyzed within the group in which they were randomized to preserve the benefits of randomization. Five studies did not reference the study protocol nor reported the intention to treat analysis and were rated as "unclear risk" (Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2007, 2000; Haran & Singh, 2013; Mohamed, 2016). One study Dibai-Filho et al. (2017) had significant differences between the registered study protocol and the actual study and was rated "high risk."

4.2.5 Other potential sources of bias

All the included studies had other sources of bias. Five studies were scored "low risk" for the criteria "similarity of baseline characteristics", as there was no significant differences in the

characteristics of demographic data and pain intensity at baseline (Dibai-Filho et al., 2017; Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2007; Haran & Singh, 2013; Mohamed, 2016). One study Esenyel et al., (2000) was rated as "unclear risk" due to the inadequate description of baseline characteristics. When the studies adequately reported co-interventions and if the co-interventions were similar for the experimental and control group or avoided, they were scored "low risk" for the co-intervention criteria. Only one study Mohamed (2016) was rated "low risk" as the co-intervention was adequately described. Most of the studies were rated "unclear risk" due to inadequate reporting. For the "acceptable compliance" criteria, if studies had reported compliance adequately, they were scored "low risk." Only one study Dibai-Filho et al. (2017) was rated " low risk." Five studies were rated "unclear risk" due to insufficient description (Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2007, 2000; Haran & Singh, 2013; Mohamed, 2016). One criterion regarding timing of outcome was described sufficiently. If the studies had a similar timeline for outcome assessments for the experiential and control groups, the study was scored "low risk." All six studies were scored "low risk" (Dibai-Filho et al., 2017; Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2007, 2000; Haran & Singh, 2013; Mohamed, 2016). Dibai-Filho et al., (2017) reported source of funding and declared conflict of interest while five studies had not (Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2007, 2000; Haran & Singh, 2013; Mohamed, 2016).

Due to the small number of studies, heterogenous ultrasound parameters, dosages and techniques, duration of treatment and differences in the timing of outcomes assessed pooling of outcomes or meta-analysis was not possible.

4.3 Effects of Intervention

4.3.1 Ultrasound as an adjuvant to exercise vs exercise

Three studies of chronic myofascial pain syndrome (Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2007, 2000) and one study of sub-acute neck pain (Mohamed,2016) evaluated the effectiveness of ultrasound including continuous ultrasound, phonophoresis, and high-power pain threshold ultrasound as an adjuvant to exercise compared to the same exercise. Exercise therapy included strengthening and stretching of neck muscles.

There were no included studies with participants experiencing acute neck pain.

4.3.1.1 Pain

For subacute myofascial neck pain (1 study, 30 participants) at immediate post-treatment, there was no beneficial effect (MD -1.09, 95% CI: -3.52 to 1.34) in reduction of pain using Visual Analogue Scale when phonophoresis with diclofenac sodium was added to exercise compared to exercise alone; *Figure 4* (Mohamed, 2016). There was no data reported for short, intermediate and long-term follow-up. In a different study for chronic myofascial neck pain, when phonophoresis with capsaicin was added to exercise, (1 study, 41 participants) there was a significant statistical difference and a minimal clinically important difference in Visual Analogue Scale score (MD -3.30, 95% CI: -4.05 to -2.55) favouring adding phonophoresis as compared to exercise alone at immediate post-treatment [very low quality of evidence due to high risk of bias, inconsistency and imprecision; *Figure 4*] (Durmus, Alayli, & Tufekci, 2014).

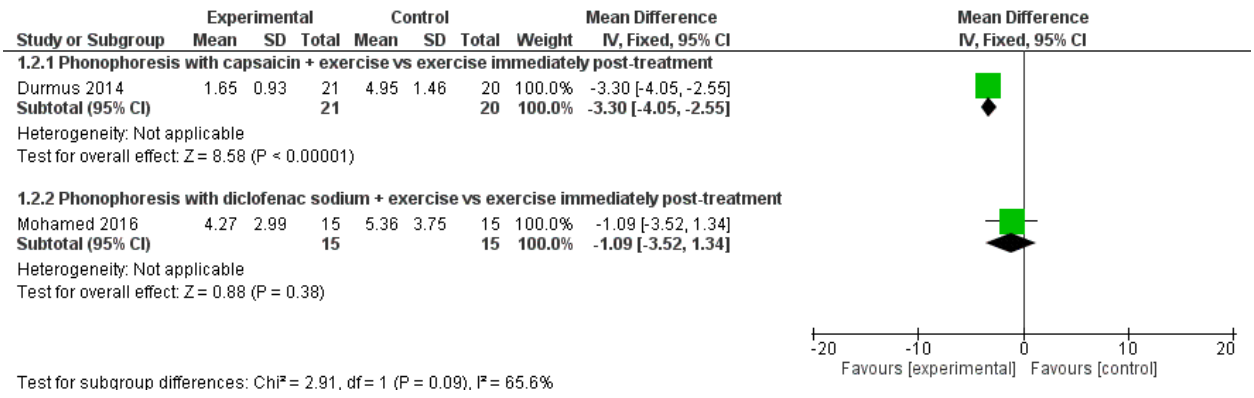

Figure 4. Forest plot of comparison: Pain: phonophoresis as adjuvant to exercise vs exercise for treatment of sub-acute to chronic neck pain.

Footnotes

(1) Durmus 2014: disorder duration: more than 12 weeks; phonophoresis with capsaicin + exercise vs exercise; duration: 6 weeks (18 sessions); follow-up: immediate post-treatment (6 weeks); instrument: VAS (0 to 10 cm)

(2) Mohamed 2016: disorder duration: less than 12 weeks; phonophoresis with diclofenac sodium + exercise vs exercise; duration: 4 days (12 sessions); follow-up: immediate post-treatment (4 weeks); instrument: VAS (0 to 10 cm)

There were 2 studies evaluating pain at immediate post-treatment in this comparison. For chronic myofascial pain syndrome (1 study, 72 participants) at immediate post-treatment, ultrasound combined with exercise demonstrated pain reduction using Visual Analogue Scale and achieved a minimal clinically important difference when compared to exercise alone [MD -3.42, 95% CI: -4.08 to -2.76, very low quality evidence due to high risk of bias, inconsistency and imprecision; *Figure 5*] (Esenyel et al., 2000). The same study (1 study, 72 participants) demonstrated no beneficial effect in improving Pressure Pain Threshold as measured by algometer when ultrasound was added to exercise at immediate post-treatment [MD 0.91, 95% CI: 0.68 to 1.14, p= < 0.01, very low quality of evidence due to high risk of bias, inconsistency and imprecision; *Figure 5*] (Esenyel et al., 2000).

For chronic myofascial pain at short-term follow-up when continuous or high-power pain threshold ultrasound was added to exercise, there was no differences in effect compared to exercise alone [very low quality of evidence due to high risk of bias, inconsistency and imprecision; *Figure 5*] (Esenyel et al., 2007).

There was one study evaluating pain at intermediate-term follow-up in this comparison. For chronic myofascial pain (1 study, 72 participants) at intermediate-term follow-up, continuous ultrasound added to exercise demonstrated beneficial effects and achieved minimal clinical important differences in pain reduction as measured by Visual Analogue Scale and compared to exercise alone [MD -2.70, 95% CI: -3.62 to -1.78, very low quality evidence due to high risk of bias, inconsistency and imprecision; *Figure 5*] (Esenyel et al., 2000). The same study (1 study, 72 participants) showed no benefit in improving Pressure Pain Threshold as measured by algometer when ultrasound was added to exercise as compared to exercise alone at intermediate-term follow-up [MD 0.27, 95% CI: 0.03 to 0.51, p= < 0.05, very low quality of evidence due to high risk of bias, inconsistency and imprecision; *Figure 5*] (Esenyel et al., 2000).

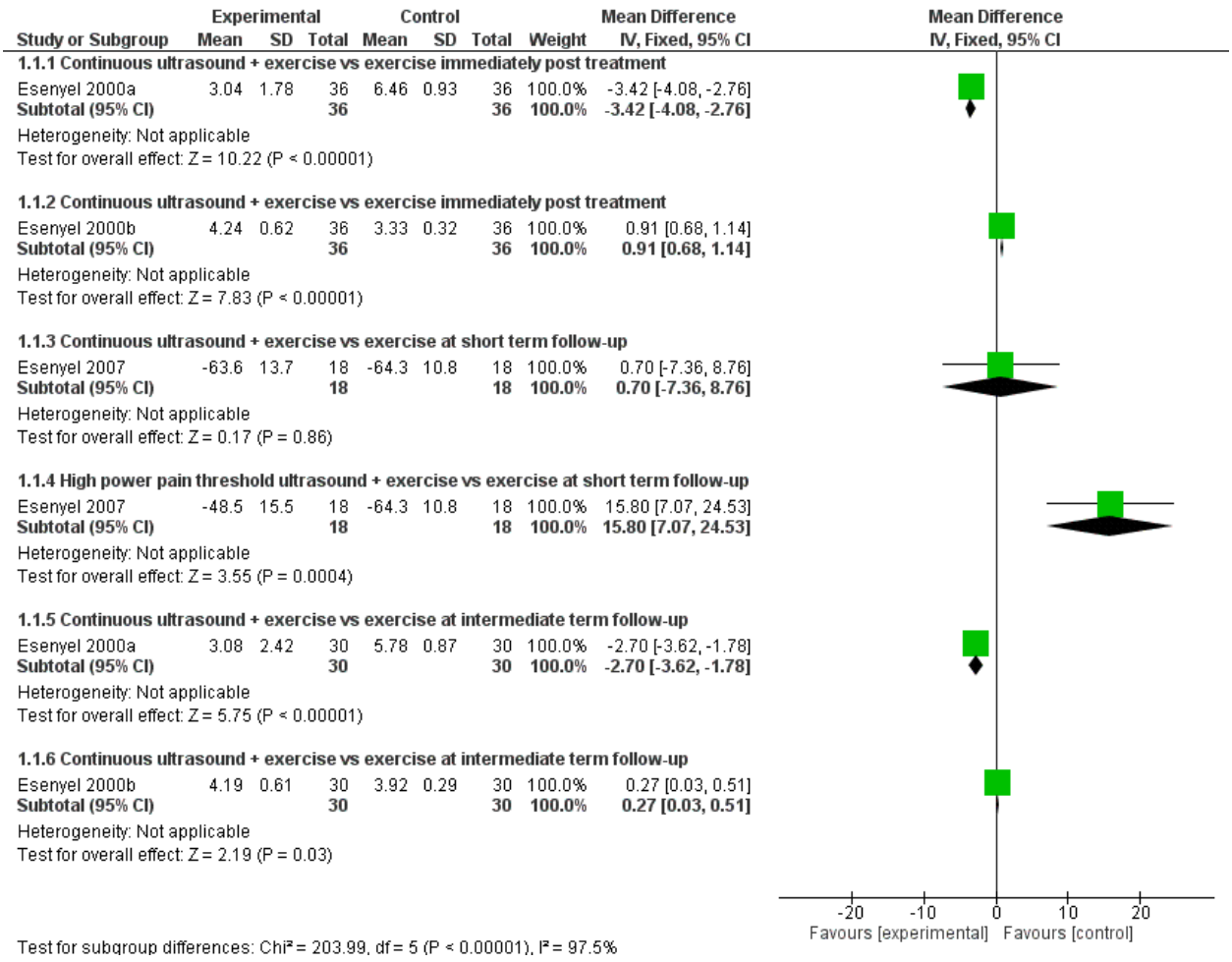

Figure 5. Forest plot of comparison: Pain: ultrasound as adjuvant to exercise vs exercise for treatment of chronic neck pain.

Footnotes

(1) Esenyel 2000a: continuous ultrasound + exercise vs exercise; duration: 2 weeks (10 sessions); follow-up: immediate post-treatment (2 weeks) and at intermediate - term (12 weeks); instrument: VAS (0 to 10 cm).

(2) Esenyel 2000b: continuous ultrasound + exercise vs exercise; duration: 2 weeks (10 sessions); follow-up: immediate post-treatment (2 weeks) and at intermediate - term (12 weeks); instrument: algometer (Pressure Pain Threshold).

(3) Esenyel 2007: continuous ultrasound + exercise or high-power pain threshold ultrasound + exercise vs exercise; duration: 10 days (10 sessions); follow-up: at short-term (2 weeks) post-treatment; instrument: VAS (0 to 10 cm).

4.3.1.2 Disability/Function

There were 2 studies evaluating disability/function at immediate post-treatment in this comparison. For subacute myofascial pain at immediate post-treatment, (1 study, 30 participants) phonophoresis with diclofenac sodium added to exercise showed no additional effect on function when compared with exercise alone (*Figure 6*) (Mohamed, 2016). At short, intermediate and long-term follow-up, there were no studies. For chronic myofascial pain at immediate post-treatment, phonophoresis with capsaicin and neck exercises (1 study, 41 participants), showed a statistically significant difference in Neck Pain and Disability score (MD -13.91, 95% CI: -18.64, -9.18, p= < 0.05); however, clinical benefits remain unknown as there was no established minimal detectable change for Neck Pain and Disability score [very low quality evidence due to high risk of bias, inconsistency and imprecision; *Figure 6*] (Durmus, Alayli, & Tufekci, 2014).

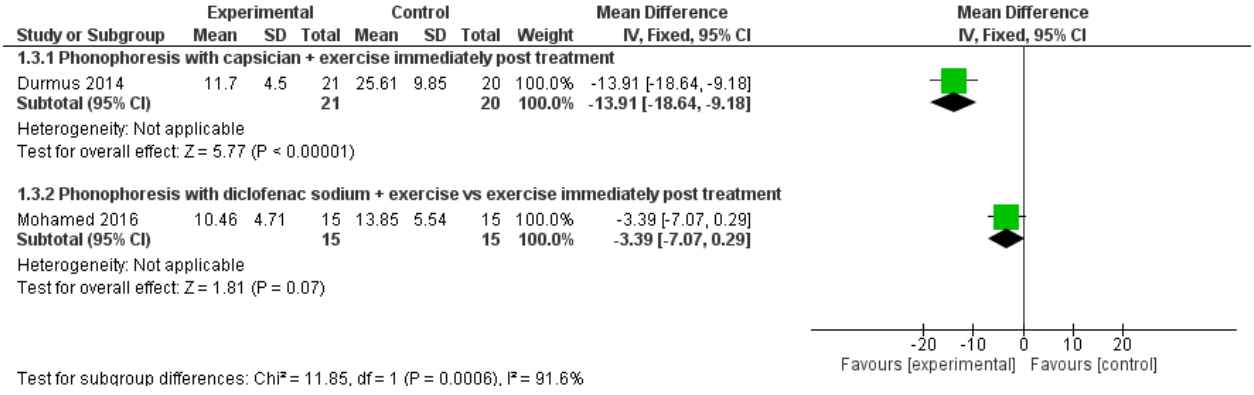

Figure 6. Forest plot of comparison: Disability/Function: phonophoresis as adjuvant to exercise vs exercise for treatment of sub-acute to chronic neck pain.

Footnotes

(1) Durmus 2014: disorder duration: more than 12 weeks; phonophoresis with capsaicin + exercise vs exercise; duration: 6 weeks (18 sessions); follow-up: immediate post-treatment (6 weeks); instrument: NPDI (0 to 100 cm).

(2) Mohamed 2016: disorder duration: less than 12 weeks; phonophoresis with diclofenac sodium + exercise vs exercise; duration: 4 days (12 sessions); follow-up: immediate post-treatment (4 weeks); instrument: NDI (0 to 50 cm).

There were no studies with short, intermediate, and long-term follow-up for disability/function.

4.3.1.3 Secondary outcomes

No studies assessed outcome such as; patient satisfaction, quality of life, global perceived effect and return to work.

4.3.2 Summary

When comparing phonophoresis with diclofenac sodium added to exercise vs exercise alone, there was very low quality evidence of no benefit for pain reduction or improvement in function/disability for sub-acute myofascial pain syndrome at immediate post-treatment. When comparing continuous ultrasound or phonophoresis with capsaicin added to exercise vs exercise alone, there was very low quality evidence of benefit for pain reduction and increase in Pressure Pain Threshold for chronic myofascial pain syndrome at immediate and intermediate-term follow-up but not at short-term follow-up. There were no studies involving continuous ultrasound and exercise examining function/disability at any time points. When comparing phonophoresis with capsaicin added to exercise vs exercise alone, there was a very low quality evidence of benefit for pain reduction demonstrating a minimal clinically important difference at immediate post-treatment.

4.3.3 Ultrasound as an adjuvant to manual therapy and exercise vs manual therapy and exercise

Two studies for chronic myofascial pain examined the effects of continuous ultrasound and high-power pain threshold ultrasound added to manual therapy and exercise (Dibai-filho et al., 2017; Haran & Singh, 2013). Dibai-filho et al. (2017) measured the outcomes immediately post-treatment and at short-term follow-up. Haran & Singh (2013) assessed the outcomes immediately post-treatment only. Continuous ultrasound treatment was provided for less than 2 minutes in Dibai-filho et al. (2017) and Haran & Singh (2013) administered high - power pain threshold ultrasound for less than 1 minute.

4.3.3.1 Pain

There were no studies examining acute and subacute neck pain populations.

For chronic myofascial pain at immediate post-treatment, (1 study, 40 participants) there was no additional benefit in reduction of pain as measured by Numerical Pain Rating Scale, when continuous ultrasound was added to manual therapy and exercise, [MD -0.75, 95% CI: -2.08 to 0.58, very low quality of evidence due to high risk of bias, inconsistency and imprecision; *Figure 7*] (Dibai-filho et al., 2017). The same study showed no significant statistical difference in Pressure Pain Threshold as compared to the manual therapy and exercise group [right side: MD 0.40, 95% CI: 0.81 to 0.01, p= 0.06. left side: MD 0.32, 95% CI: 0.83 to 0.19, p= <0.22, very low quality of evidence due to high risk of bias, inconsistency and imprecision; *Figure 7*] (Dibai-filho et al., 2017). When a high-power pain threshold ultrasound was added to manual therapy and exercise, Haran & Singh (2013) (1 study, 30 participants) demonstrated a statistically significant difference in Numerical Pain Rating Scale score (MD -0.50, 95% CI: -0.92, -0.08, p = 0.02) at immediate post-treatment as compared to manual therapy and exercise alone; however, this difference did not

achieve a minimal clinically important difference [very low quality evidence due to high risk of bias, inconsistency and imprecision; *Figure 7*].

For chronic myofascial pain at short-term follow-up, there was no additional benefit in pain reduction (MD -1.15 95% CI: -2.55 to 0.25) when continuous ultrasound was added to manual therapy and exercise compared to manual therapy and exercise alone (1 study, 40 participants) (Dibai-filho et al., 2017).

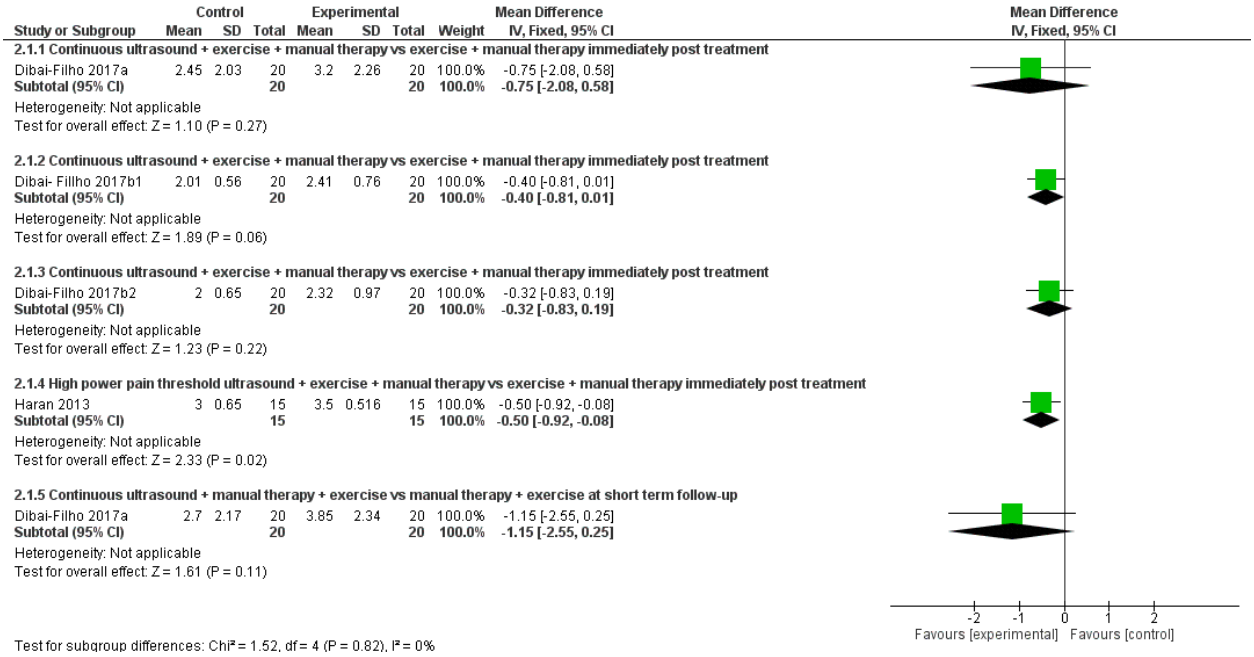

Figure 7. Forest plot of comparison: Pain: ultrasound as adjuvant to exercise and manual therapy vs exercise and manual therapy for treatment of chronic neck pain.

Footnotes

(1) Dibai-Filho 2017a: continuous ultrasound+ exercise + manual therapy vs exercise + manual therapy; duration: 5 weeks (10 sessions); follow-up: immediate post-treatment (5 weeks) and at short-term (4 weeks) after treatment; instrument: NRS (0 to 10 cm).

(2) Dibai-Filho 2017b1: continuous ultrasound+ exercise + manual therapy vs exercise + manual therapy; duration: 5 weeks (10 sessions); follow-up: immediate post-treatment (5

weeks) and at short-term (4 weeks) after treatment; instrument: algometer (Pressure Pain Threshold on right side).

(3) Dibai-Filho 2017b2: continuous ultrasound+ exercise + manual therapy vs exercise + manual therapy; duration: 5 weeks (10 sessions); follow-up: immediate post-treatment (5 weeks) and at short-term (4 weeks) after treatment; instrument: algometer (Pressure Pain Threshold on left side).

(4) Haran 2013: high - power pain threshold ultrasound + exercise + manual therapy vs exercise + manual therapy; duration: 4 weeks (8 sessions); follow-up: immediate post-treatment (4 weeks); instrument: NPRS (0 to 10 cm).

There were no included studies assessing at intermediate and long- term follow-up.

4.3.3.2 Disability/Function

There were no studies examining acute and subacute neck pain populations.

For chronic myofascial pain at immediate post-treatment, continuous ultrasound added to manual therapy and exercise (1 study, 40 participants) (MD -0.30, 95% CI: -3.14 to 2.54) or high-power pain threshold ultrasound combined with manual therapy and exercise (1 study, 30 participants) (MD 1.60, 95% CI: 0.21 to 2.99) did not show additional benefit in disability/function as measured by Neck Disability Index [very low quality evidence due to high risk of bias, inconsistency and imprecision; *Figure 8*] (Dibai-filho et al., 2017; Haran & Singh, 2013).

For chronic myofascial pain at short-term follow-up, continuous ultrasound added to manual therapy and exercise (1 study, 40 participants) did not show additional benefit in disability/function as measured by Neck Disability Index (MD-1.05, 95% CI: -4.27 to 2.17) as compared to manual therapy and exercise [very low quality evidence due to high risk of bias, inconsistency and imprecision; *Figure 8*] (Dibai-filho et al., 2017).

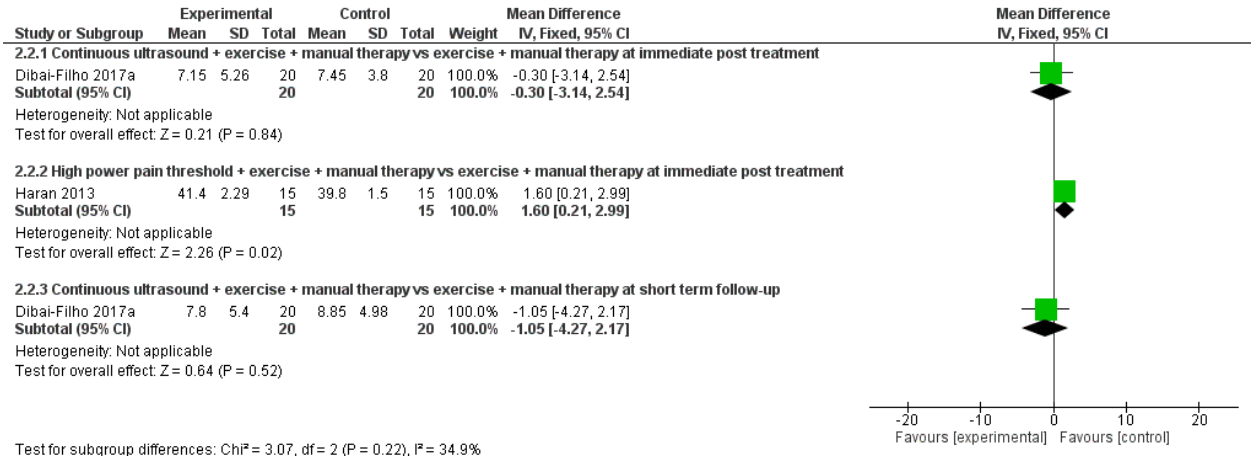

Figure 8. Forest plot of comparison: Disability/Function: ultrasound as adjuvant to exercise and manual therapy vs exercise and manual therapy for treatment of chronic neck pain.

Footnotes

(1) Dibai-Filho 2017a: continuous ultrasound+ exercise + manual therapy vs exercise + manual therapy; duration: 5 weeks (10 sessions); follow-up: immediate post-treatment (5 weeks) and at short-term (4 weeks) after treatment; instrument: NDI (0 to 50 cm).

(2) *Haran 2013: high - power pain threshold ultrasound + exercise + manual therapy vs exercise + manual therapy; duration: 4 weeks (8 sessions); follow-up: immediate post-treatment (4 weeks); instrument: NDI (0 to 50 cm).*

There were no studies with intermediate and long-term follow-up.

4.3.4 Secondary outcomes

No studies assessed outcomes such as; patient satisfaction, quality of life, global perceived effect and return to work.

4.3.5 Summary

When comparing continuous ultrasound added to manual therapy and exercise vs the same manual therapy and exercise, there was very low quality evidence of no benefit for pain reduction and increase in Pressure Pain Threshold for chronic myofascial pain syndrome at immediate post-treatment and short-term follow-up. There was very low quality evidence of benefit for pain reduction for chronic myofascial pain at immediate post-treatment when high-power pain threshold ultrasound was added to manual therapy and exercise. There was very low quality evidence of no benefit for improving function/disability at immediate or short-term follow-up for chronic myofascial pain syndrome when continuous ultrasound or high-power pain threshold ultrasound was added to manual therapy and exercise compared to manual therapy and exercise. There were no studies involving continuous ultrasound or high-power pain threshold added to manual therapy and exercise examining pain intensity and function/disability at intermediate and long-term follow-up.

4.4 Ultrasound as an adjuvant to manual therapy vs manual therapy

There were no studies examining ultrasound as an adjuvant to manual therapy vs manual therapy alone.

Chapter 5

5 Discussion

5.1 Summary of main results

Six studies assessing the effectiveness of ultrasound or phonophoresis as an adjuvant to exercise or a combination of manual therapy and exercise for neck pain met the inclusion criteria for this review. The studies assessed several outcomes, including pain intensity and function/disability. All participants in the studies experienced chronic cervical myofascial pain except in one study, which included participants with subacute myofascial pain. The evidence is as follows:

1. There was very low quality of evidence of benefit in pain reduction and increase in Pressure Pain Threshold for chronic myofascial neck pain at immediate post-treatment or intermediate-term follow-up when continuous ultrasound or phonophoresis with capsaicin was added to exercise compared to exercise alone.
2. There was no evidence of benefit for adding continuous ultrasound to manual therapy and exercise for reducing pain or improving function/disability for chronic myofascial pain compared to manual therapy and exercise alone at immediate, short-term, intermediate or long-term follow-up.
3. There was very low quality of evidence of benefit for pain reduction when high-power pain threshold ultrasound was added to manual therapy and exercise at immediate-term follow-up but no difference in improving function/disability.

Overall, the results demonstrated no conclusive beneficial effect of ultrasound owing to a very low quality of evidence; thus, we could not draw an inference from this review.

5.2 Challenges

In addition to the limited available research in the field, there were several challenges with this review, which are as follows:

1. The heterogeneity of outcome measures, including the timing of outcome assessment across the studies, made it impossible to pool the outcome data and difficult to report the results.
2. Studies such as Haran & Singh (2013) did not report on the cross-cultural adaptation and validity of outcome measures including the Neck Disability Index and Visual Analogue Scale raising concerns on the reliability and validity of the instruments used. Another study Mohamed, (2016) reported means without standard deviations, which made extraction of the outcome data challenging. When authors were contacted to provide more information or additional data, none of the authors responded. Thus, we estimated the missing data from the study with the help of a statistician.
3. Inconsistent reporting of outcomes across studies. For example; Esenyel, Caglar, & Aldemir (2000) reported overall Pressure Pain Threshold for the neck while Dibai-filho et al. (2017) reported Pressure Pain Threshold separately for left and right side of the neck.
4. None of the studies reported on minimal detectable change nor minimally clinically important differences making it unclear if the benefits of intervention were important to patients even if results demonstrated a significant statistical difference.

5.3 Overall completeness and applicability

There were several gaps found in terms of clinical applicability in the design of the included studies. First, an ideal technique outlining the parameters and dosage of ultrasound could not be

determined. All six studies described the parameters for ultrasound including dosage, intensity, frequency, duration and techniques for ultrasound therapy. Two studies, Esenyel et al. (2007) and Haran & Singh (2013), involving high-power pain threshold ultrasound, used similar dosage and parameters recommended by Majlesi & Unalan (2004). However, most studies utilized different frequencies and dosage of ultrasound, which made it difficult to determine the most effective dosage.

Second, details of participants were adequately described in most of the studies, and at least one of the primary outcomes such as pain intensity or function/disability was reported. However, most studies measured outcomes immediately post-treatment (Dibai-Filho et al., 2017; Durmus, Alayli, & Tufekci, 2014; Esenyel et al., 2000; Haran & Singh, 2013; Mohamed, 2016). Only half of the included studies assessed outcomes at short-term or intermediate - term follow-up and none of the studies measured outcomes at long-term follow-up (Dibai-filho et al., 2017; Esenyel et al., 2007, 2000). It is unknown whether ultrasound may have beneficial effects for reduction of pain or improving function for participants with neck pain when used for a longer period or at long-term follow-up.

Third, none of the studies reported on patient satisfaction, quality of life, global perceived effect, and return to work. It is unknown whether ultrasound may have a beneficial effect on these outcomes. These outcome measures should be considered in future studies.

Fourth, the included studies only involved subacute mechanical and chronic myofascial pain associated with neck pain. There were no studies that included participants with acute neck pain or Whiplash- Associated Disorders. In addition, no studies were also found which evaluated the benefit of ultrasound as an adjuvant to manual therapy for acute or chronic neck pain. Therefore,

the effectiveness of treating acute or chronic myofascial pain associated with neck pain with ultrasound as an adjuvant treatment to manual therapy remains unclear.

5.4 Quality of the evidence

The quality of evidence was assessed using the GRADE approach with results indicating very low quality evidence. The critical methodological limitations included a small number of included studies that were largely of unclear or high risk of selection bias, lack of blinding, small sample size and lack of long-term follow-up. Selection bias was apparent, as all the included studies were rated as "unclear" or "high risk" for selection bias. All of the studies inadequately described the methods of randomization or allocation concealment except for one, Dibai-filho et al. (2017) which reported on allocation concealment. When the authors potentially knew about the participants' group allocation, studies were at risk of selection bias.

All studies were rated as high risk of performance and detection bias. This was due to the nature of a study design in which blinding of the patient, care provider and outcome assessor was not possible. Due to the perceptible differences in group allocation, participants would easily recognize if they had received ultrasound as an adjuvant to manual therapy or exercise. Similarly, blinding of the care provider was not possible. All studies involved self-reported outcomes, including pain intensity and function/disability; thus, outcome assessors cannot be blinded as they were aware of their treatment allocation. Furthermore, a lack of blinding can lead to exaggerated treatment effect estimates. In addition, other areas of concern included selective reporting, which were rated “unclear” for all studies except for one Dibai-filho et al. (2017), which referenced a study protocol. However, due to a significant difference in the study design in the published study protocol and published study report, it was scored " high risk." The presence of a study protocol

published before the commencement of the study, and strict adherence to the protocol, reduce the risk of reporting bias. Furthermore, except for one study Dibai-Filho et al. (2017), funding sources or conflicts of interest were not reported. Not disclosing the source of funding of clinical trials and conflicts of interest are serious concerns in clinical trials (Buffel, Boutron, Perrodeau, & Ravaud, 2014). Studies have shown that financial affiliation amongst medical device manufacturing industries or pharmaceutical companies, researchers and academic institutions could affect reporting of clinical trials results (Buffel et al., 2014; Lundh, Lexchin, Mintzes, Schroll, & Bero, 2017). Empirical evidence demonstrated that clinical trials investigating the effectiveness of drugs or medical devices which were funded by pharmaceutical or medical equipment manufacturing industries often report positive results compared to non-industry sponsored studies (Buffel et al., 2014; Lundh et al., 2017). It is possible that ultrasound manufacturing companies funded some of the studies which could promote favourable findings.

There were high numbers of "unclear" for the co-intervention and treatment compliance item which could potentially exaggerate the estimate of effect. None of the studies adequately described co-intervention during the study period, and only one study Dibai-filho et al. (2017) sufficiently described the intervention compliance.

5.5 Strengths of the review

This review has several strengths. The review was performed according to standardized procedures developed by the Cervical Overview Group and followed Cochrane guidelines for a systematic review. Multiple databases were searched, including a database maintained by the Cervical Overview Group. Two reviewers independently performed the selection of studies and extracted data. The “risk of bias” was assessed by two people and verified by one senior validity

team member of Cervical Overview Group. Similarly, two people evaluated the external validity of the studies using GRADE analysis.

5.6 Limitations

The limitations of this review were a product of the inherent weaknesses of the primary studies, including:

- Inability to perform meta-analysis mainly due to the small number of studies, heterogenous ultrasound parameters, dosages and techniques, duration of treatment and differences in the timing of outcomes assessed;
- Inclusion of studies published in English only, which could increase the risk of selection bias;
- Overrepresentation of women participants. One study Durmus et al. (2014), involved 100% female participants, and another study Dibai-filho et al. (2017) had 90% female participants. Three studies included more than 60% female participants (Esenyel et al., 2007, 2000; Haran & Singh, 2013). One study Mohamed (2016) had not reported on the sex of the participants. The effect of ultrasound on non-specific neck pain may be different in females and males, considering the higher prevalence rate of neck pain in females.
- Inability to determine publication bias due to a small number of studies; it is possible that only positive trials were published; and
- Inability to perform subgroup analysis due to high clinical heterogeneity.

5.7 Agreements and disagreements with other reviews

This is the first systematic review that examined the effectiveness of ultrasound as an adjuvant treatment for non-specific neck pain. The lack of reviews makes it challenging to make comparisons to other reviews. While the findings cannot be compared directly to other studies, examination of other studies evaluating the effectiveness of ultrasound in other conditions is worthwhile.

Findings showed very low quality evidence of benefit in pain reduction for chronic myofascial associated neck pain at immediate post-treatment and intermediate-term follow-up when continuous ultrasound or high-power pain threshold was added to exercise or manual therapy and exercise compared to control. These findings were consistent with earlier studies (Graham, 2013; Noori, Rasheed, Aiyer, Jung, & Bansal, 2019; Xia et al., 2017). Previous reviews which examined the effectiveness of ultrasound as an adjuvant treatment for myofascial pain compared to placebo or no treatment concluded there was not sufficient evidence to support the use of ultrasound as an effective treatment to decrease pain intensity and improve function for myofascial pain associated neck pain (Noori et al., 2019; Xia & Wang, 2017). However, Xia et al. (2017) found evidence of benefit for reduction of pain with continuous ultrasound or high-power pain threshold ultrasound over pulsed ultrasound in patients with myofascial pain syndrome at immediate post-treatment. Similar findings were reported by Graham (2013) who reported very low quality evidence of benefit for reduction in pain intensity immediately post-treatment, and at short-term, with continuous ultrasound or high-power pain threshold ultrasound plus exercise compared to placebo and exercise alone for management of chronic myofascial pain syndrome. Findings showed no beneficial effects when ultrasound was applied in pulsed mode for chronic myofascial pain (Graham, 2013).

A review examining the efficacy of ultrasound for chronic low-back pain reported low quality evidence of no additional benefit of ultrasound for pain reduction and improving function at short-term follow-up when ultrasound was added to exercise compared to exercise alone (Ebadi, Henschke, Nakhostin Ansari, Fallah, & Tulder, 2014). Desmeules, Boudreault, Dionne, Pierre & MacDermid (2015) examined the effectiveness of ultrasound for rotator cuff tendinopathy and concluded ultrasound added to exercise was no better than exercise alone for pain management and improvement of function. Although the reviews of Desmeules et al. (2015) and Ebadi et al. (2014) did not involve non-specific neck pain, the results were similar to our findings. In contrast, Richardson & Macintyre (2010) found that ultrasound when used in pulsed mode at low intensity ($<1.0 W/cm^2$) was most effective in pain reduction for osteoarthritis of the knee when compared to continuous ultrasound. They reported that the benefits might last for ten months after ultrasound therapy.

Schandelmaier et al. (2017) concluded that low-intensity pulsed ultrasound had no effect on bone healing and did not improve essential patient outcomes, including pain and function following any fractures regardless of location. These studies, Byl et al. (1993); Graham (2013); Richardson & Macintyre (2010); Schandelmaier et al. (2017); Xia et al. (2017), showed variability in benefits and effectiveness of ultrasound for treating various musculoskeletal disorders potentially demonstrating heterogeneity in response that could be due to many factors including the frequency and dosage of ultrasound used, high risk of bias, and different response to treatment by different tissues. Therefore, these findings suggest parameters of ultrasound including technique, frequency, dose and duration of treatment might be important considerations for future research. It has been hypothesized that the absorption of ultrasound waves and its effectiveness to produce biophysiological changes varies across various types of tissue (Shanks, Curran, Fletcher,

& Thompson, 2010). Some authors suggest the intensity of ultrasound should depend on the duration of the condition, including chronicity of tissues involved (Robertson, Ward, Low, & Reed, 2006; Watson, 2008). However, in most cases, it is not appropriate or ethical to perform a histological and pathological examination of tissue biopsy to determine the abovementioned claims conclusively. When a uniform dose of ultrasound is applied to participants during randomized controlled trials, it is assumed that all participants have homogenous conditions at comparable stages of healing. This assumption may be improbable, and it is possible that the negative findings for studies on the effectiveness of ultrasound are a result of inappropriate dosages.

5.8 Implications for practice

Ultrasound is mostly used in combination with other treatment techniques such as manual therapy, exercise or other electrotherapy modalities (Shanks et al., 2010). The use of multimodal interventions has been recommended for management of neck pain by clinical practice guidelines and is based on scientific evidence (Bier et al., 2017; Blanpied et al., 2017). Moreover, the overall benefit of multimodal interventions may be the result of small effects produced by each intervention, which are trivial on their own but significant when interventions were combined. However, the results of this systematic review demonstrated no significant benefit in pain reduction or improvement in function/disability with chronic myofascial associated - neck pain when ultrasound was used as an adjuvant to exercise or manual therapy and exercise.

In addition, when there is no high quality evidence of benefit, it is important to consider socio-economic costs. Ultrasound therapy may increase the socio-economic burden on patients and health care providers. For patients, several visits to healthcare centers are necessary as

ultrasound therapy is provided over weeks. This could increase the socio-economic burden to the patient and their family. Costs associated with health care providers' time, purchase and maintenance of ultrasound machines may be significant. Clinicians currently using ultrasound therapy as an adjuvant intervention for management of chronic myofascial associated neck pain, should carefully consider the available evidence on ultrasound, including the benefits and costs involved. Therefore, based on the abovementioned factors, including a lack of high quality evidence, we conclude that there is not enough evidence to support the use of ultrasound as an adjuvant treatment for participants with chronic myofascial associated neck pain.

5.9 Future recommendations

Ultrasound has been used as a therapeutic intervention for more than seven decades, but still, there is no high level evidence to support its effectiveness (Baker et al., 2001). The mechanism of ultrasound in which it produces physiological or therapeutic effects has been studied only in animals or in vitro (Baker et al., 2001; Draper et al., 1995; Dyson, Franks, & Suckling, 1976). There were no studies replicated in humans, and the beneficial effects demonstrated in animals, or in-vitro studies have little relevance to clinical practice. Reviews examining the effectiveness of ultrasound over a decade ago concluded there was little or no evidence that active ultrasound is better than placebo ultrasound (Baker et al., 2001).

Similar results were demonstrated by a recent review (Xia et al., 2017). Current healthcare practice emphasizes and focuses on evidence-based practice. Therefore, a healthcare provider should utilize therapeutic interventions which are investigated by rigorous studies and supported with high quality evidence. Unfortunately, there is no high quality evidence supporting the use of ultrasound therapy and future high quality randomized control trials, are imperative to support or

refute its benefits. Future research should also include objective observer-based outcome measures and other designs that may mitigate the risk for lack of blinding.

Moreover, it might be possible that the frequency or intensity of ultrasound could influence effectiveness as discussed above. Studies with strong methodological quality and of larger scale should evaluate the effectiveness of low, medium and high-powered ultrasound as an adjunct treatment for non-specific neck pain.

5.10 Knowledge Translation

There is growing evidence that a substantial number of the treatments provided by healthcare practitioners are either not required or have no to little effect (Grol, 2000; Straus, Tetroe, & Graham, 2009). Sackett et al. (2000) defined Evidence-Based Practice (EBP) as "Integration of best research evidence with clinical expertise and patient values" (Sackett, Straus, Richardson, Rosenberg,Haynes & Livingstone, 2000, p. 3). It is evident from the above definition that EBP attempts to incorporate the best research findings in clinical practice. The best research evidence includes the evidence generated from systematic reviews, meta-analyses, and randomized controlled trials (Titler, 2008).

Knowledge translation (KT) is a process which incorporates evidence-based information into the practices of health care providers to enhance healthcare and healthcare system outcomes (Khoddam, Mehrdad, Peyrovi & Schultz, 2013). The KT process involves a variety of stakeholders within the healthcare system, unlike EBP, which involves only the individual practitioner (Salbach, 2010). The terminology of KT in healthcare was first introduced by the Canadian Institutes of Health Research (CIHR) in the year 2000, and since then it has gained tremendous popularity and now is an established discipline of science (Armstrong, Waters, Roberts, Oliver, & Popay, 2006;

Davis 2003; khoddam et al., 2013; Salbach, 2010). CIHR defines KT as a: “Dynamic and iterative process that includes synthesis, dissemination, exchange and ethically sound application of knowledge to improve the health of Canadians, provide more effective health services and products and strengthen the health care system" (Canadian Institutes of Health Research, 2016).

According to Malla, Aylward, & Ward (2018), there is a lack of awareness and knowledge of KT for public health in Low and Middle-Income Countries (LMIC). These findings are evident in Bhutan as the concept of KT is relatively unheard of. According to my observations and experiences working as an educator and physiotherapist in Bhutan, stakeholders in healthcare including, policymakers, leaders, educators and clinicians appear unaware of the KT concept. The healthcare system in Bhutan has improved significantly over the past two decades, including an increase in healthcare professionals and expansion of clinics. The Bhutanese government provides free healthcare; however, like the rest of the world, the health care costs are increasing every year. Therefore, it is essential that the stakeholders in the Bhutanese healthcare system make evidence-informed decisions for sustainable free healthcare.

Physiotherapy and rehabilitation services were introduced in Bhutan in the mid-1980s at the Jigme Dorji Wangchuk National Referral Hospital (JDWNRH) by an expatriate physiotherapist. Physiotherapists in Bhutan have a broad scope of practice, ranging from patient examination and assessment to providing diagnosis and treatment. Patients have direct access to physiotherapy services, and the number of patients obtaining physiotherapy services has been growing every year (Quality Assurance and Standardization Division, 2011). In the year 2017, the physiotherapy department at the JDWNRH provided 53,829 treatment sessions, which is a 32% increase over 2016 (https://www.jdwnrh.gov.bt/departments/clinical/physiotherapy/). The number of participants obtaining physiotherapy services is significant since the city has a population of

only a little more than a hundred thousand, according to the National Statistical Bureau of Bhutan (National Statistics Bureau, 2017). The broad scope of physiotherapy and the increasing number of participants highlights the need for physiotherapists to provide evidence-based quality care.

Physiotherapy literature is growing, and there are many clinical practice guidelines, systematic reviews and meta-analyses published every year. Several studies conducted in developing countries have identified factors such as lack of resources, difficulty in obtaining full text paper, language, not able to critically appraise the research findings and lack of quality of evidence as barriers to knowledge translation (Silva, Costa, & Costa, 2015; Ramírez-Vélez, Bagur-Calafat, Correa-Bautista, & Girabent-Farrés, 2015; Yahui & Swaminathan, 2017). The situation is similar in Bhutan as senior physiotherapists and managers in the physiotherapy department have expressed similar concerns and also based on my observations working as a physiotherapist in Bhutan for more than five years. It is most likely that there is a considerable gap in knowledge uptake in the current clinical practice of Bhutanese physiotherapists. It will require proper planning, sufficient resources, persistent effort and long-term commitment to address all the barriers identified above. Therefore, it would be more realistic and feasible to initiate modest KT strategies that could be incorporated into the existing system. For example, the physiotherapy department at JDWNR hospital conducts regular workshops, telemedicine conferences and continuing medical education, which provides a perfect platform to create awareness and present research findings or clinical practice guidelines. Empirical evidence shows continued medical education involving live or multiple media, multiple educational techniques, outreach visits and systematic practice-based education as effective interventions to improve health care provider performance and increase health care outcomes (Davis, Thomson, Oxman, & Haynes, 1992; Davis, Thomson, Oxman, & Brian, 1995; Davis & Galbraith, 2008). Recommended KT interventions

include multidimensional strategies, distribution of printed or electronic clinical practice guidelines, audit and feedback, conferences conducted outside the practice and reminders. (Mazmanian & Davis, 2002). Therefore, it is imperative that any future knowledge translation intervention, including continued medical education or conferences/workshops, incorporate strategies that have demonstrated evidence of benefit.

5.11 Conclusion

This was the first systematic review examining the effectiveness of ultrasound as an adjuvant to exercise, manual therapy and manual therapy and exercise for the management of non-specific neck pain. Neck pain is a complex disorder, and several diagnostic classifications have been proposed over the last two decades to help organize the entity and guide intervention strategies. Healthcare practitioners widely use ultrasound therapy, and most clinical practice guidelines recommend multimodal interventions for management of neck pain; however, currently, there is insufficient evidence to support the benefit of ultrasound as an adjuvant treatment for non-specific neck pain owing to the very low quality of evidence. High quality randomized controlled trials are warranted.

5.12 Differences between protocol and review

The published study protocol did not include phonophoresis; however, due to a small number of studies examining ultrasound as an adjuvant treatment for non-specific neck pain, studies which examined phonophoresis as an adjuvant treatment were included in this review.

References

Ajimsha, M. S., Al-Mudahka, N. R., & Al-Madzhar, J. A. (2015). Effectiveness of myofascial release: Systematic review of randomized controlled trials. *Journal of Bodywork and Movement Therapies*, 19(1), 102–112. https://doi.org/10.1016/j.jbmt.2014.06.001

Armstrong, R., Waters, E., Roberts, H., Oliver, S., & Popay, J. (2006). The role and theoretical evolution of knowledge translation and exchange in public health. *Journal of Public Health*, 28(4), 384–389. https://doi.org/10.1093/pubmed/fdl072

Baker, Robertson, V. J., & Duck, F. A. (2001). A review of therapeutic ultrasound : *Physical Therapy*, 81(7), 1351–1358. https://doi.org/10.1093/ptj/81.7.1339

Balagué, F., Cardon, G., Eriksen, H. R., Henrotin, Y., Lahad, A., Leclerc, A., Leboeuf-yde, C. (2006). Chapter 2: European guidelines for prevention in low back pain, 15, 136–168. https://doi.org/10.1007/s00586-006-1070-3

Bertozzi, L., Gardenghi, I., Turoni, F., Villafane, J. H., Capra, F., Guccione, A. A., & Pillastrini, P. (2013). Effect of therapeutic exercise on pain and disability in the management of chronic nonspecific neck pain: Systematic review and meta-analysis of randomized trials. *Physical Therapy*, 93(8), 1026–1036. https://doi.org/10.2522/ptj.20120412

Bialosky, J. E., Bishop, M. D., Price, D. D., Robinson, M. E., & George, S. Z. (2010). The mechanisms of manual therapy in the treatment of musculoskeletal pain: A comprehensive model. *Manual Therapy*, 14(5), 531–538. https://doi.org/10.1016/j.math.2008.09.001.

Bier, J. D., Scholten-Peeters, W. G. M., Bart Staal, J., Pool, J., Van Tulder, M. W., Beekman, E., Verhagen, A. P. (2017). Clinical practice guideline for physical therapy assessment and treatment in patients with nonspecific neck pain. *American Physical Therapy Association*, 98(3), 162–171. https://doi.org/10.1111/trf.13900

Binder, A.I. (2008). Clinical Evidence: Neck pain. *British Medical Journal*, 11(3), 1 -34. https://doi.org/10.1136/bmj.39127.608299.80

Bishop, M. D., Torres-Cueco, R., Gay, C. W., Lluch-Girbés, E., Beneciuk, J. M., & Bialosky, J. E. (2015). What effect can manual therapy have on a patient's pain experience? *Pain Management*, 5(6), 455–464. https://doi.org/10.2217/pmt.15.39

Blanpied, P. R., Gross, A. R., Elliott, J. M., Devaney, L. L., Clewley, D., Walton, D. M., & Boeglin, E. (2017). Neck pain: revision 2017: Clinical practice guidelines linked to the international classification of functioning, disability and health from the orthopaedic section of the American Physical Therapy Association. *Journal of Orthopaedic & Sports Physical Therapy*, 47(7), A1-A83. https://doi.org/10.2519/jospt.2017.0302

Bogduk, N. (2011). The Anatomy and Pathophysiology of Neck Pain. *Physical Medicine and Rehabilitation Clinics of North America*, 22(3), 367–382.

https://doi.org/10.1016/j.pmr.2011.03.008

Buffel, C., Boutron, I., Perrodeau, E., & Ravaud, P. (2014). Reporting funding source or conflict of interest in abstracts of randomized controlled trials , no evidence of a large impact on general practitioners ' confidence in conclusions , a three-arm randomized controlled trial. *BMC Medicine*, 12(1), 1–9. https://doi.org/10.1186/1741-7015-12-69

Byl. (1995). The use of ultrasound as an enhancer for transcutaneous drug delivery: Phonophoresis. *Physical Therapy*, 75(6), 539–553. https://doi.org/10.1093/ptj/75.6.539

Byl, N. N., Mckenzie, A., Wong, T., & Hunt, T. K. (1993). lncisional Wound Healing: *Jaurnal of Orthopaedic Sports Physical Therapy*, (4), 619–628. https://doi.org/10.2519/jospt.1993.18.5.619

Canadian Institutes of Health Research. (2016). Knowledge translation. Retrieved May 31, 2019, from http://www.cihr-irsc.gc.ca/e/29418.html#2

Carette, S., Phil, M., & Fehlings, M. G. (2005). Cervical radiculopathy. *New England Journal of Medicine*, *353*(4), 392-399. https://doi.org/10.1056/nejmcp043887

Carlesso, L. C., MacDermid, J. C., Gross, A. R., Walton, D. M., & Santaguida, P. (2014). Treatment preferences amongst physical therapists and chiropractors for the management of neck pain: results of an international survey. *Chiropractic & Manual Therapies*, *22*(1), 1-15. https://doi.org/10.1186/2045-709X-22-11

Carroll, L. J., Hogg-Johnson, S., van der Velde, G., Haldeman, S., Holm, L. W., Carragee, E. J., & Guzman, J. (2010). Course and prognostic factors for neck pain in the general population: results of the Bone and Joint Decade 2000–2010 Task Force on Neck Pain and Its Associated Disorders. *Journal of manipulative and physiological therapeutics*, 32(2), S87-S96. https://doi.org/10.1016/j.jmpt.2008.11.013

Childs, J., Fritz, J., Piva, S., & Whitman, J. (2004). Proposal of a classification system for patients with neck pain. *Journal of Orthopaedic & Sports Physical Thearpy*, 34(11). 686-700. https://doi.org/10.2519/jospt.2004.34.11.686

Clare, H. A., Adams, R., & Maher, C. G. (2003). Reliability of Mckenzie classification of patients with cervical or lumbar pain. *Journal of Manipulative and Physiological Therapeutics*, 28(2), 122–127. https://doi.org/10.1016/j.jmpt.2005.01.003

Cleland, J. A., Childs, J. D., & Whitman, J. M. (2008). Psychometric properties of the Neck Disability Index and numeric pain rating scale in patients with mechanical neck pain. *Archives of Physical Medicine and Rehabilitation*, 89(1), 69–74. https://doi.org/10.1016/j.apmr.2007.08.126

Cohen. (2015). Epidemiology, Diagnosis, and Treatment of Neck Pain. *Mayo Clinic Proceedings*, *90*(2), 284–299. https://doi.org/10.1016/j.mayocp.2014.09.008

Cohen, J. (1988). *Statistical power analysis for the behavioural sciences* (2nd ed.). Hillsdale, N.J: L. Erlbaum Associates

Côté, P., Cassidy, J. D., Carroll, L. J., & Kristman, V. (2004). The annual incidence and course of neck pain in the general population: A population-based cohort study. *Pain*, 112(3), 267–273. https://doi.org/10.1016/j.pain.2004.09.004

Côté, P., van der Velde, G., Cassidy, J. D., Carroll, L. J., Hogg-Johnson, S., Holm, L. W., Peloso, P. M. (2008). The burden and determinants of neck pain in workers. *Spine*, *33*(Supplement), S60–S74. https://doi.org/10.1097/BRS.0b013e3181643ee4

Sackett, D.L., Straus, S.E., Richardson, W.S., Rosenberg, W., & Haynes, R. B. (2000). Evidence-Based Medicine: How to practice and teach EBM (2 nd ed.). London, England: Churchill Livingstone.

Davis, D. (2003). The case for knowledge translation: shortening the journey from evidence to effect. *BMJ*, 327(7405), 33–35. https://doi.org/10.1136/bmj.327.7405.33

Davis, D. A., Thomson, M. A., Oxman, A. D., & Haynes, N. R. (1992). Evidence for the effectiveness of CME. A review of 50 randomized controlled trials. *American Medical Association*, 268(9), 1111–1117. https://doi.org/10.1001/jama.268.9.1111

Davis, D. A., Thomson, M. A., Oxman, D., & Brian, R. (1995). Changing physician performance. A systematic review of the effect of continuing medical education strategies. *Journal of American Medical Association*, 274(9), 700–705. https://doi.org/10.1001/jama.274.9.700

Davis, D., & Galbraith, R. (2008). Continuing medical education effect on practice performance. *American College of Chest Physicians*, 135(3), 42S-48S. https://doi.org/10.1378/chest.08-2517

De Silva, T. M., Costa, L. C. M., & Costa, L. O. P. (2015). Evidence-based practice: A survey regarding behavior, knowledge, skills, resources, opinions and perceived barriers of Brazilian physical therapists from Sao Paulo state. *Brazilian Journal of Physical Therapy*, *19*(4), 294–303. https://doi.org/10.1590/bjpt-rbf.2014.0102

Desmeules, F., Boudreault, J., Joy, J. S., Dionne, C., Pierre, F., & MacDermid J.C. (2015). The efficacy of therapeutic ultrasound for rotator cuff tendinopathy. A systematic review and meta-analysis. *Physical Therapy in Sport*, 16(3), 276-284. https://doi.org/10.1016/j.ptsp.2014.09.004

Dibai-Filho, A. V., de Oliveira, A. K., Girasol, C. E., Dias, F. R. C., & Guirro, R. R. de J. (2017). Additional effect of static ultrasound and diadynamic currents on myofascial trigger points in a manual therapy program for patients with chronic neck pain. *American Journal of Physical Medicine & Rehabilitation*, *96*(4), 243–252.

https://doi.org/10.1097/PHM.0000000000000595

Doan, N., Reher, P., Meghji, S., & Harris, M. (1999). In vitro effects of therapeutic ultrasound on cell proliferation, protein synthesis, and cytokine production by human fibroblasts, osteoblasts, and monocytes. *Journal of Oral and Maxillofacial Surgery, 57*(4), 409–420. https://doi.org/10.1016/S0278-2391(99)90281-1

Draper, D. O., Castel, J. C., & Castel, D. (1995). Rate of temperature increase in human muscle during 1 MHz and 3 MHz continuous ultrasound. *Journal of Orthopaedic & Sports Physical Therapy*, 22(4), 142–150. https://doi.org/10.2519/jospt.1995.22.4.142

Dündar, Ü., Solak, Ö., Kavuncu, V., Üniversitesi, K., Fakültesi, T., Fiziksel, T., & Dal, A. (2010). Effectiveness of ultrasound therapy in cervical myofascial pain syndrome. A double blind , placebo-controlled Study. *Turkish Journal of Rheumatology*, 25(5), 110–115. https://doi.org/10.5152/tjr.2010.13

Durmus, D., Alayli, G., Tufekci, T., & Kuru, O. (2014). A randomized placebo-controlled clinical trial of phonophoresis for the treatment of chronic neck pain. *Rheumatology International*, 34(5), 605–611. https://doi.org/10.1007/s00296-013-2928-4

Dyson, M., Franks, C., & Suckling, J. (1976). Stimulation of healing of varicose ulcers by ultrasound. *Ultrasonics*, 14(5), 232–236. https://doi.org/10.1016/0041-624X(76)90024-X

Dyson, M., Pond, J., Joseph, J., & Warwick, R. (1968). The stimulation of tissue regeneration by means of ultrasound. *Clinical Science*, 35(2), 273-285. https://doi.org/10.1016/0041-624x(68)90004-8

Ebadi, S., Henschke, N., Nakhostin Ansari, Fallah, E., & Tulder, V. (2014). Therapeutic ultrasound for chronic low-back pain. *Cochrane Database of Systematic Reviews*, 2014(3), 1-50. https://doi.org/10.1002/14651858.CD009169.pub2.

Ehsani, Fa., Mosallanezhad, Z., & Vahedi, G. (2017). The prevalence , risk factors and consequences of neck pain in office employees. *Middle Ease Journal of Rehabilitation Health*, 4(2), 1- 8. https://doi.org/10.5812/mejrh.42031

Engel, G. L. (1981). The clinical application of the biopsychosocial model. *Journal of Medicine and Philosophy*, 6(2), 101–123. https://doi.org/10.1093/jmp/6.2.101

Engel, L. G. (1997). The need for a new medical model: A challenge for biomedicine. *Science*, 196(4286), 129–136. https://doi.org/10.1126/science.847460

Esenyel, M., Aldemir, T., Esra, G., Esenyel, C.M., Demir, S., & Durmusoglu, G., (2007). Myofascial pain syndrome : Efficacy of different therapies. *Journal of Back and Musculoskeletal Rehabilitation*, 20(1), 43–47. https://doi.org/10.3233/bmr-2007-20107

Esenyel, M., Caglar, N., & Aldemir, T. (2000). Treatment of myofascial pain. *American Journal of Physical Medicine & Rehabilitation*, 79(1), 48–52. https://doi.org/10.1097/00002060-200001000-00011

Farooq, M. N., Mohseni-Bandpei, M. A., Gilani, S. A., Ashfaq, M., & Mahmood, Q. (2018). The effects of neck mobilization in patients with chronic neck pain: A randomized controlled trial. *Journal of Bodywork and Movement Therapies*, 22(1), 24–31. https://doi.org/10.1016/j.jbmt.2017.03.007

Farrar, J. T., Polomano, R. C., Berlin, J. A., & Strom, B. L. (2010). A comparison of change in the 0-10 numeric rating scale to a pain relief scale and global medication performance scale in a short-term clinical trial of breakthrough pain intensity. *Anesthesiology*, 112(6), 1464–1472. https://doi.org/10.1097/ALN.0b013e3181de0e6d

Farre, A., & Rapley, T. (2017). The new old and old new medical model: Four decades navigating the biomedical and psychosocial understandings of health and illness. *Healthcare*, 5(4), 88. https://doi.org/10.3390/healthcare5040088

Fredin, K., & Lorås, H. (2017). Manual therapy, exercise therapy or combined treatment in the management of adult neck pain. A systematic review and meta-analysis. *Musculoskeletal Science and Practice*, 31(2), 62–71. https://doi.org/10.1016/j.msksp.2017.07.005

Fritz, J. M., & Brennan, G. P. (2007). Interventions for neck pain. *Physical Therapy*, 87(5), 1–12. https://doi.org/10.2522/ptj.20060192

Furlan, A. D., Malmivaara, A., Chou, R., Maher, C. G., Deyo, R. A., Schoene, M.,Van Tulder, M. W. (2015). 2015 updated method guideline for systematic reviews in the cochrane back and neck group. *Spine*, 40(21), 1660–1673. https://doi.org/10.1097/BRS.0000000000001061

Garcia, A. N., & Saragiotto, B. T. (2016). Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. *British Journal of Sports Medicine*, 50(4), 251–252. https://doi.org/10.1136/bjsports-2015-095413

Gatchel, R. J., Peng, Y. B., Peters, M. L., Fuchs, P. N., & Turk, D. C. (2007). The biopsychosocial approach to chronic pain: Scientific advances and future directions. *Psychological Blletin*, 133(4), 581–624. https://doi.org/10.1037/0033-2909.133.4.581

Gliedt, J. A., Schneider, M. J., Evans, M. W., King, J., & Eubanks, J. E. (2017). The biopsychosocial model and chiropractic: A commentary with recommendations for the chiropractic profession. *Chiropractic and Manual Therapies*, 25(1), 1–9. https://doi.org/10.1186/s12998-017-0147-x

Graham, N. (2013). An ICON overview on physical modalities for neck pain and associated disorders. *The Open Orthopaedics Journal*, 7(1), 440–460. https://doi.org/10.2174/1874325001307010440

Grol, R. (2000). Between evidence-based practice and total quality management: The implementation of cost-effective care. *International Journal for Quality in Health Care*, 12(4), 297–304. https://doi.org/10.1093/intqhc/12.4.297

Gross, A., Langevin, P., Burnie, S. J., Bédard-Brochu, M.-S., Empey, B., Dugas, E., LeBlanc, F. (2015). Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database of Systematic Review*, 2015(9), 1-238. http://dx.doi.org/10.1002/14651858.CD004249.pub4

Gross, A., Kay, TM.,Paquin, JP., Blanchette, S., Lalonde, P., Christie, T., Doupont, G., Graham, N., Burnie, J., Gelley, G., Goldsmith, CH., Forger, M., Hoving, JL., Brønfort, G., Santaguida, PL., & Cervical Overview Group (2015). Exercises for mechanical neck disorders. *Cochrane Database of Systematic Review, 2015* (1), 1-225. https://doi.org/10.1002/14651858.CD004250.pub5.Copyright

Guzman, J., Haldeman, S., Carroll, L. J., Carragee, E. J., Hurwitz, E. L., Peloso, P., Hogg-Johnson, S. (2008). Clinical practice implications of the bone and joint decade 2000–2010 task force on neck pain and its associated disorders. *European Spine Journal*, 17(S1), 199–213. https://doi.org/10.1007/s00586-008-0637-6

Guzman, J., Hurwitz, E. L., Carroll, L. J., Haldeman, S., Côté, P., Carragee, E. J., Cassidy, J. D. (2009). A new conceptual model of neck pain linking onset, course, and care: The bone and joint decade 2000-2010 task force on neck pain and its associated disorders. *Journal of Manipulative and Physiological Therapeutics*, *32*(2), S17–S28. https://doi.org/10.1016/j.jmpt.2008.11.007

Hall, H., McIntosh, G., Alleyne, J., & Cote, P. (2015). A pain in the neck. *Journal of Current Clinical Care*, 5(1), 25–34. https://doi.org/10.1007/978-1-59745-258-8_4

Haran, H., & Singh, A. K. (2013). Effect of high power pain threshold static ultrasound combined with transverse friction massage and stretching on upper trapezius myofascial trigger point. *Indian Journal of Physiotherapy and Occupatioal Therapy*, 7(3), 113–118. https://doi.org/10.5958/j.0973-5674.7.3.076

Hidalgo, B., Hall, T., Bossert, J., Dugeny, A., Cagnie, B., & Pitance, L. (2017). The efficacy of manual therapy and exercise for treating non-specific neck pain. *Journal of Back and Musculoskeletal Rehabilitation*, 30(6), 1149–1169. https://doi.org/10.3233/BMR-169615

Hogg-Johnson, S., van der Velde, G., Carroll, L. J., Holm, L. W., David Cassidy, J., Guzman, J., Peloso, P. (2000). The burden and determinants of neck pain in the general population results of the bone and joint decade 2000 –2010 task force on neck pain and its associated disorders. *Spine*, 33(4S), 39–51. https://doi.org/10.1016/j.jmpt.2008.11.010

khoddam, H., Mehrdad, M., Peyrovi, H., & Schultz, A. M. A. (2013). Knowledge translation in health care: a concept analysis. *The CANNT Journal*, 23(2), 48-50. Retrieved from

http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=4301207

Hoy, D., March, L., Woolf, A., Blyth, F., Brooks, P., Smith, E., Buchbinder, R. (2014). The global burden of neck pain: Estimates from the global burden of disease 2010 study. *Annals of the Rheumatic Diseases*, 73(7), 1309–1315. https://doi.org/10.1136/annrheumdis-2013-204431

Hoy, D., Protani, M., De, R., & Buchbinder, R. (2010). The epidemiology of neck pain. Best practice and research*: Clinical Rheumatology*, 24(6), 783–792. https://doi.org/10.1016/j.berh.2011.01.019

Hurwitz, E. L., Carragee, E. J., van der Velde, G., Carroll, L. J., Nordin, M., Guzman, J., Haldeman, S. (2009). Treatment of neck pain: Noninvasive interventions. Rresults of the bone and joint decade 2000-2010 task force on neck pain and its associated disorders. *Journal of Manipulative and Physiological Therapeutics*, 32(2), S141–S175. https://doi.org/10.1016/j.jmpt.2008.11.017

Hurwitz, E. L., Randhawa, K., Yu, H., Côté, P., & Haldeman, S. (2018). The global spine care initiative: A summary of the global burden of low back and neck pain studies. *European Spine Journal*, 27(s6), 796–801. https://doi.org/10.1007/s00586-017-5432-9

Johns, L. D. (2002). Nonthermal effects of therapeutic ultrasound: The frequency resonance hypothesis. *Journal of Athletic Training*, 37(3), 293–299. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC164359/pdf/attr_37_03_0293.pdf

Jull, G., & Sterling, M. (2009). Bring back the biopsychosocial model for neck pain disorders. *Manual Therapy*, 14(2), 117–118. https://doi.org/10.1016/j.math.2009.01.004

Jun, D., Zoe, M., Johnston, V., & O'Leary, S. (2017). Physical risk factors for developing non-specific neck pain in office workers: A systematic review and meta-analysis. *International Archives of Occupational and Environmental Health* 90(5), 373-410. https://doi.org/10.1007/s00420-017-1205-3

Kaur, J., & Kapila, T. (2006). To compare the efficacy of deep transverse friction massage and ultrasound in patients with upper trapezius trigger points. *Indian Journal of Physiotherapy and Occupational Therapy*,8(4), 207–213. Retrieved from http://www.indianjournals.com/ijor.aspx?target=ijor:ijpot&volume=8&issue=4&article=039

Kavadar, G., Çağlar, N., Özen, Ş., Tütün, Ş., & Demircioğlu, D. (2015). Efficacy of conventional ultrasound therapy on myofascial pain syndrome: A placebo controlled study. *The Journal of The Turkish Society of Algology*, 27(4), 190–196. https://doi.org/10.5505/agri.2015.48569

Kennedy, A. B., Cambron, J. A., Sharpe, P. A., Travillian, R. S., & Saunders, R. P. (2016). Clarifying definitions for the massage therapy profession: The results of the best practices

symposium. *International Journal of Therapeutic Massage and Bodywork*, 9(3), 15–26. https://doi.org/10.3822/ijtmb.v9i3.312

Kenney, W. L., Wilmore, J., & Costill, D. (2015). Physiology of sport and exercise (6th ed.).Windsor, Canada: Human kinetics.

Ketenci, A., Celik, O., Esmaeilzadeh, S., & Sindel, D. (2014). The effectiveness of therapeutic ultrasound in non specific mechanical cervical pain and comparison of different application methods for clinical practice. *PM and R*, *6*(8), S140. https://doi.org/10.1016/j.pmrj.2014.08.130

Kisner, C. & Colby, L. & Borstad, J. (2018). Therapeutic exercise: foundations and techniques (7th ed.). Philadephia, PA: F.A. Davis Company.

Korhonen, T., Ketola, R., Toivonen, R., Luukkonen, R., Häkkänen, M., & Viikari-Juntura, E. (2003). Work related and individual predictors for incident neck pain among office employees working with video display units. *Occupational and Environmental Medicine*, 60(7), 475–482. https://doi.org/10.1136/oem.60.7.475

Kyvik, K. O., & Hartvigsen, J. (2006). The prevalence of neck pain in the world population : A systematic critical review of the literature. *Eurppean Spine Journal*, 15(6), 834–848. https://doi.org/10.1007/s00586-004-0864-4

Langenfeld, A., Humphreys, B. K., Swanenburg, J., & Peterson, C. K. (2015). Prognostic factors for recurrences in neck pain patients up to 1 year after chiropractic care. *Journal of Manipulative and Physiological Therapeutics*, 38(7), 458–464. https://doi.org/10.1016/j.jmpt.2015.06.014

Linton, S. J. (2000). A review of psychological risk factors in back and neck pain. *Spine*, *25*(9), 1148–1156. https://doi.org/10.1097/00007632-200005010-00017

Loch, E. G., Fischer, A. B., & Kuwert, E. (1971). Effect of diagnostic and therapeutic intensities of ultrasonics on normal and malignant human cells in vitro. *American Journal of Obstetrics and Gynecology*, 110(4), 457–460. https://doi.org/10.1016/0002-9378(71)90683-1

Louw, S., Makwela, S., Manas, L., Meyer, L., Terblanche, D., & Brink, Y. (2017). Effectiveness of exercise in office workers with neck pain: A systematic review and meta-analysis. *South African Journal of Physiotherapy*, 73(1), 1-11. https://doi.org/10.4102/sajp.v73i1.392

Ludewig, P. M., Lawrence, R. L., & Braman, J. P. (2013). What's in a name? Using movement system diagnoses versus pathoanatomic diagnoses. *Journal of Orthopaedic & Sports Physical Therapy*, 43(5), 280–283. https://doi.org/10.2519/jospt.2013.0104

Lundh, A., Lexchin, J., Mintzes, B., Schroll, & Bero, L. (2017). Industry sponsorship and research outcome, *Cochrane Database fo Systematic Reviews*, 2017(2), 1-140. https://doi.org/10.1002/14651858.MR000033.pub3.

MacDermid, J. C., Walton, D. M., Avery, S., Blanchard, A., Etruw, E., McAlpine, C., & Goldsmith, C. H. (2009). Measurement properties of the Neck Disability Index: A systematic review. *Journal of Orthopaedic & Sports Physical Therapy*, 39(5), 400-412. https://doi.org/10.2519/jospt.2009.2930

Machet, L., & Boucaud, A. (2002). Phonophoresis: Efficiency, mechanisms and skin tolerance. *International Journal of Pharmaceutics*, 243(1–2), 1–15. https://doi.org/10.1016/S0378-5173(02)00299-5

Maeda, K., Murao, F., Yoshiga, T., Yamauchi, C., & Tsuzaki, T. (1986). Experimental studies on the suppression of cultured cell growth curves after irradiation with CW and pulsed ultrasound. *IEEE Transactions on Ultrasonics, Ferroelectrics, and Frequency Control*, 33(2), 186–193. https://doi.org/10.1109/T-UFFC.1986.26813

Majlesi, J., & Unalan, H. (2004). High-Power Pain Threshold Ultrasound technique in the treatment of active myofascial trigger points. *Archives of Physical Medicine and Rehabilitation*, 85(5), 833–836. https://doi.org/10.1016/j.apmr.2003.07.023

Malla, C., Aylward, P., & Ward, P. (2018). Knowledge translation for public health in low- and middle- income countries: a critical interpretive synthesis. *Global Health Research and Policy*, 3(1), 1–12. https://doi.org/10.1186/s41256-018-0084-9

Mazmanian, P. E., & Davis, D. A. (2002). Continuing medical education and the physician as a learner: guide to the evidence. *American Medical Association*, 288(9), 1057–1060. https://doi.org/10.1001/jama.288.9.1057

Minaire, P. (1992). Disease, illness and health: theoretical models of the disablement process. *Bulletin of the World Health Organization*, *70*(3), 373–379. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2393270/pdf/bullwho00042-0081.pdf

Mohamed, M. S. M., & Ammar, T. A. (2016). Shock wave versus phonophoresis on mechanical neck dysfunction. *Journal of Pain Management*, *9*(1), 49–56. Retrieved from https://searchproquestcom.libaccess.lib.mcmaster.ca/docview/1841326719/fulltextPDF/75D698628B4B4E85PQ/1?accountid=12347

Ghaemi, N. S. (2009). The rise and fall of the biopsychosocial model. *British Journal of Psychiatry*, 195(1), 3–4. https://doi.org/10.1192/bjp.bp.109.063859

National Statistics Bureau. (2017). Census Reports. Retrieved May 31, 2019, Retrieved from http://www.nsb.gov.bt/publication/publications.php?id=2

Nielson, W. R., & Weir, R. (2001). Biopsychosocial Approaches of the treatment of chronic pain. *The Clinical Journal of Pain*, 17(4), 114–127. https://doi.org/10.1097/00002508-200112001-00020

Noori, S. A., Rasheed, A., Aiyer, R., Jung, B., & Bansal, N. (2019). Therapeutic ultrasound for pain management in chronic low back pain and chronic neck pain : A Systematic Review. *Pain Medicine*, *10*(1), 1–12. https://doi.org/10.1093/pm/pny287

Noormohammadpour, P., Farahbakhsh, F., Farahbakhsh, M. T., & Kordil, R. (2018). Prevalence of neck pain among athletes. Asian Spine Journal, *12*(6), 1146–1153. https://doi.org/10.31616/asj.2018.12.6.1146

Nordin, M., Carragee, E. J., Hogg-Johnson, S., Weiner, S. S., Hurwitz, E. L., Peloso, P. M., Haldeman, S. (2008). Assessment of neck pain ant its associated disorders. Results of the bone and joint decade 2000– 2010 task force on neck pain and its associated disorders. *Spine*, 33(4), S101–S122. https://doi.org/10.1371/journal.pgen.1004593

Nunley, P. D., Jawahar, A., Kerr, E. J., Gordon, C. J., Cavanaugh, D. A., Birdsong, E. M., Danielson, G. (2012). Factors affecting the incidence of symptomatic adjacent-level disease in cervical spine after total disc arthroplasty: 2- to 4-year follow-up of 3 prospective randomized trials. *Spine*, 37(6), 445–451. http://dx.doi.org/10.1097/BRS.0b013e31822174b3

O'Riordan, C., Clifford, A., Van De Ven, P., & Nelson, J. (2014). Chronic neck pain and exercise interventions: Frequency, intensity, time, and type principle. *Archives of Physical Medicine and Rehabilitation*, 95(4), 770–783. https://doi.org/10.1016/j.apmr.2013.11.015

Ökmen, B. M., Ökmen, K., & Altan, L. (2018). Investigation of the effectiveness of therapeutic ultrasound with high-resolution ultrasonographic cross-sectional area measurement of cervical nerve roots in patients with chronic cervical radiculopathy: Aprospective, controlled, single-blind study. *Journal of Medical Ultrasonics*, 45(3), 479–486. https://doi.org/10.1007/s10396-017-0855-9

Pizzarello, D. J., Wolsky, A., Becker, M. H., & Keegan, A. F. (1975). A new approach to testing the effect of ultrasound on tissue growth and differentiation. *Oncology*, 31(3–4), 226–232. Retrieved from https://www.karger.com/DOI/10.1159/000225026

Quality Assurance and Standardization Division. (2011). National standards for physiotherapy services quality assurance and standardization division: Ministry of health (1st ed.). Thimphu, Bhutan

Ramírez-Vélez, R., Bagur-Calafat, M. C., Correa-Bautista, J. E., & Girabent-Farrés, M. (2015). Barriers against incorporating evidence-based practice in physical therapy in Colombia: Current state and factors associated. *BMC Medical Education*, *15*(1), 1–11. https://doi.org/10.1186/s12909-015-0502-3

Richardson, J., & Macintyre, N. J. (2010). Efficacy of ultrasound therapy for the management of knee osteoarthritis : a systematic review with meta-analysis. *Osteoarthritis and Cartilage*, *18*(9), 1117–1126. https://doi.org/10.1016/j.joca.2010.06.010

Robertson, V., Ward, A., Low, J., & Reed, A. (2006). *Electrotherapy explained: principles and practice* (4th ed.). Edinburg, Scotland: Elsevier Health Sciences.

Rodríguez-Huguet, M., Gil-Salú, J. L., Rodríguez-Huguet, P., Cabrera-Afonso, J. R., & Lomas-Vega, R. (2017). Effects of myofascial release on Pressure Pain Thresholds in patients with neck pain. *American Journal of Physical Medicine & Rehabilitation*, *97*(1), 16-22. https://doi.org/10.1097/PHM.0000000000000790

Rose, J. S. (1989). Physical therapy diagnosis: Role and function. *Physical Therapy*, *69*(7), 535-537. Retrieved from http://link.galegroup.com.libaccess.lib.mcmaster.ca/apps/doc/A7804051/AONE?u=ocul_mcmaster&sid=AONE&xid=84ef0ee7

Rubin, D. I. (2007). Epidemiology and Risk Factors for Spine Pain. *Neurologic Clinics*, *25*(2), 353–371. https://doi.org/10.1016/j.ncl.2007.01.004

Rushton, A., Beeton, K., Ronel, J., Langendoen, J., Levesque, L.,… Pool, J. (2016). *International Federation of Orthopaedic Manipulative Physical Therapists* (Ifompt) Inc, Educational standards 2016. Retrieved from http://www.ifompt.org/site/ifompt/IFOMPT Standards document definitive 2016.pdf

Salaffi, F., Stancati, A., Silvestri, C. A., Ciapetti, A., & Grassi, W. (2004). Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. *European Journal of Pain*, *8*(4), 283–291. https://doi.org/10.1016/j.ejpain.2003.09.004

Salbach, N. M. (2010). Knowledge translation, evidence-based practice, and you. *University of Toronto Press and the Canadian Physiotherapy Association*, *62*(4), 293–294. https://doi.org/10.3138/physio.62.4.293

Schandelmaier, S., Kaushal, A., Lytvyn, L., Heels-ansdell, D., Siemieniuk, R. A. C., Agoritsas, T., Busse, J. W. (2017). Low intensity pulsed ultrasound for bone healing : systematic review of randomized controlled trials, 1–16. https://doi.org/10.1136/bmj.j656

Shanks, P., Curran, M., Fletcher, P., & Thompson, R. (2010). The foot the effectiveness of therapeutic ultrasound for musculoskeletal conditions of the lower limb : A literature review. *The Foot*, *20*(4), 133–139. https://doi.org/10.1016/j.foot.2010.09.006

Sterne, J. A. C., Egger, M., Moher, D., Higgins, J. P. T., & Green, S. (2011). *Cochrane handbook for systematic reviews of interventions.* Version 5.1.0. Retrieved from www.handbook.cochrane.org.

Straus, S. E., Tetroe, J., & Graham, I. D. (2009). Defining knowledge translation Review. *Journal of the Canadian Medical Association*, *181*(3–4), 165–168. https://doi.org/10.1503/cmaj.081229

Takasaki, H., & May, S. (2014). ‘ wait and see ’ and other approaches in people with neck pain : A systematic review. *Journal of Physiotherapy*, *60*(2), 78–84. https://doi.org/10.1016/j.jphys.2014.05.006

Takla, M. K. N., & Rezk-Allah Rezk, S. S. (2017). Immediate effects of simultaneous application of transcutaneous electrical nerve stimulation and ultrasound phonophoresis on active myofascial trigger points. *American Journal of Physical Medicine & Rehabilitation*, *97*(5), 332-338. https://doi.org/10.1097/PHM.0000000000000876

Taylor, N. F., Dodd, K. J., Shields, N., & Bruder, A. (2007). Therapeutic exercise in physiotherapy practice is beneficial: A summary of systematic reviews 2002-2005. *Australian Journal of Physiotherapy*, *53*(1), 7–16. https://doi.org/10.1016/S0004-9514(07)70057-0

Titler, M. G. (2008). The evidence for evidence-based practice implementation: *Patient Safety and Quality: An Evidence-Based Handbook for Nurses: 1*, 113–132. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK2659/pdf/Bookshelf_NBK2659.pdf

Tyle, P., & Agrawala, P. (1989). Drug delivery by phonophoresis. *Pharmaceutical Research*, *6*(5), 355–361. https://doi.org/10.1023/a:1015967012253

Ustun, N., Arslan, F., & Mansuroglu, A. (2014). Efficacy of EMLA cream phonophoresis comparison with ultrasound therapy on myofascial pain syndrome of the trapezius : a single - blind , randomized clinical study, 34(4), 453–457. https://doi.org/10.1007/s00296-013-2881-2

Vitor, C., Santos, D., Machado, N., Paulo, T., Bento, F., Fiorelli, S.,Vitta, A. De. (2017).Prevalence and factors associated with neck pain : A population-based study. *Brazilian Journal of Physical Therapy*, *21*(4), 274–280. https://doi.org/10.1016/j.bjpt.2017.05.005

Vos, T., Flaxman, A. D., Naghavi, M., Lozano, R., Michaud, C., Ezzati, M., … Murray, C. J. L. (2014). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990 – 2010 : A systematic analysis for the global burden of disease study 2010. *The lancet, 380(3),* 2163–2196. https://doi.org/10.1016/S0140-6736(12)61729-2

Vos, Verhagen, A., Passchier, J., & Koes, B. (2007). Management of acute neck pain in general practice: a prospective study. *The British Journal of General Practice : The Journal of the Royal College of General Practitioners*, *57*(534), 23–28. Retrieved from http://bjgp.org/content/57/534/23

Walton, D. M., Carroll, L. J., Kasch, H., Sterling, M., Verhagen, A. P., Macdermid, J. C., Carlesso, L. (2013). An overview of systematic reviews on prognostic factors in neck pain : Results from the International Collaboration on Neck Pain (ICON) Project. *The Open Orthopaedics Journal*, 7(1), 494–505.

Waschl, S., Morrissey, M. C., & Rugelj, D. (2015). The efficacy of ultrasound-facilitated electrical stimulation as an adjunct to exercise in treating chronic neck and shoulder pain. Journal of Musculoskeletal Pain, 22(1), *78-88*. https://doi.org/10.3109/10582452.2014.883009

Watson, T. (2008). *Electrotherapy E-Book: Evidence-based practice* Edinburg, Scotland: Elsevier Health Sciences.

Williamson, A., & Hoggart, B. (2005). Pain: A review of three commonly used rating scales. *Journal of Clinical Nursing*, *14*(7), 798–804. https://doi.org/10.1111/j.1365-2702.2005.01121.x

Wise, C. H. (2015). *Orthopaedic manual physical therapy from art to evidence*: From art to evidence Philadephia, PA: F.A. Davis Company.

Wong, J. J., Shearer, H. M., Mior, S., Jacobs, C., Côté, P., Randhawa, K., Taylor-Vaisey, A. (2016). Are manual therapies, passive physical modalities, or acupuncture effective for the management of patients with whiplash-associated disorders or neck pain and associated disorders? An update of the bone and joint decade task force on neck pain and its associated disorders. *Spine journal*, *16*(12), 1598–1630. Retrieved from http://dx.doi.org/10.1016/j.spinee.2015.08.024

Xia, P., Wang, X., Lin, Q., Cheng, K., & Li, X. (2017). Effectiveness of ultrasound therapy for myofascial pain syndrome: A systematic review and meta-analysis. *Journal of Pain Research*, *101(1*), 545–555. https://doi.org/10.2147/JPR.S131482

Yahui, H. C., & Swaminathan, N. (2017). Knowledge, attitudes, and barriers towards evidence-based practice among physiotherapists in Malaysia. *Hong Kong Physiotherapy Journal*, *37*(1), 10–18. https://doi.org/10.1016/j.hkpj.2016.12.002

Yıldırım, A., Akbaş, A., Dost Sürücü, G., Karabiber, M., Eken Gedik, D., & Aktürk, S. (2016). Effectiveness of ultrasound therapy on myofascial pain syndrome of the upper trapezius: A randomized, single-blind, placebo-controlled study. *Turkish Society of Physical Medicine and Rehabilitation*, *62*(4), 337–345. https://doi.org/10.5606/tftrd.2016.95777

Ylinen, J. (2007). Physical exercises and functional rehabilitation for the management of chronic neck pain. *Eura Medicophys*, *43*(1), 119–132.

Appendixes

Appendix A: Search strategy

MEDLINE [1946 – March, 2019]

1. exp Neck Pain/
2. neck pain.mp.
3. (neck adj3 pain*).mp.
4. exp Neck Injuries/
5. neck injur*.mp.
6. exp WHIPLASH INJURIES/
7. whiplash injur*.mp.
8. cervical pain.mp.
9. cervical.mp.
10. exp SPONDYLITIS/
11. exp SPONDYLOLYSIS/
12. exp SPONDYLOLISTHESIS/
13. exp ARTHRITIS/
14. facet joint syndrome.mp.
15. 10 or 11 or 12 or 13 or 14
16. 9 and 15
17. trapezius.mp.
18. torticollis.mp.
19. exp MYALGIA/
20. Myofascial Pain Syndromes/
21. myofascial pain.mp.
22. exp Trigger Points/
23. 17 or 18 or 19 or 20 or 21 or 22
24. 9 and 23
25. exp Intervertebral Disc Degeneration/ or exp Intervertebral Disc Displacement/
26. intervertebral disk degeneration.mp.
27. 25 or 26
28. 9 and 27
29. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 16 or 24 or 28
30. exp Ultrasonic Therapy/
31. Therapeutic ultrasound.mp.
32. (ultrasound adj3 therap*).mp.
33. 30 or 31 or 32
34. chiropractic/
35. ((neck or spine or spinal or cervical or chiropractic* or musculoskeletal* or musculo-skeletal*) adj3 (adjust* or manipulat* or mobiliz* or mobilis*)).tw.
36. (manual adj therap*).tw.
37. (manipulati* adj (therap* or medicine)).tw.
38. Nimmo.mp.
39. exp Vibration/tu [Therapeutic Use]
40. (vibration adj5 (therap* or treatment*)).tw.

41. (Chih Ya or Shiatsu or Shiatzu or Zhi Ya).tw.
42. (flexion adj2 distraction*).tw.
43. (myofascial adj3 (release or therap*)).tw.
44. muscle energy technique*.tw.
45. proprioceptive Neuromuscular Facilitation*.tw.
46. trigger point release.mp.
47. myofascial release technique*.mp.
48. cyriax friction.tw.
49. (lomilomi or lomi-lomi or trager).tw.
50. aston patterning.tw.
51. (amma or ammo or effleuurage or petrissage or hacking or tapotment).tw.
52. Complementary Therapies/
53. ((complement* or alternat* or osteopthic*) adj (therap* or medicine)).tw.
54. (Tui Na or Tuina).tw.
55. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56. exp EXERCISE/
57. exercise.mp.
58. exp Exercise Therapy/
59. exercise therapy.mp.
60. exp Exercise Movement Techniques/
61. isometric exercise.mp.
62. exp Muscle Stretching Exercises/
63. 56 or 57 or 58 or 59 or 60 or 61 or 62
64. exp randomized controlled trials as topic/
65. randomized controlled trial.pt.
66. controlled clinical trial.pt.
67. (random* or sham or placebo*).tw.
68. placebos/
69. random allocation/
70. single blind method/
71. double blind method/
72. ((singl* or doubl* or trebl* or tripl*) adj25 (blind* or dumm* or mask*)).ti,ab.
73. (rct or rcts).tw.
74. (control* adj2 (study or studies or trial*)).tw.
75. 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74
76. 55 or 63
77. 33 and 76
78. 29 and 75 and 77

EMBASE [1974 – March, 2019]

1. exp Neck Pain/
2. NECK PAIN.mp.
3. (neck adj3 pain*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
4. exp neck injury/

5. neck injury.mp.
6. exp whiplash injury/
7. whiplash injuries.mp.
8. cervical pain.mp.
9. cervical.mp.
10. exp SPONDYLITIS/
11. exp SPONDYLOLYSIS/
12. exp SPONDYLOLISTHESIS/
13. exp ARTHRITIS/
14. facet joint syndrome.mp.
15. exp intervertebral disk degeneration/
16. exp intervertebral disk hernia/
17. intervertebral disc displacement.mp.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19. 9 and 18
20. exp cervical dystonia/
21. exp myalgia/
22. exp myofascial pain/
23. exp torticollis/
24. exp trapezius muscle/
25. exp trigger point/
26. 21 or 22 or 23 or 24 or 25
27. 9 or 26
28. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 19 or 20 or 27
29. exp ultrasound therapy/
30. Therapeutic ultrasound.mp.
31. (ultrasound adj3 therap*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
32. 29 or 30 or 31
33. exp chiropractic/
34. ((neck or spine or spinal or cervical or chiropractic* or musculoskeletal* or musculo-skeletal*) adj3 (adjust* or manipulat* or mobiliz* or mobilis*)).tw.
35. (manual adj therap*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
36. (manipulati* adj (therap* or medicine)).tw.
37. Nimmo.mp.
38. exp vibration/
39. (flexion adj2 distraction*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
40. myofascial release.mp.
41. (myofascial adj3 (release or therap*)).tw.
42. trigger point release.mp.
43. proprioceptive Neuromuscular Facilitation*.mp.
44. exp neuromuscular facilitation/
45. exp manipulative medicine/

46. exp orthopedic manipulation/
47. muscle energy technique*.mp.
48. (lomilomi or lomi-lomi or trager).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
49. exp alternative medicine/
50. Complementary Therapies.mp.
51. (complement* or alternat* or osteopthic).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
52. 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51
53. exp exercise/
54. exp stretching exercise/
55. exp kinesiotherapy/
56. Therapeutic exercise.mp.
57. exp isometric exercise/
58. exercise movement techniques.mp.
59. resistance training/
60. 53 or 54 or 55 or 56 or 57 or 58 or 59
61. controlled clinical trial.m_titl.
62. randomized controlled trial.m_titl.
63. (random* or sham or placebo*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
64. exp placebo/
65. exp randomization/
66. single blind procedure/
67. double blind procedure/
68. (rct or rcts).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
69. (singl* or doubl* or trebl* or tripl*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
70. 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71. 52 or 60
72. 32 and 71
73. 28 and 70 and 72

AMED [1985 – March, 2019]

1. exp Neck pain/
2. neck pain.mp.
3. (neck adj3 pain*).mp. [mp=abstract, heading words, title]
4. exp Neck injuries/
5. exp Whiplash injuries/
6. whiplash injurie$.mp.

7. cervical.mp.
8. exp Spondylolysis/
9. exp Spondylitis/
10. exp Spondylolisthesis/
11. exp Arthritis/
12. exp Intervertebral Disk Degeneration/
13. intervertebral disc degeneration.mp.
14. 8 or 9 or 10 or 11 or 12 or 13
15. 7 and 14
16. myalgia.mp.
17. exp myofascial pain syndromes/
18. myofascial pain.mp.
19. trigger point.mp.
20. exp Torticollis/
21. exp Dystonia/
22. trapezius.mp.
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. 7 and 23
25. 1 or 2 or 3 or 4 or 5 or 6 or 15 or 24
26. exp Ultrasonic therapy/
27. ultrasonic therapy.mp.
28. (ultrasound adj3 therap*).mp. [mp=abstract, heading words, title]
29. (ultrasonic adj3 therap*).mp. [mp=abstract, heading words, title]
30. therapeutic ultrasound.mp.
31. 26 or 27 or 28 or 29 or 30
32. exp Musculoskeletal manipulations/
33. manual therapy.mp.
34. (manual adj3 therap*).mp. [mp=abstract, heading words, title]
35. exp Chiropractic/
36. (neck or spine or spinal or cervical or chiropractic* or musculoskeletal* or musculo-skeletal*).mp. [mp=abstract, heading words, title]
37. exp Massage/
38. exp Vibration/
39. Nimmo.mp.
40. (Chih Ya or Shiatsu or Shiatzu or Zhi Ya).tw.
41. (flexion adj2 distraction*).tw.
42. trigger point release.mp.
43. myofascial release technique*.mp.
44. proprioceptive Neuromuscular Facilitation*.mp.
45. (effleuurage or petrissage or hacking or tapotment).mp. [mp=abstract, heading words, title]
46. (complement* or alternat* or osteopthic*).mp. [mp=abstract, heading words, title]
47. exp Complementary therapies/
48. 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
49. exp Exercise therapy/
50. exercise therapy.mp.
51. Therapeutic exercise.mp.

52. exp Exercise movement techniques/
53. exp Isometric contraction/
54. stretching exercise.mp.
55. exp Muscle contraction/
56. 49 or 50 or 51 or 52 or 53 or 54 or 55
57. exp randomized controlled trials/
58. controlled clinical trial.mp.
59. randomized controlled trial.mp.
60. randomized controlled trial.m_titl.
61. controlled clinical trial.m_titl.
62. (random* or sham or placebo*).mp. [mp=abstract, heading words, title]
63. exp Placebos/
64. exp Random allocation/
65. (singl* or doubl* or trebl* or tripl*).mp. [mp=abstract, heading words, title]
66. 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65
67. 48 or 56
68. 31 and 67
69. 25 and 66 and 68

CINHAL [1981- March, 2019]

S61 S60 AND S58 AND S25
S60 S30 AND S59
S59 S41 OR S49
S58 S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57
S57 (MM "Triple-Blind Studies")
S56 (MM "Double-Blind Studies")
S55 (MM "Single-Blind Studies")
S54 (MM "Placebos")
S53 "random allocation"
S52 (MH "Random Assignment")
S51 "controlled clinical trial"
S50 (MM "Randomized Controlled Trials")
S49 S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48
S48 "stretching exercises"
S47 (MH "Resistance Training") OR (MH "Open Kinetic Chain Exercises") OR "strengthening exercises"
S46 "exercise movement techniques"
S45 (MM "Isotonic Exercises")
S44 (MM "Isometric Exercises")
S43 "exercise therapy"
S42 (MM "Therapeutic Exercise+")
S41 S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40
S40 (MM "Therapeutic Touch")
S39 (MH "Alternative Therapies")
S38 (MM "Deep Tissue Massage")
S37 "muscle energy technique"

S36 (MM "Neuromuscular Massage")
S35 (MM "Massage+")
S34 (MM "Myofascial Release")
S33 (MH "Manipulation, Orthopedic") OR (MM "Manipulation, Chiropractic") OR (MH "Manipulation, Osteopathic")
S32 "manual therapy"
S31 (MM "Manual Therapy+")
S30 S26 OR S27 OR S28 OR S29
S29 "therapeutic ultrasound"
S28 "ultrasound therapy"
S27 "ultrasonic therapy"
S26 (MM "Ultrasonic Therapy")
S25 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S16 OR S24
S24 S7 AND S23
S23 S17 OR S18 OR S19 OR S20 OR S21 OR S22
S22 (MM "Trapezius Muscles")
S21 (MM "Torticollis")
S20 (MM "Trigger Point")
S19 (MM "Myofascial Pain Syndromes+")
S18 "myalgia"
S17 (MM "Muscle Pain")
S16 S7 AND S15
S15 S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S14 (MM "Spondylolysis")
S13 (MM "Spondylolisthesis")
S12 (MM "Spondylosis+")
S11 (MH "Arthritis+")
S10 "intervertebral disc degeneration"
S9 "intervertebral disc herniation"
S8 (MM "Intervertebral Disk Displacement")
S7 "cervical"
S6 "cervical pain"
S5 "whiplash injury"
S4 (MM "Whiplash Injuries")
S3 (MM "Neck Injuries+")
S2 "neck pain"
S1 (MH "Neck Pain")

CENTRAL [Inception to March 2019]

#1 MeSH descriptor: [Neck Pain] explode all trees
#2 neck pain:ti,ab,kw (Word variations have been searched)
#3 MeSH descriptor: [Neck Injuries] explode all trees
#4 neck injuries:ti,ab,kw (Word variations have been searched)
#5 MeSH descriptor: [Whiplash Injuries] explode all trees
#6 "whiplash injuries":ti,ab,kw (Word variations have been searched)
#7 cervical pain:ti,ab,kw (Word variations have been searched)

#8 MeSH descriptor: [Cervical Vertebrae] explode all trees
#9 MeSH descriptor: [Spondylitis] explode all trees
#10 MeSH descriptor: [Spondylolisthesis] explode all trees
#11 MeSH descriptor: [Spondylolysis] explode all trees
#12 MeSH descriptor: [Arthritis] explode all trees
#13 MeSH descriptor: [Intervertebral Disc Degeneration] explode all trees
#14 #9 or #10 or #11 or #12 or #13
#15 #14 and #8
#16 MeSH descriptor: [Myalgia] explode all trees
#17 "trapezius":ti,ab,kw (Word variations have been searched)
#18 MeSH descriptor: [Myofascial Pain Syndromes] explode all trees
#19 MeSH descriptor: [Torticollis] explode all trees
#20 MeSH descriptor: [Trigger Points] explode all trees
#21 #16 or #17 or #18 or #19 or #20
#22 #21 and #8
#23 #1 or #1 or #3 or #4 or #5 or #6 or #7 or #15 or #22
#24 MeSH descriptor: [Ultrasonic Therapy] explode all trees
#25 ultrasound therapy:ti,ab,kw (Word variations have been searched)
#26 "therapeutic ultrasound":ti,ab,kw (Word variations have been searched)
#27 #24 or #25 or #26
#28 MeSH descriptor: [Musculoskeletal Manipulations] explode all trees
#29 manual therapy:ti,ab,kw (Word variations have been searched)
#30 MeSH descriptor: [Massage] explode all trees
#31 muscle energy technique:ti,ab,kw (Word variations have been searched)
#32 MeSH descriptor: [Complementary Therapies] explode all trees
#33 #28 or #29 or #30 or #31 or #32
#34 MeSH descriptor: [Exercise Therapy] explode all trees
#35 exercise therapy:ti,ab,kw (Word variations have been searched)
#36 "therapeutic exercise":ti,ab,kw (Word variations have been searched)
#37 MeSH descriptor: [Muscle Stretching Exercises] explode all trees
#38 MeSH descriptor: [Resistance Training] explode all trees
#39 MeSH descriptor: [Exercise Movement Techniques] explode all trees
#40 MeSH descriptor: [Exercise] explode all trees
#41 #34 or #35 or #36 or #37 or #38 or #39 or #40
#42 MeSH descriptor: [Randomized Controlled Trial] explode all trees
#43 "randomised control trial":ti,ab,kw (Word variations have been searched)
#44 MeSH descriptor: [Controlled Clinical Trial] explode all trees
#45 "controlled clinical trial":ti,ab,kw (Word variations have been searched)
#46 MeSH descriptor: [Random Allocation] explode all trees
#47 MeSH descriptor: [Placebos] explode all trees
#48 MeSH descriptor: [Single-Blind Method] explode all trees
#49 MeSH descriptor: [Double-Blind Method] explode all trees
#50 singl* or doubl* or trebl* or tripl:ti,ab,kw (Word variations have been searched)
#51 #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
#52 #33 or #41
#53 #27 and #52

#54 #23 and #51 and #53

Appendix B: Study Selection Form

Study Selection Form

Author: Reviewer: Date (dd-mm-yy):

1. Methodology: RCT/ quasi-RCT
   - ☐ YES RCT = one of the following study designs were used (mark the one that applies)
     - ☐ RCT
     - ☐ RCT protocol
     - ☐ quasi-RCT
   - ☐ YES, systematic review or meta-analysis
   - ☐ UNSURE or can't tell. Specify reason:
   - ☐ NO = anything else
2. Population: any human with neck disorder
   - ☐ YES = study subjects meet inclusion criteria (mark all that apply)
     - ☐ 1. mechanical neck disorders
     - ☐ 2. neck disorders with radicular symptoms or signs
     - ☐ 3. neck disorder with headache

     AND study subjects do NOT meet any of the following exclusion criteria:

     1. long tract signs
     2. other pathological entities
     3. headache not of cervical origin, co-existing headache, a 'mixed' headache group
   - ☐ UNSURE or can't tell. Specify reason
   - ☐ NO = anything else
3. Intervention: any conservative management strategy
   - ☐ YES = one of the conservative management strategies (check category below)

     Specify comparison (i.e. US vs TENS):
     - ☐ manual therapy
     - ☐ physical medicine modalities
     - ☐ drug therapy
     - ☐ patient education or communication
   - ☐ UNSURE or can't tell. Specify reason:
   - ☐ NO = anything else
4. Outcome Measure: at least one outcome measure was used
   - ☐ YES = at least one outcome measure was used (mark all that apply)
     1. Knowledge and decision making
        - ☐ A. ergonomic knowledge
     2. Health care use
        - ☐ A. compliance measure
        - ☐ B. additional use of health care services
     3. Health and well being
        - ☐ A. disability measure
        - ☐ B. impairment measure
        - ☐ C. general health status measure
        - ☐ D. Adverse events / side effects
     4. Economic Measures
        - ☐ A. costs (cost of care, cost of treatment, other associated costs)
        - ☐ B. sick time measures (sick time, sickness level, return to work status)
     5. Other outcome measures
        - ☐ A. experience of health care, patient preference
        - ☐ B. skill performance
        - ☐ C. client behaviour
        - ☐ D. psychological outcomes
        - ☐ E. systems outcomes
        - ☐ F. other outcomes not already noted which appear to be relevant. Specify:
   - ☐ UNSURE or can't tell. Specify reason:
   - ☐ NO = anything else
5. Should this paper be included?
   - ☐ 'YES' was marked for all four of the previous criteria
   - ☐ 'UNSURE' was marked for any of the four previous criteria
   - ☐ 'NO' was marked for any of the four previous criteria
6. Are there additional references cited that should be retrieved?
   - ☐ YES ☐ No

Appendix C. Data Abstraction Form A

Data Abstraction Form A- Table of Included Studies

Author / year: Reviewer: Date (yyyy/mm/dd):

METHODS:

Type of Trial: ☐ RCT-Parallel group design; ☐ RCT- Cross over design;
☐ RCT – Stratified randomization; ☐ RCT – Cluster randomization;
☐ RCT-Factorial design; ☐ RCT – Restricted randomization (i.e. blocking)

Number Analyzed/Randomized:
☐ Arm 1 ____/____;
☐ Arm 2 ____/____;
☐ Arm 3 ____/____;
☐ Arm 4 ____/____;

Intension to Treat Analysis: ☐ not calculated, ☒ calculated; ☐ not specified
Power Analysis: ☐ not calculated, ☐ calculated (specify beta value per comparison: _____

Funding Source: _____
Declaration of Interest: _____
Location of Study (i.e. country): _____
Setting: (i.e. community private practice (out-patient), hospital, university | primary, secondary, tertiary (specialist service)**:**_____

PARTICIPANTS:

☐ Non-specific cervical disorder (specify type tick response)
☐ mechanical neck pain (sprain, strain, facet joint dysfunction/syndrome)
☐ myofascial pain syndrome
☐ other (record type: _____)

☐ Specific cervical disorder (specify type tick response)
☐ Neck disorder with radicular symptoms or signs (NDR) (specify type: _____)
☐ Cervicogenic headache (specify type: _____)
☐ Whiplash associated disorder (WAD) (specify type: _____)
☐ Neck disorder associated with degenerative changes (DC) (specify type: _____)
☐ other (record type: _____)

Radicular symptoms/signs: ☐ not specified; ☐ absent; ☐ present
(specify: % of cases with radicular (dermatomal, myotomeal, reflex) changes at baseline = ___%;
% of control with radicular (dermatomal, myotomeal, reflex) changes at baseline= ___%;
Gender (%female/male): _____
Age: mean (SD) _____;
Severity using Pain Scale: Treatment (i.e. VAS score mean) _____Control: _____
Duration of Complaint for Cases at baseline: ☐ time: _____; ☐ not specified
Duration of Complaint for Controls at baseline: ☐ time: _____; ☐ not specified

INTERVENTION:

Arm 1 (specify: _____); Arm 2 (specify: _____); Arm 3 (specify: _____)	Control 1 (specify: _____); Control 2 (specify: _____);

Treatment Description: (see HELP FILE, use back of page if necessary)

Arm 1 Type (mode, technique) defined	Dosage parameters (timing, frequency, dose, duration, route)
A)	Timing: Frequency: Dose: Duration: Route: Monitoring (technique, compliance):
Arm 2 Type (mode, technique) defined	Dosage parameters (timing, frequency, dose, duration, route)
A)	Timing: Frequency: Dose: Duration: Route: Monitoring (technique, compliance):
Control 1	Type (specify: placebo, no treatment, wait list, same treatment both arms); describe

Control 2	Type (specify: placebo, no treatment, wait list, same treatment both arms); describe

INTERVENTION (cont.):

Duration of Treatment: (mark the one that applies) ☐ not specified
☐ time (specify: _____ days; _____weeks, _____months; _____other);
Duration of Follow-up after completion of treatment: (mark the one that applies) ☐ not specified
☐time (specify: _____ days; _____ weeks, _____months; _____other); ☐ no follow-up (measures at baseline and end of treatment only)
Co-intervention: (mark the one that applies) ☐ not specified; ☐ not avoided
☐ avoided in trial design; ☐ comparable between index and control groups (specify:_____)

OUTCOME:

Outcome Measure (mark all that apply)

☐ knowledge and decision making (specify: _____); ☐ health care use (specify: _____);
☐ health and well-being (specify: _____); ☐ other (specify: _____)

Number of outcomes assessed: _____

Main Outcome(s): (list outcome for which data are abstractable and scale)

1.	scale:	☐ high score = better; ☐ low score = better
2.	scale:	☐ high score = better; ☐ low score = better

Timing of outcome:

Arm1 (specify: 1. _____, 2. _____, 3. _____, 4. _____, 5. _____)

Arm2 (specify: 1. _____, 2. _____, 3. _____, 4. _____, 5. _____)

Control 1(specify: 1. _____, 2. _____, 3. _____, 4. _____, 5. _____)

Control 2(specify: 1. _____, 2. _____, 3. _____, 4. _____, 5. _____)

Lost to follow-up:

☐ N/A; ☐ not specified; ☐ reported (specified: _____%)

Reason for Dropouts:

☐ N/A; ☐ not specified; ☐ dropouts noted
Specify:

Side Effects:

☐ not reported; ☐ reported

1.:	Index treatment #: _____; number: _____ (n) randomized: _____ Control #: _____; number: _____ (n) randomized: _____ Relative risk: _____ NNT to produce one episode of harm: _____

Cost of Care:

☐ specified (indicate cost: _____); ☐ not specified/not reported

Appendix D. Data Abstraction Form B

Data Abstraction Form B – Comparisons and Data		
Author/ Year	Reviewer:	Date (yyyy/mm/dd):
Able to extract data: __Yes for all outcomes reported; __ Partial, for some outcomes reported; __ No (if answer Yes or Partial, complete the rest of Form B)		
Comparison (ensure this is the same as in DATA EXTRACTION FORM A):		
Arm 1_____;	Arm 2 _____;	Arm 3 _____
Control 1 _____;	Control 2 _____	
Outcome: type (ie. pain): _____;	instrument (ie. VAS, tick direction): _____	__ high score = better; __ low score = better

Continuous Data

	Arm 1			Arm 2			Arm 3			Control 1		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
baseline												
T1												
	N	Median	25^{th} – 75 quartiles	N	Median	25^{th}-75^{th} quartile	N	Median	25^{th}-75^{th} quartile	N	Median	25^{th}-75^{th} quartile
baseline												
T1												

Dichotomous Data

	Arm 1		Arm 2		Arm 3		Control 1	
	n	N	n	N	n	N	n	N
T1								

Reported Results

T1	__ significant; __ not clear; __ not significant
T2	__ significant; __ not clear; __ not significant
T3	__ significant; __ not clear; __ not significant
Other statistical values are reported: __ No __ Yes (specify):	
Help from a statistician is needed: __ Yes __ No	

Appendix E. Source of Risk of Bias

Reviewer:	Date (year/mm/dd):	Reference ID:
A	Was the method of randomization adequate?	Yes / No / Unsure
B	Was the treatment allocation concealed?	Yes / No / Unsure
	Was knowledge of the allocated interventions adequately prevented during the study?	
C	1. Was the patient blinded to the intervention?	Yes / No / Unsure
D	2. Was the care provider blinded to the intervention?	Yes / No / Unsure
E	3. Was the outcome assessor blinded to the intervention?	Yes / No / Unsure
	Were incomplete outcome data adequately addressed?	
F	1. Was the drop-out rate described and acceptable?	Yes / No / Unsure
G	2. Were all randomized participants analyzed in the group to which they were allocated?	Yes / No / Unsure
H	Are reports of the study free of suggestion of selective outcome reporting?	Yes / No / Unsure
	Other sources of potential bias:	
I	1. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes / No / Unsure
J	2. Were co-interventions avoided or similar?	Yes / No / Unsure
K	3. Was the compliance acceptable in all groups?	Yes / No / Unsure
L	4. Was the timing of the outcome assessment similar in all groups?	Yes / No / Unsure
M	Is there a serious and fatal flaw with this study? (focus on the impact of selection bias, information bias, reporting errors and confounding)	Acceptable/ Flawed Yes / No / Unsure

Appendix F. Characteristics of included Studies and Risk of bias assessment

Dibai-Filho 2017

Methods	**Type of Trial:** parallel group RCT with 3 Arms **Number Analyzed/Randomized**: 60/60 (manual therapy plus stretching 20/20; static ultrasound plus manual therapy plus stretching 20/20; diadynamic currents plus manual therapy plus stretching 20/20) **Intention-to-treat Analysis**: not reported **Power Analysis**: 80% **Funding Source**: funding statements provided **Declaration of Interest**: reported
Participants	**Disorder:** chronic neck pain with active myofascial trigger points in the upper trapezius muscle **Radicular symptoms/signs**: not reported **Sex**: 90% female **Age range**: 18 to 45 years **Severity** (Baseline score measured by Numerical Rating Scale 0 to 10): manual therapy plus stretching; 3.50 (1.47); static ultrasound plus manual therapy plus stretching; 3.40 (2.21); diadynamic current plus manual therapy plus stretching; 3.00 (2.02) **Duration of complaint:** at least three months **Setting**: Laboratory of Physiotherapeutic Resources of the Ribeiro preto Medical School of the University of Sao Paulo **Location of Study**: Sao Paulo, Brazil
Interventions	**INDEX TREATMENT** **Arm 1:** continuous ultrasound plus manual therapy plus stretching; ***Activity 1*:** static ultrasound was applied over the myofascial trigger points on the upper trapezius muscle, participants remained seated during the application of ultrasound; ***Timing**:* determined by the lottery (sequence not reported); ***Frequency***: 10 sessions; ***Dose:*** 1.5 wcm^2 ,1 MHz ; ***Duration**:* 1.5 minutes; ***Route***: myofascial trigger points on upper trapezius muscle; ***Monitoring***: not reported; ***Activity 2*:** manual cervical traction, grade III posterio anterior mobilisation on spinous process of C2 to C7 with 10 oscillations for each vertebra, myofascial release of the upper trapezius muscle in three, 1-minute series for each muscle; ***Timing***: determined by the lottery (sequence not reported); ***Frequency***: 2 sessions a week for 5 weeks; ***Dose**:* 10 sessions. ***Duration***: three, one-minute sessions with 30-second rest between sessions. ***Route***: cervical spine; ***Monitoring**:* not reported; ***Activity 3***: static stretching of upper trapezius muscle for three 30 second series, with 30 second intervals between series; ***Timing***: following manual therapy and ultrasound; ***Frequency*:** 2 sessions a week for 5 weeks; ***Dose*:** 10 sessions; ***Duration:*** three, 30 second series with 30 second rest between sessions*;* ***Route:*** upper trapezius muscle; **Monitoring***:* not reported **COMPARISON TREATMENT** ***Arm 2:*** manual therapy plus stretching*;* ***Activity 1:*** manual cervical traction, grade

	III posterio anterior mobilisation on spinous process of C2 to C7 with 10 oscillations for each vertebra, myofascial release of the upper trapezius muscle in three, 1-minute series for each muscle; ***Timing:*** pre-stretching; ***Frequency***: 2 sessions a week for 5 weeks. ***Dose***: 10 sessions; ***Duration****:* three, one minute sessions with 30 second rest between sessions; ***Route****:* cervical spine; ***Monitoring****:* not reported; ***Activity 2****:* static stretching of upper trapezius muscle for three 30 second series, with 30 second intervals between series; ***Timing****:* following manual therapy; ***Frequency:*** 2 sessions a week for 5 weeks*;* ***Dose:*** 10 sessions; ***Duration:*** three, 30 second series with 30 second rest between sessions; **Route:** upper trapezius muscle. ***Monitoring***: not reported **Treatment Schedule:** 5 weeks (10 sessions) **Timing of outcomes**: baseline, 48 hours after the 1st session, 48 after 10th session. **Duration of Follow-up:** 4 weeks **Co-intervention**: not reported
Outcomes	**PAIN INTENSITY:** Numerical Rating Scale (scale from 0 to 10, low score is better) **Baseline Mean**: pain at rest: Arm 1: 3.40, Arm 2: 3.50; pain during movement: Arm 1: 5.15, Arm 2: 5.50 **End of Study Mean:** pain at rest: Arm 1: 1.30, Arm 2: 1.90; pain during movement: Arm 1: 2.45, Arm 2: 3.20 **Absolute Benefit:** Mean difference (pain during movement): at immediate post-treatment: -0.75 [95% CI: -2.08, 0.58]; at short-term follow-up: -1.15 [95% CI: -2.55, 0.25] **FUNCTION:** Neck Disability Index (scale from 0 to 50, low score is better) **Baseline Mean**: Arm 1: 11.90, Arm 2: 12.20 **End of Study Mean:** Arm 1: 7.15, Arm 2: 7.45 **Absolute Benefit**: Mean difference: at immediate post-treatment: -0.30 [95% CI: -3.14, 2.54]; at short-term follow-up: -1.05 [95% CI: -4.27, 2.17] **PATIENT SATISFACTION**: not reported **QUALITY OF LIFE**: not reported **GLOBAL PERCEIVED EFFECT**: not reported **RETURN TO WORK**: not reported **ADVERSE EVENT**: not reported

Risk of Bias

Bias	Authors' judgement	Support for judgement
A) Adequate randomization	Unclear risk	Comment: not adequately reported
B) Allocation concealment (selection bias)	Low risk	Quote: page 244, " Concealed allocation of individuals was carried out with opaque envelopes sealed and sequentially numbered. Envelopes were only opened at the moment of the intervention"
C) Blinding (patient)	High risk	Comment: unable due to study design
D) Blinding (care provider)	High risk	Comment: unable due to study design
E) Blinding (outcome assessor)	Low risk	Quote: page 244, "The physical therapist responsible for assessment did not know which group the participants had been allocated"
F) Incomplete outcome data (attrition bias)	Low risk	Comment: page 247, figure 1, analysed n = 60
G) Randomised participants analyzed in their groups (reporting bias)	Low risk	Comment: page 247, figure 1, analysed n = 60
H) Selective reporting (reporting bias)	High risk	Quote: page 244, "Registered in ClinicalTrials.gov (NCT01869283)" Comment: registered protocol had four arms, but the trial included only three arms
I) Similarity of baseline characteristics	Low risk	Comment: page 248, Table 1, there were no differences in gender, age, duration of symptoms or body mass index
J) Co-intervention avoided or similar	Unclear risk	Comment: not reported
K) Acceptable compliance	Low risk	Quote: page 247, " There was high adherence to the 10 proposed physical therapy interventions with mean (SD) of 9.35 (2.15) session in group 1, a mean (SD) of 9.75(0.91) in group 2, and a mean (SD) of 9.60 (1.27) session in group 3"
L) Timing outcome assessments similar	Low risk	Comment: baseline, 48 hours after the 1st session, 48 hours after the 10th session, 4 weeks
M) Other potential sources of bias	Unclear risk	Comment: the registered protocol had four arms, but the trial included only three arms. Randomization process was not reported Funding source: Quote, page 243, "The study received funding from the Sao Paulo Research Foundation (FAPESP, grants

		2013/19368-8, 2015/04076-7, and 2013/09753-1)" Conflict of interest: Quote: page 243, Footnote right column, "No conflict of interest has been reported by the authors or by any individuals in control of the content of this article"

Durmus 2014

Methods	**Type of Trial:** parallel group RCT with 3 Arms **Number Analyzed/Randomized**: 61/64. (phonophoresis with capsaicin plus exercise 21/22; placebo phonophoresis plus exercise 20/21; Exercise 20/31) **Intention-to-treat Analysis**: not reported **Power Analysis**: 80% **Funding Source**: not reported **Declaration of Interest**: reported
Participants	**Disorder:** chronic neck pain **Radicular symptoms/signs**: not reported **Sex**: 100% female **Age range**: phonophoresis with capsaicin plus exercise (mean); 55.71, placebo phonophoresis plus exercise (mean); 54.15, Exercise (mean); 54.75 **Severity** (baseline score measured by Visual Analog during activity: Scale 0 to 10): phonophoresis with capsaicin plus exercise; 6.65(1.42), placebo phonophoresis plus exercise; 6.35(1.89), Exercise; 6.61(1.74) **Duration of complaint:** at least three months **Setting**: Outpatient, Department of Physical Medicine and Rehabilitation of Medical Faculty of Ondokuz Mayis Univesity, Samsun **Location of Study**: Samsun, Turkey
Interventions	**INDEX TREATMENT** ***Arm 1:*** phonophoresis with capsaicin plus exercise; ***Activity 1:*** ultrasound was applied with 5 cm diameter applicator in circular motion with 2-3 mm thickness topical gel containing capsaicin over the paravertebral neck region; ***Timing***: before exercise; ***Frequency:*** 3 days a week, 18 sessions; ***Dose:*** 1.5 wcm^2 , 1 MHz; ***Duration:*** 10 minutes; ***Route:*** paravertebral neck region; ***Monitoring:*** immediate; ***Topical drug***: capsaicin (10% capsicum oleoresin 0.20%); ***Activity 2*:** A group exercise program composed of 60 minutes of cervical, thoracic, lumbar and abdominal exercises with a warm-up and cool-down period of 10 minutes and tretching exercises 3 days a week was provided under the supervision of physiatrist. Neck exercise program including isotonic, isometric, and stretching exercises was given. Additional exercise program including: (1) flexibility and strengthening exercise of the thoracic and lumbar spine, stretching of erector spine muscle, hamstring muscle and abdominal muscles; pelvic tilt, cat and camel, back extension and lower abdominal exercise; (2) stability exercise, mobility exercise and flexibility exercise of lower limbs muscles; (3) functional exercise to improve postural control, dynamic body balance and coordination; (4) progressive relaxation exercises to normalize muscle tension.. Participants came to the outpatient department to perform the exercise; ***Timing***: after application of

	phonophoresis; ***Frequency:*** 3 days/ week. ***Dose:*** not reported, ***Duration:*** 60 minutes***; Route:*** cervical spine, thoracic spine, lumbar spine, abdomen, pelvis, and lower limb. ***Monitoring***: immediate **COMPARISION TREATMENT** ***Arm 2:*** exercise; ***Activity 1*****:** A group exercise program composed of 60-minutes of cervical, thoracic, lumbar and abdominal exercise with a warm-up and cool-down period of 10 minutes was performed. A neck stretching exercises 3 days a week was provided under the supervision of physiatrist. A neck exercise program including isotonic, isometric, and stretching was given. Additional exercise program including: (1) flexibility and strengthening exercise of the thoracic and lumbar spine, stretching of erector spine muscle, hamstring muscle and abdominal muscles; pelvic tilt, cat and camel, back extension and lower abdominal exercise; (2) stability exercise, mobility exercise and flexibility exercise of lower limbs muscles; (3) functional exercise to improve postural control, dynamic body balance and coordination; (4) progressive relaxation exercises to normalize muscle tension.. Participants came to the outpatient department to perform the exercise; ***Timing:*** after application of phonophoresis; ***Frequency:*** 3 days/ week. ***Dose***: not reported, ***Duration***: 60 minutes***; Route:*** cervical spine, thoracic spine, lumbar spine, abdomen, pelvic, and lower limb. ***Monitoring:*** immediate **Treatment Schedule:** 6 weeks (18 sessions) **Timing of outcomes**: baseline, and at immediate post-treatment (6 weeks) **Duration of Follow-up:** immediate post-treatment **Co-intervention**: use of NSAIDs, analgesics, antidepressant drugs had to be discontinued 7 days before the start of the study and were not allowed during the study period
Outcomes	**PAIN INTENSITY:** Visual Analog Scale (scale from 0 to 10, low score is better) **Baseline Mean**: pain at rest: Arm 1: 4.50, Arm 2: 3.85; pain during movement: Arm 1: 6.65, Arm 2: 6.61 **End of Study Mean:** pain at rest: Arm 1: 0.70, Arm 2: 2.76; pain during movement: Arm 1: 1.65, Arm 2: 4.95 **Absolute Benefit:** Mean difference (pain during movement): at immediate post-treatment: -3.30 [95% CI: -4.05, -2.55] **FUNCTION:** Neck Pain Disability Index (scale from 0 to 100, low score is better) **Baseline Mean**: Arm 1: 31.10, Arm 2: 33.52 E**nd of Study Mean:** Arm 1: 11.70, Arm 2: 25.61 **Absolute Benefit:** Mean difference: at immediate post-treatment: -13.91 [95% CI: -18.64, -9.18] **PATIENT SATISFACTION**: not reported **QUALITY OF LIFE:** not reported

	GLOBAL PERCEIVED EFFECT: not reported **RETURN TO WORK**: not reported **ADVERSE EVENT**: not reported

Risk of Bias

Bias	**Authors' judgement**	**Support for judgement**
A) Adequate randomisation	Unclear risk	Comment: not adequately described
B) Allocation concealment (selection bias)	Unclear risk	Comment: not adequately described
C) Blinding (patient)	High risk	Comment: unable due to study design
D) Blinding (care provider)	High risk	Comment: unable due to study design
E) Blinding (outcome assessor)	High risk	Comment: unable due to study design
F) Incomplete outcome data (attrition bias)	Unclear risk	Comment: dropouts not described
G) Randomised participants analyzed in their groups (reporting bias)	High risk	Comment: page 609, table 2, three dropouts not included in analyses
H) Selective reporting (reporting bias)	Unclear risk	Comment: no report of protocol
I) Similarity of baseline characteristics	Low risk	Comment: page 608: table 1, groups demonstrated no difference in age, body mass index, duration of symptom
J) Co-intervention avoided or similar	Unclear risk	Comment: not adequately described
K) Acceptable compliance	Unclear risk	Comment: not adequately described
L) Timing outcome assessments similar	Low risk	Comment: baseline and 6 weeks
M) Other potential sources of bias	Unclear risk	Comment: study protocol was not registered and inadequate randomization and allocation concealment Funding source: not reported Conflict of interest: reported

Esenyel 2000

Methods	**Type of Trial:** parallel group RCT with 3 Arms **Number Analyzed/Randomized**: 102/102 (continuous ultrasound plus stretching 36/36; lidocaine trigger point injection plus stretching 36/36; stretching 30/30) **Intention-to-treat Analysis**: not reported **Power Analysis**: not reported **Funding Source**: not reported

	Declaration of Interest: reported
Participants	**Disorder:** chronic myofascial pain **Radicular symptoms/signs**: not reported **Sex**: 62.75% female **Age range**: 31 (6.7) years **Severity** (baseline score measured by Visual Analog Scale 0 to 10): continuous ultrasound plus stretching 7.24 (1.62); lidocaine trigger point injection plus stretching 7.16 (1.66); stretching 6.50 (0.93) **Duration of complaint:** from 6 months to 7 years **Setting**: Outpatient, Pain clinic, SSk Vakif Gureba Teaching Hospital, Department of Physical Medicine and Rehabilitation, Adnam Menderes Bulvari, Capa, Istanbul, Turkey **Location of Study**: Istanbul, Turkey
Interventions	**INDEX TREATMENT** ***Arm 1****:* continuous ultrasound plus active stretching; ***Activity 1:*** continuous ultrasound therapy was provided over the trigger points and pain referral zone; ***Timing****:* before active stretching of trapezius muscle; ***Frequency****:* 10 sessions. ***Dose****:* 1.5 wcm^2; ***Duration****:* 6 minutes; ***Route****:* over the active myofascial trigger points in trapezius muscle and pain referral zone. ***Monitoring***: immediate and intermediate; ***Activity 2:*** neck stretching exercise were assigned; ***Timing****:* after application of ultrasound; ***Frequency****:* not reported. ***Duration****:* not reported; ***Route****:* cervical spine; ***Monitoring****:* immediate and intermediate **COMPARISION TREATMENT** ***Arm 2:*** stretching; ***Activity 1:*** neck stretching exercises were assigned; ***Timing****:* after application of ultrasound; ***Frequency****:* not reported. ***Duration****:* not reported; ***Route****:* cervical spine; ***Monitoring****:* immediate and intermediate **Treatment Schedule:** 2 weeks (10 sessions) **Timing of outcomes**: baseline and immediate post-treatment (2 weeks) **Duration of Follow-up:** 12 weeks **Co-intervention**: not reported
Outcomes	**PAIN INTENSITY:** Visual Analog Scale (scale from 0 to 10, low score is better) **Baseline Mean**: pain at rest: Arm 1: 3.12, Arm 2: 6.50 **End of Study Mean:** pain at rest: Arm 1: 3.04, Arm 2: 6.46 **Absolute Benefit:** Mean difference (pain during movement): at immediate post-treatment: -3.42 [95% CI: -4.08, -2.76] at intermediate - term follow-up -2.70 [95% CI: -3.62, -1.78] **PATIENT SATISFACTION**: not reported **QUALITY OF LIFE:** not reported **GLOBAL PERCEIVED EFFECT**: not reported **RETURN TO WORK**: not reported

	ADVERSE EVENT: not reported

Risk of Bias

Bias	**Authors' judgement**	**Support for judgement**
A) Adequate randomisation	Unclear risk	Comment: randomization technique not described
B) Allocation concealment (selection bias)	Unclear risk	Comment: not adequately described
C) Blinding (patient)	High risk	Comment: unable due to study design
D) Blinding (care provider)	High risk	Comment: unable due to study design
E) Blinding (outcome assessor)	High risk	Comment: unable due to study design
F) Incomplete outcome data (attrition bias)	Unclear risk	Comment: not described
G) Randomised participants analyzed in their groups (reporting bias)	High risk	Comment: intention to treat was not stated
H) Selective reporting (reporting bias)	Unclear risk	Comment: study protocol not reported
I) Similarity of baseline characteristics	Unclear risk	Comment: no baseline demographic data were described
J) Co-intervention avoided or similar	Unclear risk	Comment: not reported
K) Acceptable compliance	Unclear risk	Comment: not reported
L) Timing outcome assessments similar	Low risk	Comment: baseline, 2 weeks, and 3 months
M) Other potential sources of bias	Unclear risk	Comment: lack of description on almost all criteria Funding source: not reported Conflict of interest: not reported

Esenyel 2007

Methods	**Type of Trial:** quasi RCT with 5 Arms **Number Analyzed/Randomized**: 90/90 (botox trigger point injection plus stretching 18/18; lidocaine trigger point injection plus stretching 18/18; continuous ultrasound plus stretching 18/18; high - power pain threshold ultrasound plus stretching 18/18; stretching 18/18) **Intention-to-treat Analysis**: not reported **Power Analysis**: not reported **Funding Source**: not reported **Declaration of Interest**: reported
Participants	**Disorder:** chronic myofascial pain **Radicular symptoms/signs**: not reported

	Sex: 73.33% female **Age range**: 25 - 40 years **Severity** (baseline score measured by Visual Analog Scale 0 to 10): not reported **Duration of complaint:** at least 6 months **Setting**: Physical therapy and Rehabilitation Medicine Department, Algology Departmen of a teaching and research hospital. SSK Vakif Gureba Teaching Hospital, Department of Physical Medicine and Rehabilitation, Adnam Menderes Bulvari, Capa, Istanbul, Turkey **Location of Study**: Istanbul, Turkey
Interventions	**INDEX TREATMENT** ***Arm 1:*** continuous ultrasound plus stretching; ***Activity 1:*** continuous ultrasound therapy was delivered by a physiatrist. The applicator is moved in smooth overlapping sweeps or circles at rates of a few centimetres per second over areas of 25 to 100cm^2 *;* ***Timing****:* before active stretching of trapezius muscle; ***Frequency****:* once daily for 10 days. ***Dose****:* 1.5 wcm^2; ***Duration****:* 5 minutes; ***Route****:* over the active myofascial trigger points in the trapezius muscle. ***Monitoring****:* immediate; ***Activity 2:*** patient actively stretched the upper trapezius muscle by bending and rotating the head to the contralateral side of the involved myofascial trigger point of the upper trapezius muscle; ***Timing****:* not reported; ***Frequency***: once daily for 10 days; ***Dose****:* 15 repetitions/day. **Duration**: not reported; ***Route****:* cervical spine and upper back; ***Monitoring:*** immediate ***Arm 2:*** HPPT ultrasound plus stretching; ***Activity 1:*** ultrasound was applied in continuous mode with a probe over the trigger point and held motionlessly. To elicit threshold pain, the probe is kept static on the trigger point and, the intensity was gradually increased to the level of maximum pain the patient could bear. It was kept at that intensity for 4-5 seconds and then reduced to half the intensity for another 15 seconds. This procedure was repeated 3 times; ***Timing:*** before active stretching of trapezius muscle; ***Frequency:*** 10 sessions; ***Dose:*** as tolerated by the patient; ***Duration:*** not reported; ***Route:*** over the active myofascial trigger points in trapezius muscle; ***Monitoring***: immediate; ***Activity 2:*** patient actively stretched the upper trapezius muscle by bending and rotating the head to the contralateral side of the involved myofascial trigger point of the upper trapezius muscle; ***Timing****:* not reported; ***Frequency***: once daily for 10 days; ***Dose****:* 15 repetitions/day. ***Duration***: not reported; ***Route****:* cervical spine and upper back; ***Monitoring:*** immediate **COMPARISION TREATMENT** ***Arm 3:*** active stretching; ***Activity 2:*** patient actively stretched the upper trapezius muscle by bending and rotating the head to the contralateral side of the involved myofascial trigger point of the upper trapezius muscle; ***Timing****:* not reported; ***Frequency****:* once daily for 10 days; ***Dose****:* 15 repetitions/day. ***Duration****:* not reported; ***Route****:* cervical spine and upper back; ***Monitoring:*** immediate **Treatment Schedule:** 10 days (10 sessions) **Timing of outcomes**: 1 week and 4 weeks

	Duration of Follow-up: 3 weeks **Co-intervention**: not reported
Outcomes	**PAIN INTENSITY:** Visual Analog Scale (scale from 0 to 100, low score is better) **1 Week Mean**: Arm 1: -31.2, Arm 2: -38.6, Arm 3: -28.7 **4 Week Mean:** Arm 1: -63.6, Arm 2: -48.5, Arm 3: - 64.3 **Absolute Benefit:** Mean difference (Arm 1 vs Arm 3): at short-term follow-up 0.70 [95% CI: -7.36, 8.76] Mean difference (Arm 2 vs Arm 3): at short-term follow-up 15.80 [95% CI: 7.07, 24.53] **PATIENT SATISFACTION**: not reported **QUALITY OF LIFE:** not reported **GLOBAL PERCEIVED EFFECT**: not reported **RETURN TO WORK**: not reported **ADVERSE EVENT**: Continuous ultrasound plus stretching: not reported HPPT ultrasound plus stretching severe pain during the session (9/18)

Risk of Bias

Bias	**Authors' judgement**	**Support for judgement**
A) Adequate randomisation	Unclear risk	Comment: not adequately described
B) Allocation concealment (selection bias)	High risk	Comment: unable due to the consecutive allocation
C) Blinding (patient)	High risk	Comment: unable due to study design
D) Blinding (care provider)	High risk	Comment: unable due to study design
E) Blinding (outcome assessor)	Unclear risk	Comment: not reported
F) Incomplete outcome data (attrition bias)	Low risk	Comment: page 45, table 2, n = 90
G) Randomised participants analyzed in their groups (reporting bias)	Low risk	Comment: page 45, table 2, n = 90
H) Selective reporting (reporting bias)	Unclear risk	Comment: no protocol was referenced
I) Similarity of baseline characteristics	Low risk	Quote: "There were no statistically significant differences when pre-treatment VAS scores of all groups were compared (p =0.052)"
J) Co-intervention avoided or similar	Unclear risk	Comment: not reported

K) Acceptable compliance	Unclear risk	Comment: not reported
L) Timing outcome assessments similar	Low risk	Comment: 1 week, 1-month follow-up
M) Other potential sources of bias	Unclear risk	Comment: a high number of high risks including improper randomization and protocol was not registered Funding source: not reported Conflict of interest: not reported

Haran 2013

Methods	**Type of Trial:** parallel group RCT with 2 Arms **Number Analyzed/Randomized**: 30/30 (High - power pain threshold (HPPT) plus transverse frictional massage (TFM) plus stretching 15/15; Transverse frictional massage and stretching 15/15) **Intention-to-treat Analysis**: not reported **Power Analysis**: not reported **Funding Source**: not reported **Declaration of Interest**: not reported
Participants	**Disorder:** chronic myofascial pain **Radicular symptoms/signs**: not reported **Sex**: 56.66% female. **Age range**: between 18 to 45 years **Severity** (baseline score measured by Visual Analog Scale 0 to 10): HPPT ultrasound plus transverse frictional massage plus stretching 6.80 (0.94); transverse frictional massage and stretching 6.80(0.77) **Duration of complaint:** at least 3 months **Setting**: Department of Physiotherapy, Maharishi Markandeshwar University, Mullana, Ambala **Location of Study**: Ambala, India
Interventions	**INDEX TREATMENT** ***Arm 1****:* HPPT ultrasound plus transverse frictional massage plus stretching; ***Activity 1:*** ultrasound is applied with applicator kept motionless over the trigger points to elicit threshold pain. Intensity is gradually increased to the level of maximum pain that the patient could bear. It is kept at that level for 4-5 seconds and then reduced to half-intensity level for another 15 seconds. The procedure is repeated 3 times; ***Timing***: not reported; ***Frequency****:* 2 days a week for 4 weeks. ***Dose****:* as tolerated by the patient; ***Route****:* over the myofascial trigger points on the upper trapezius muscle. ***Monitoring****:* immediate; ***Activity 2:*** transverse frictional massage was provided for two minutes for each trigger points; ***Timing:*** not reported; ***Frequency:*** 2 days a week for 4 weeks; ***Dose:*** three repetitions with 30 second interval; ***Duration****:* 2 minutes for each trigger point; ***Route:*** over the trigger points in upper trapezius muscle; ***Monitoring****:* immediate; ***Activity 3:*** participants were given passive stretching of upper trapezius muscle in supine lying. It is given to muscle-tendon unit by slowly placing it in a maximal position

	of stretch and sustaining it there for an extended period. The maximal stretching position is determined by discomfort/pain that patient experiences; ***Timing:*** following high - power pain threshold ultrasound; Frequency: 2 days a week for 4 weeks. ***Dose****:* not reported. ***Duration****:* 2 minutes for each trigger point; ***Route:*** upper trapezius muscle; ***Monitoring****:* immediate **COMPARISION TREATMENT** ***Arm 2:*** transverse frictional massage plus stretching; ***Activity 2:*** transverse frictional massage was provided for two minutes for each trigger point; ***Timing:*** not reported; ***Frequency:*** 2 days a week for 4 weeks; ***Dose*****:** three repetitions with 30 second interval; ***Duration****:* 2 minutes for each trigger point; ***Route:*** over the trigger points in upper trapezius muscle; ***Monitoring****:* immediate; ***Activity 3:*** participants were given passive stretching of upper trapezius muscle in supine lying. It is given to muscle-tendon unit by slowly placing it in a maximal position of stretch and sustaining it there for an extended period. The maximal stretching position is determined by discomfort/pain that patient experiences; ***Timing:*** following high - power pain threshold ultrasound; Frequency: 2 days a week for 4 weeks. ***Dose****:* not reported. ***Duration****:* 2 minutes for each trigger point; ***Route:*** upper trapezius muscle; ***Monitoring****:* immediate **Treatment Schedule:** twice a week for 4 weeks (8 sessions) **Timing of outcomes**: baseline, 2 week and 4 weeks **Duration of Follow-up:** immediate post-treatment **Co-intervention**: not reported
Outcomes	**PAIN INTENSITY:** Numerical Rating Scale (scale from 0 to 10, a low score is better) **Baseline Mean**: Arm 1: 6.80, Arm 2: 6.8 **End of Study Mean:** Arm 1: 3.00, Arm 2: 3.50 **Absolute Benefit:** Mean difference: at immediate post-treatment: -0.50 [95% CI: -0.92, -0.08] **FUNCTION:** Neck Pain Disability Index (scale from 0 to 50, a low score is better) **Baseline Mean**: Arm 1: 34.3, Arm 2: 34.2 E**nd of Study Mean:** Arm 1: 41.4, Arm 2: 39.8 **Absolute Benefit:** Mean difference: at immediate post-treatment: 1.60 [95% CI: 0.21, 2.99] **PATIENT SATISFACTION**: not reported **QUALITY OF LIFE:** not reported **GLOBAL PERCEIVED EFFECT**: not reported **RETURN TO WORK**: not reported

	ADVERSE EVENT: not reported

Risk of Bias

Bias	**Authors' judgement**	**Support for judgement**
A) Adequate randomisation	Unclear risk	Comment: not reported
B) Allocation concealment (selection bias)	Unclear risk	Comment: not reported
C) Blinding (patient)	High risk	Comment: unable due to study design
D) Blinding (care provider)	High risk	Comment: unable due to study design
E) Blinding (outcome assessor)	Unclear risk	Comment: not reported
F) Incomplete outcome data (attrition bias)	High risk	Comment: not reported
G) Randomised participants analyzed in their groups (reporting bias)	Unclear risk	Comment: not adequately reported
H) Selective reporting (reporting bias)	Unclear risk	Comment: no protocol referenced
I) Similarity of baseline characteristics	Low risk	Comment: page 115, table 1
J) Co-intervention avoided or similar	Unclear risk	Comment: not described
K) Acceptable compliance	Unclear risk	Comment: not reported
L) Timing outcome assessments similar	Low risk	Comment: baseline, 2 weeks and 4 weeks
M) Other potential sources of bias	Unclear risk	Comment: A high number of high risk and unclear risk including inadequately described randomization, allocation concealment and reporting outcomes. Inadequate description of outcome measures or intervention. The methodology was poorly described. Funding source: not reported Conflict of interest: not reported

Mohamed 2016

Methods	**Type of Trial:** parallel group RCT with 3 Arms **Number Analyzed/Randomized**: 45/45 (traditional exercise 15/15; phonophoresis with diclofenac sodium gel plus traditional exercise 15/15; extracorporeal shock wave 15/15) **Intention-to-treat Analysis**: not reported **Power Analysis**: 80% **Funding Source**: not reported

	Declaration of Interest: not reported
Participants	**Disorder:** mechanical neck dysfunction **Radicular symptoms/signs**: not reported **Sex**: not reported **Age range**: 20 to 45 years **Severity** (baseline score measured by Visual Analog Scale 0 to 10): traditional exercise; 6.6(2.90), phonophoresis plus traditional exercise; 6.67(2.68) **Duration of complaint:** pain less than 12 weeks **Setting**: Department of Physical Therapy for Basic Sciences, Faculty of Physical Therapy, Ciro University, Cairo, Egypt **Location of Study**: Ciro, Egypt
Interventions	**INDEX TREATMENT** ***Arm 1:*** phonophoresis with diclofenac sodium plus traditional exercise; ***Activity 1:*** ultrasound was applied in continuous mode with 5 cm diameter applicator using diclofenac sodium gel over the paraspinal muscles of the neck and on the upper fibres of trapezius muscle*;* ***Timing****:* not reported; ***Frequency****:* 3 sessions a week for 4 weeks; ***Dose****:* 1.0 wcm^2 , 1 MHz ***Duration****:* not reported; ***Route****:* cervical paraspinal muscle and upper fibers of trapezius muscle; ***Monitoring****:* immediate; ***Topical drug****:* diclofenac sodium gel. ***Activity 2:*** traditional exercise composed of isometric and stretching exercises. A group performed the isometric exercise for neck flexors, extensors and side benders. They were asked to hold each contraction for six seconds and then relax for another six seconds. Stretching exercises included stretching of the levator scapula, upper fibres of trapezius and sternocleidomastoid muscles holding for 30 seconds and relaxing for another 30 seconds; ***Timing****:* not reported; ***Frequency****:* 3 sessions a week for 4 weeks. ***Dose****:* five repetitions, ***Duration****:* not reported; ***Route****:* cervical spine and thoracic spine. ***Monitoring****:* immediate **COMPARISION TREATMENT** ***Arm 2*****:** exercise; ***Activity 1:*** traditional exercise composed of isometric and stretching exercises. Participants performed group exercise including the isometric exercise for neck flexors, extensors and side benders. They were asked to hold each contraction for six seconds and then relax for another six seconds. Stretching exercises included stretching of the levator scapula, upper fibres of trapezius and sternocleidomastoid muscles holding for 30 seconds and relaxing for another 30 seconds; ***Timing***: not reported; ***Frequency****:* 3 sessions for 4 weeks. ***Dose****:* five repetitions, ***Duration****:* not reported; ***Route****:* cervical spine and thoracic spine. ***Monitoring****:* immediate **Treatment Schedule: 4** weeks (12 sessions) **Timing of outcomes**: baseline, and at immediate post-treatment (4 weeks) **Duration of Follow-up:** immediate post-treatment **Co-intervention**: participants were asked to refrain from other forms of physiotherapy or medical procedures for pain during the study

Outcomes	**PAIN INTENSITY:** Numeric Pain Rating Scale (scale from 0 to 10, a low score is better) **Baseline Mean**: Arm 1: 6.60, Arm 2: 6.67 **End of Study Mean:** Arm 1: 5.36, Arm 2: 4.27 **Absolute Benefit:** Mean difference: at immediate post-treatment: -1.09 [95% CI: -3.55, 1.37] **FUNCTION:** Neck Disability Index (scale from 0 to 50, low score is better) **Baseline Mean**: Arm 1: 17.60, Arm 2: 17.86 E**nd of Study Mean:** Arm 1: 13.85, Arm 2: 10.46 **Absolute Benefit:** Mean difference: at immediate post-treatment: -3.39 [95% CI: -7.07, 0.29] **PATIENT SATISFACTION**: not reported **QUALITY OF LIFE:** not reported **GLOBAL PERCEIVED EFFECT**: not reported **RETURN TO WORK**: not reported **ADVERSE EVENT**: not reported

Risk of Bias

Bias	**Authors' judgement**	**Support for judgement**
A) Adequate randomization	Unclear risk	Comment: not adequately described
B) Allocation concealment (selection bias)	Unclear risk	Comment: not reported
C) Blinding (patient)	High risk	Comment: not possible due to study design
D) Blinding (care provider)	High risk	Comment: not possible due to study design
E) Blinding (outcome assessor)	High risk	Comment: not possible due to study design
F) Incomplete outcome data (attrition bias)	High risk	Comment: not reported
G) Randomised participants analyzed in their groups (reporting bias)	Unclear risk	Comment: not reported
H) Selective reporting (reporting bias)	Unclear risk	Comment: protocol not referenced
I) Similarity of baseline characteristics	Low risk	Comment: table 1, figure 1 and figure 2
J) Co-intervention avoided or similar	Low risk	Comment: page 50, " Participants were asked to refrain from other forms of physical therapy or other medical procedures for pain during the study"

K) Acceptable compliance	Unclear risk	Comment: not reported
L) Timing outcome assessments similar	Low risk	Comment: at baseline and 4 weeks
M) Other potential sources of bias	Unclear risk	Comment: not enough information was provided to determine the selection bias Funding source: reported Conflict of interest: reported

Appendix G. Characteristics of excluded study

Authors	Reason for exclusion
Ay 2011	Comparison: placebo ultrasound plus exercise vs active ultrasound plus exercise
Cheng-Zern 1993	Intervention: head to head comparison of ultrasound and massage
Costello 2016	Population: participants had head and neck pain Intervention: head to head comparison of soft tissue mobilization and ultrasound
Farooq 2018	Intervention: multimodal therapy including an infrared lamp and TENS
Fernández-de-las-Peñas 2004	Intervention: multimodal therapy
Flynn 1987	Comparison: ultrasound plus exercise vs sham ultrasound plus exercise
Gam 1998	Comparison: ultrasound plus massage plus exercise vs sham ultrasound plus massage plus exercise
Gur 2013	Intervention: head to head comparison of ultrasound and extracorporeal shock wave therapy
Kaur 2006	Intervention: multimodal therapy
Koes 1990	Population: participants had chronic back and neck pain
Mart 2009	Intervention: head to head comparison of ultrasound and ischemic compression
Ruiz-Molinero 2014	Intervention: head to head comparison of sham vs active ultrasound
Ucar 2014	Population: participants had temporomandibular joint disorder
Umit 2010	Intervention: head to head comparison of sham and active ultrasound
Unalan 2011	Intervention: head to head comparison of high-power pain threshold ultrasound and local anesthetic injection
Walker 2008	Population: participants had mechanical neck pain with or without unilateral upper extremity symptoms
Waschl 2014	Intervention: multimodal therapy
Rodriguez-Huguet 2017	Intervention: multimodal therapy
Yıldırım 2016	Intervention: multimodal therapy

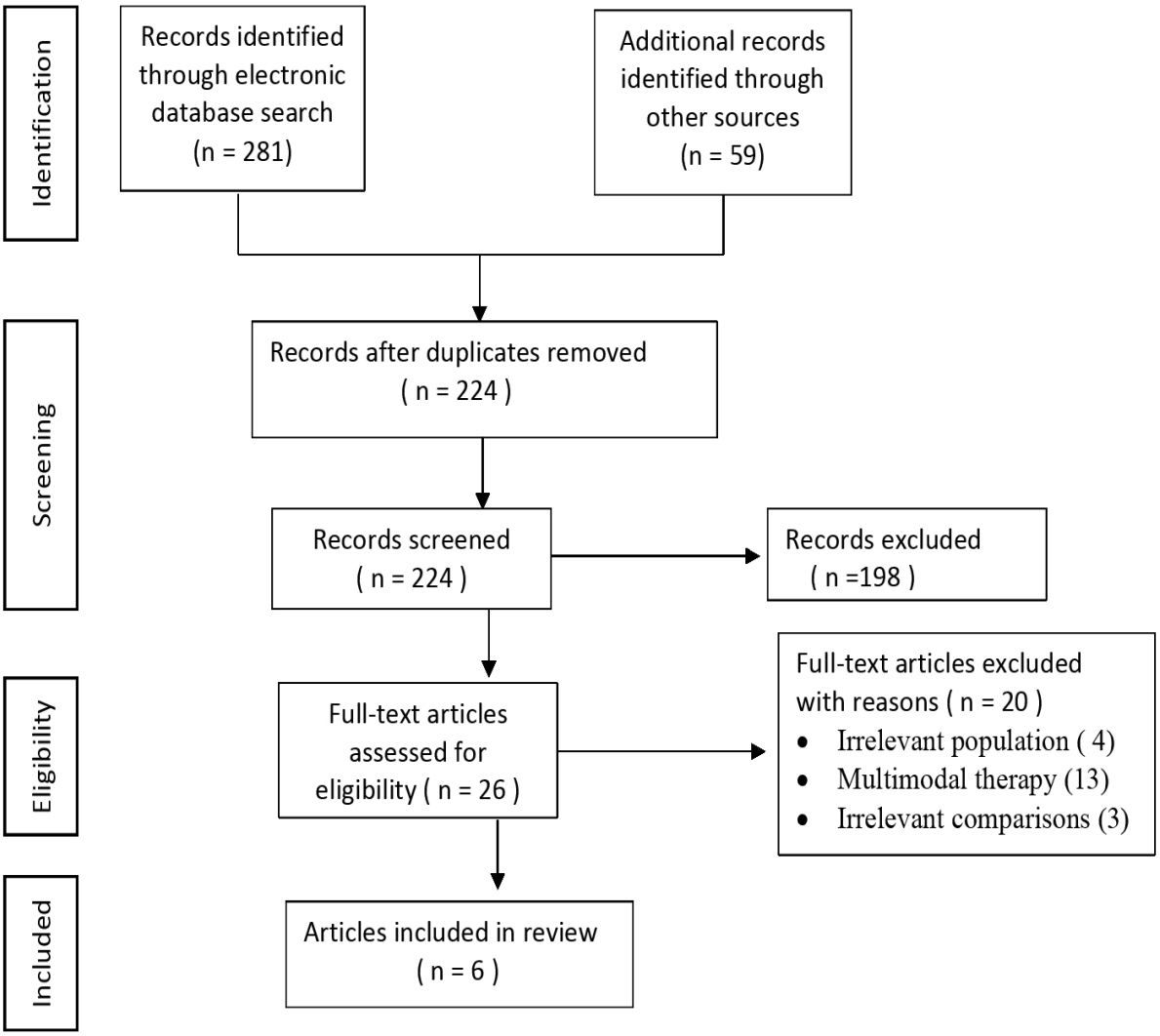

Figure 2. *PRISMA flow diagram of literature search and selection process*

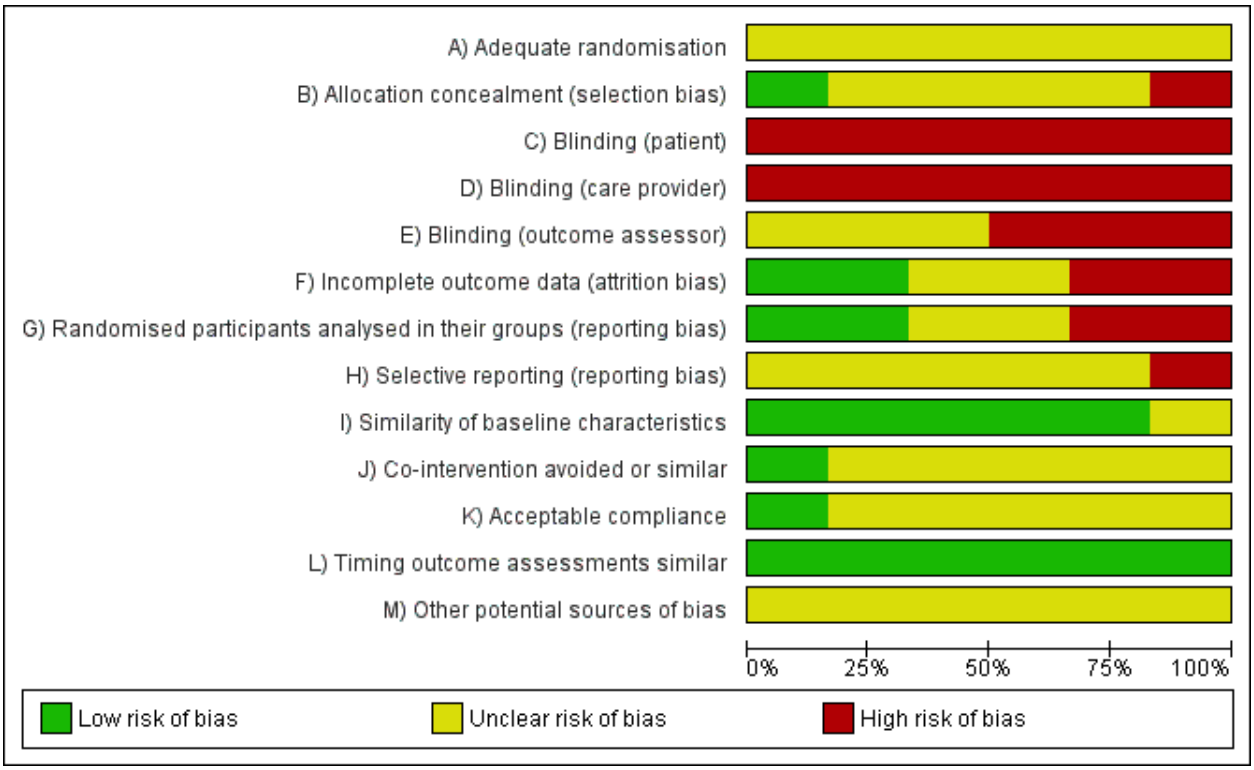

Figure 3. *'Risk of bias' graph: review authors' judgements about each risk of bias criteria presented as percentages across all included studies.*

Summary of Findings (SoF)

Ultrasound as an adjuvant to exercise for chronic myofascial neck pain.

Patient or population: chronic myofascial neck pain **Setting:** primary care **Intervention:** ultrasound or phonophoresis + exercise **Comparison:** exercise					
Outcomes	**Illustrative Comparative Risk (95% CI)**		**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with exercise	**Risk with ultrasound and exercise**			
Pain intensity: at immediate post-treatment assessed with: VAS (scale from 0 to 10cm).	The mean pain intensity in the control group was 6.46	The mean pain intensity in the intervention group was **3.42 lower** [4.08 lower to 2.76 higher]	72 [1 RCT: Esenyel 2000]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + exercise to exercise alone. A decrease in score of more than 1 point is shown to be important to patients. The difference is statistically and clinically significant.
Pain intensity: at immediate post-treatment assessed with: VAS (scale from 0 to 10)	The mean pain intensity in the control group was 4.95	The mean pain intensity in the intervention group was **3.30 lower** [4.05 lower to 2.55 higher]	41 [1 RCT: Durmus 2014]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared phonophoresis with capsaicin plus exercise vs exercise alone. A decrease in score of more than 1 point is shown to be important to patients. The difference is statistically and clinically significant.

Pain intensity: at short-term assessed with VAS (scale from 0 to 100).	The mean pain intensity in the control group was 10.08	The mean pain intensity in the intervention group was **0.70 higher** [-7.36 lower to 8.76 higher]	36 [1 RCT: Esenyel 2007]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + exercise to exercise alone.
Pain intensity: at intermediate - term assessed with: VAS (scale from 0 to 10).	The mean pain intensity in the control group was 5.78	The mean pain intensity in the intervention group was **2.70 lower** [3.62 lower to 1.78 higher]	60 [1 RCT: Esenyel 2000]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + exercise to exercise alone. A decrease in score of more than 7 point is shown to be important to patients. The difference is statistically and clinically significant.
Disability/function: at immediate post-treatment assessed with: NPAD (scale from 0 to 100).	The mean disability score in the control group was 25.61	The mean disability score in the intervention group was **13.91 lower** [18.64 lower to 9.18 higher]	41 [1 RCT: Durmus 2014]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared phonophoresis with capsaicin plus exercise vs exercise alone. Lower score indicates better function/less disability in favour of ultrasound plus exercise.
Patient satisfaction	-	-	-	-	not measured
Quality of life	-	-	-	-	not measured
Global perceived effect	-	-	-	-	not measured
Return to work	-	-	-	-	not measured

*The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; VAS: Visual Analogue Scale; NRS: Numerical Rating Scale; NDI: Neck Disability Index; NPAD: Neck Pain and Disability scale; MD: Mean Difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Footnotes
[1] Downgraded due to imprecision.
[2] Downgraded due to high risk of bias.
[3] Downgraded due to inconsistency.

Ultrasound as an adjuvant to exercise and manual therapy for chronic myofascial neck pain

Patient or population: chronic myofascial neck pain
Setting: primary care
Intervention: ultrasound + exercise + manual therapy
Comparison: exercise + manual therapy

Outcomes	Illustrative Comparative Risk (95% CI)		No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with exercise	**Risk with ultrasound and exercise**			
Pain intensity: at Immediate post-treatment assessed with: NRS (scale from 0 to 10 points).	The mean pain intensity in the control group was 3.2	The mean pain intensity in the intervention group was **0.75 lower** [2.08 lower 0.58 higher]	40 [1 RCT: Dibai-Filho 2017]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + manual therapy and exercise to manual therapy and exercise. A decrease in score of more than 1 is shown to be important to patients. The difference is not statistically and clinically significant.
Pain intensity: at Immediate post-treatment assessed with:	The mean pain intensity in the control	The mean pain intensity in the intervention group was **0.50 lower** [-	30 [1 RCT: Haran 2013]	⊕⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared high - power pain threshold ultrasound + manual therapy and exercise vs manual therapy and exercise.

NRS (scale from 0 to 10).	group was 3.0	0.92 lower -0.58 higher]			
Pain intensity: at short - term assessed with NRS (scale from 0 to 10).	The mean pain intensity in the control group was 3.85	The mean pain intensity in the intervention group was **1.15 lower** [2.55 lower to 0.25 higher]	40 [1 RCT: Dibai-Filho 2017]	⨁ ⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + manual therapy and exercise to manual therapy and exercise. A decrease in score of more than 1 point is shown to be important to patients. The difference is not statistically and clinically significant.
Disability -function: at immediate post-treatment assessed with NDI (scale from 0 to 50).	The mean disability score in the control group was 7.45	The mean disability score in intervention group was **0.30 lower** [-3.14 lower to 2.54 higher]	40 [1 RCT: Dibai-Filho 2017]	⨁ ⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + manual therapy and exercise to manual therapy and exercise. A decrease in score of more than 7 points is shown to be important to patients. The difference is not statistically and clinically significant.
Disability -function: at immediate post-treatment assessed with NDI (scale from 0 to 50).	The mean disability score in the control group was 39.8	The mean disability score in intervention group was **1.60 higher** [0.21 lower to 2.99 higher]	30 [1 RCT: Haran 2013]	⨁ ⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared high - power pain threshold ultrasound + manual therapy and exercise vs manual therapy and exercise. A decrease in score of more than 7 points is shown to be important to patients. The difference is not statistically and clinically significant.

Disability -function: at short - term assessed with NDI (scale from 0 to 50).	The mean disability score in the control group was 8.85	The mean disability score in intervention group was **1.05 lower** [-4.27 lower to 2.17 higher]	40 [1 RCT: Dibai-Filho 2017]	⨁⊖⊖⊖[1 2 3] **very low**	This analysis includes one study which compared continuous ultrasound + manual therapy and exercise to manual therapy and exercise. A decrease in score of more than 7 points is shown to be important to patients. The difference is not statistically and clinically significant.
Patient satisfaction	-	-	-	-	not measured
Quality of life	-	-	-	-	not measured
Global perceived effect	-	-	-	-	not measured
Return to work	-	-	-	-	not measured

*The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: confidence interval; VAS: Visual Analogue Scale; NRS: Numerical Rating Scale; NDI: Neck Disability Index; NPAD: Neck Pain and Disability scale; MD: Mean Difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Footnotes
[1] Downgraded due to imprecision.
[2] Downgraded due to high risk of bias.
[3] Downgraded due to inconsistency.