Pharmacological Interventions Including Medical Injections for Neck Pain: An Overview as Part of the ICON§ Project

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Abstract: Objectives: To conduct an overview (review-of-reviews) on pharmacological interventions for neck pain.

Search Strategy: Computerized databases and grey literature were searched from 2006 to 2012.

Selection Criteria: Systematic reviews of randomized controlled trials (RCT) in adults with acute to chronic neck pain reporting effects of pharmacological interventions including injections on pain, function/disability, global perceived effect, quality of life and patient satisfaction.

Data Collection & Analysis: Two independent authors selected articles, assessed risk of bias and extracted data The GRADE tool was used to evaluate the body of evidence and an external panel provided critical review.

Main Results: We found 26 reviews reporting on 47 RCTs. Most pharmacological interventions had low to very low quality methodologic evidence with three exceptions. For chronic neck pain, there was evidence of:

1) a small immediate benefit for eperison hydrochloride (moderate GRADE, 1 trial, 157 participants);
2) no short-term pain relieving benefit for botulinum toxin-A compared to saline (strong GRADE; 5 trial meta-analysis, 258 participants) nor for subacute/chronic whiplash (moderate GRADE; 4 trial meta-analysis, 183 participants) including reduced pain, disability or global perceived effect; and
3) no long-term benefit for medial branch block of facet joints with steroids (moderate GRADE; 1 trial, 120 participants) over placebo to reduce pain or disability;

Reviewers’ Conclusions: While in general there is a lack of evidence for most pharmacological interventions, current evidence is against botulinum toxin-A for chronic neck pain or subacute/chronic whiplash; against medial branch block with steroids for chronic facet joint pain; but in favour of the muscle relaxant eperison hydrochloride for chronic neck pain.

Keywords: Neck pain, pharmacological interventions, medical injections, review of reviews.

INTRODUCTION

Neck pain is common, is experienced by approximately one third of adults over the course of one year [1], can be severely disabling and is contributing to rising socio-economic costs and societal burden [2]. Patients most commonly seek care from medical doctors, and physicians typically prescribe pharmacological interventions [3]. A variety of medications and medicinal injections are used to reduce transient, recurrent or persisting neck pain and disability in the acute or chronic stages of the disorder. Physicians may choose from various classes of medications (see APPENDIX 1) including: non-opioid analgesics, oral and topical NSAIDs, opioids, muscle relaxants, benzodiazepines, tricyclic antidepressants and GABA derivatives. Medicinal injections might also be used including: corticosteroids, anesthetics, and neuromuscular paralytic agent (botulinum toxins).

The choice of a specific agent often considers the mechanism of action of the specific drug [4-6], it presumed efficacy and adverse events, the individual patient, including past therapies tried, and should also be informed by evidence
that the chosen intervention will lead to the therapeutic objective in that patient population. For non-opioid analgesics like acetaminophen (e.g. Tylenol\textsuperscript{R}) the mechanism of action remains unclear but may include inhibition of cyclooxygenase (COX) enzymes; it typically well tolerated with limited adverse effects, NSAIDs act by blocking cyclo-oxygenase (COX) enzymes 1 & 2. It’s thought that blocking COX-2 decreases pain and inflammation while also reducing the risk of gastrointestinal adverse effects (ulcers, bleeding) that result from COX-1 inhibition on the GI mucosa and platelets, whereas controversy remains over the role of NSAIDs and cardiovascular adverse effects [4]. Common oral NSAIDS include ibuprofen (e.g. advil\textsuperscript{R}), naproxen (e.g. aleve\textsuperscript{R}, naprosyn\textsuperscript{R}), diclofenac (e.g. voltaren\textsuperscript{R}) with celecoxib (celebrex\textsuperscript{R}) an example of a COX-1 sparing NSAID. Opioid medications' analgesia is obtained principally through mu-opioid receptors, with opioids most often used for chronic pain refractory to other therapies. Opioids can produce respiratory depression, nausea, vomiting, dizziness and addictive behavior in susceptible individuals. Societal concerns of diversion also limit their use. Tricyclic antidepressants increase serotonin and norepinephrine and commonly produce drowsiness, dry mouth, blurred vision, constipation, urinary retention and weight gain. Selective serotonin and norepinephrine reuptake inhibitors (e.g. duloxetine, venlafaxine) antidepressants increase serotonin and norepinephrine and have common side effects of nausea and dizziness. Anticonvulsants such as gabapentin or pregabalin decrease excitatory neurotransmitters such as glutamate and their side effects commonly include drowsiness, dizziness, unsteadiness and unclear thinking. Topical anesthetics such as lidocaine block sodium channels and are well tolerated as a 5\% topical gel. Injections include botulinum toxins and specifically Type A that are used for the treatment of muscle pain disorders and act presynaptically through inhibition of acetylcholine synthesis or its release. This blocks neuromuscular transmission at the neuromuscular junction, causing paralysis of the injected skeletal muscle. It’s presumed that injecting an overactive muscle will decrease its level of contraction and allow improved reciprocal motion, improving movement and the ability to exercise. Side effects are generally minor and temporary but rare allergic reactions can occur. Finally, corticosteroid injections are administered intraarticularly and intramuscularly with the thought that they reduce inflammation (pain and swelling) at the injury site. Short term problems with injections include flushing, transient hypertension, and serum glucose fluctuation. Chronic corticosteroid use can lead to hyperglycemia, insulin resistance, hypertension, weight gain, osteoporosis, anxiety, depression and cataracts.

In a previous 2009 overview, we found an insufficient evidence base on the benefits and risks of most pharmacological interventions for neck pain including the commonly used injections, which limits the ability to provide strong clinical guidance on appropriate use [7]. We found limited evidence supporting methylprednisone for acute whiplash, intramuscular lidocaine for chronic neck pain and epidural methylprednisone and lidocaine for chronic neck pain. We recommended against botulinum toxin-A as it was not found superior to saline for chronic neck pain.

There have been further clinical trials in neck pain patients since our 2009 review and since neck pain continues to be a common potentially disabling clinical condition, we wanted to update the evidence on oral, topical and injected medications for neck pain. The purpose of this overview is to systematically review existing reviews of randomized controlled trials published after 2006 and to consider establishing evidence-based recommendations on medicines and medicinal injections for neck pain, regardless of pain duration across several diagnostic groups (e.g. including non-specific and specific neck pain with and without cervicogenic headache, radiculopathy or associated whiplash injury), while also considering varying duration of study patient follow-up (short- and long-term) and differing control groups (placebo control or active treatment) in these trials. Clinical trial outcomes we considered of primary interest were pain, function, disability, work related function, patient satisfaction, global perceived effect and quality of life as well as adverse effects of these medicines.

METHODS

Our systematic overview process included comprehensive computerized search strategies from January 2000 to August 2010: MEDLINE, EMBASE, CINAHL, ILC, CENTRAL, and LILACS, with selection criteria listed in Table 1 and at least 2 independent reviewers selecting articles, performing methodological quality assessment using the AMSTAR tool [8] qualitative assessment of the strength of evidence. We used a team consensus approach to qualitatively assess the totality of the evidence, using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [9]. Further details on the methodological approach are provided in our ICON methods report [10] including search terms and strategies. Two separate searches were performed, one for treatment benefits and one for harms. The protocol for this overview was not registered.

We supplemented our computerized search strategy by identifying on-going systematic reviews in the grey literature nearing completion (e.g. Cochrane Reviews) up to July 2012, by asking our expert panel to identify ongoing reviews and by scrutinizing the reference lists of all of the primary studies.

Data extraction was performed using forms we piloted - first by one reviewer and then checked by a second. Disagreements were resolved through review of data extraction forms, discussion and consensus. We systematically extracted data from selected systematic reviews and produced evidence tables. Key factors extracted from the original reviews included the following three items: 1) descriptive features of the original review (e.g. authors, publication year, disorder, symptom duration, intervention, and comparator used such as placebo, no care, usual care, and other treatment), as well as noting the authors of primary studies included in the review; 2) methodological details of the original review (e.g. search period, AMSTAR score, quality ranking system, evidence statement and final GRADE). If the original review did not report using GRADE methodology, an estimate for GRADE was made by us based
on the methodological details in the systematic review; and 3) data on benefits and risks (e.g. effect size, effect direction, duration of follow-up, reports of harm). Summary statements on harms included information reported in the original reviews as well as information obtained from the second literature search on harms.

We employed the following a priori triage rules to facilitate decisions on including/excluding reviews:

1) **Type of treatment** (analgesic, NSAID, opioid, etc.) reviews by drug class. See APPENDIX 1 for a complete list of medications and injections considered by medicine treatment category.

2) **Within a treatment drug class** we grouped data by type of comparator (placebo, active treatments, etc.).

3) We prioritized the highest quality reviews based on the rules below, PER grouping.
   a. If there were few reviews, we retained them all.
   b. If there were several reviews reporting on the same treatments and comparators, we retained the highest quality reviews, using the approach recommended by Whitlock [11]. Whitlock has suggested considering the following factors: i. **Year of publication**. We selected the most recent reviews when the data was similar across reviews and there was no loss of studies contained in the older reviews. We further ensured consistency among reviews' conclusions before eliminating older reviews. Inconsistency and discordance were highlighted and potential reasons for differences were discussed; ii. **AMSTAR - risk of bias**. We prioritized reviews with a low risk of bias. Reviews that scored 8 or higher on the 11-point AMSTAR scale were considered at low risk of bias; moderate risk of bias was considered for scores between 5 and 7; and a high risk of bias was assigned to scores of 4 or less. These various reviews were then further summarized in a “Summary of Findings” table to facilitate incorporating this information into clinical practice. Inconsistency and discordance were highlighted and discussed across reviews; iii. **Effect size estimates**: We considered effect sizes as the primary summary measure. Within our defined groups of treatments and comparators, we selected a review that best represented the treatment effect sizes (including through meta-analysis) although we also report the range of estimates from the other included reviews. In cases where there was a large discordance between reviews, we reported our own analysis using the individual studies included in the reviews. Additional data on magnitude of effects such as number-needed-to-treat (NNT) and weighted mean difference (WMD) were also extracted when possible. Further we also considered the clinical importance of these effects using several guiding principles. We considered the published data on the minimal detectable change and the minimal clinically important difference for that outcome. We used a change from baseline of \( \geq 15\% \) to represent the MCID when it was not otherwise published. We also considered the magnitude of the treatment effect (represented by WMD, NNT, absolute benefit, treatment advantage), the evidence for a dose-response gradient, and evidence on the duration of effect (See APPENDIX 2) [12-15] in our assessment of clinical relevance.

4) **Strength of Evidence using GRADE approach**: We considered the same prioritized systematic review to represent the body of evidence for any treatment and assigned an overall GRADE on the strength of evidence. If the selected (prioritized) reviews already reported a GRADE table, we used that. As a reminder, the GRADE approach assessing the quality of evidence from primary trials considers information on design (randomized controlled trials or RCT), information on timing of outcomes (immediately post treatment or IP to long term or LT follow-up); risk of bias; imprecision based on sample size; inconsistency across trials; indirectness and reporting bias.

### Table 1. Inclusion and Exclusion Criteria Set a Priori

| PIC OSS | Criteria |
|---------|----------|
| **Participant** | Adult (\( \geq 18 \) years), acute to chronic non-specific or specific neck pain with or without cervicogenic headache or radiculopathy or whiplash associated disorders (WAD) |
| **Intervention** | Pharmacological interventions including medical injections; Exclusion: Alternative medicines such as homeopathy, herbal medicines, naturopathic medicines |
| **Comparison** | Placebo control or comparison (i.e. standard care, another treatment) |
| **Outcomes** | Primary: pain, function, disability, work related, quality of life. Secondary: global perceived effect and patient satisfaction |
| **Study Design** | Systematic reviews of randomized trials; Exclusion: narrative reviews were excluded |
| **Study Timeframe** | Immediate post-treatment (IP), short-term (ST: closest to 3 months); intermediate-term (IT: closest to 6 months); long-term (LT: closest to 1 year) |
RESULTS

From 10,055 reviews that were screened and 117 eligible reviews relating to neck pain filters and adverse events filters, 43 reviews related to medicines were ultimately considered for inclusion in this report. A total of 26 treatment reviews and 6 harm related reviews were included for this topic (see Fig. 1 - PRISMA diagram [16]). Excluded reviews are presented in Appendix 3, along with an accompanying rationale for their exclusion. Using the selected (prioritized) reviews, we report on trial findings by “overall quality of evidence” using the GRADE approach and stratified by the pre-determined treatment category in the Summary of Findings table (Table 2) [17-90]. We report on conflicting evidence across reviews in Table 3 [91, 92]. Our final recommendations are summarized in the Evidence-based Recommendation table and provided in Table 4. The AMSTAR assessment (see Table 5) revealed that the most common methodological limitations among the included reviews were incomplete reporting on: publication bias; conflict of interest; and full reporting of excluded studies.

Details on risk of bias (AMSTAR scoring) are available in the companion methods paper by Santaguida et al. APPENDIX 2 to this report provides the details on why 17 medicines reviews were excluded. Table 2 provides summary findings by treatment category and includes the primary trials and related systematic review(s) used to compile recommendations in this systematic review. The evidence tables, 'Characteristics of Included Studies and GRADE rationale', underpinning the summary provided in Table 2 are available from the authors. Table 6 [93-98] summarizes the findings on harms. The primary reviews included in our analyses considered the following medicines and medical injection therapies: anti-inflammatory and analgesics in combination, anti-inflammatories alone, analgesics alone, anesthetics such as lidocaine intramuscular (IM and topical nerve blocks), muscle relaxants, neurotropic multivitamins (IM), psychotropic agents, sterile water (IM, subcutaneous and intracutaneous), subcutaneous insufflation, botulinum toxin-A (IM), and corticosteroids (intra-articular, intravenous, epidural).

![Fig. (1). PRISMA diagram showing the flow of reviews.](image-url)
| Category | Treatments Details | vs Comparison Authors | Quality of Evidence (GRADE*) |
|----------|--------------------|-----------------------|-----------------------------|
|          | Disorder Characteristic | Primary Authors | Strong | Moderate | Low | Very Low |
| EVIDENCE of BENEFIT – Medical Injections and Oral Medication | | | |
| Medical Injection | Intravenous Glucocorticoid for acute WAD | vs placebo Petterson 1998 [17] (PELOSO 2007 [7]; CONLIN 2005 [18]) | IT sick leave IT pain (neg) |
| Medical Injection | Intramuscular injection lidocaine + stretch for chronic MND (myofascial pain) | vs saline + stretch Esenyl 2000 [19] (PELOSO 2007 [7]; GROSS 2007 [20]) | ST pain |
| Medical Injection | Intramuscular injection lidocaine for chronic non-specific mechanical neck pain | vs dry needling Hong 1994 [21] (PELOSO 2007 [7]; TSARKITZIDIS 2009 [22]) | ST pain |
| Medical Injection | Intramuscular injection Botulinum A + exercise /medication for subacute/chronic WAD and non-specific neck pain | vs saline + exercise/medication Braker et al. 2008 [23]; Lew et al. 2008 [24]; Ferrante et al. 2005 [25] (LANGEVIN 2011 [26]) | ST pain |
| Medical Injection | Epidural steroid injection +/- lidocaine for a), b) chronic neck pain with radiculopathy c) chronic neck pain with radiation | vs intramuscular injection steroid and lidocaine a) Stav et al. 1993 [27], b) Castagnara et al. 1994 [28], vs continuous epidural c) Pasqualucci et al. 2007 [29] (BENYANMIN 2009 [30]; PELOSO 2007 [7]; ABDI 2007 [31], ABDI 2005 [32]) | a) LT pain, LT return to work, LT range of movement b) LT pain c) IT pain, IT sleep |
| Medical Injection | Subcutaneous sterile water injection for chronic neck pain after whiplash | vs placebo Bryn et al. 1993 [37] (TEASELL 2010 [38, 39]) | ST pain |
| Oral Medication | Cyclobenzaprine (psychotropic agent) + Lysine Cloniximate (NSAID) for subacute MND | vs lysine cloniximate Nasswetter et al. 1998 [40] (PELOSO 2007 [7]) | IP pain ST pain |
| Oral Medication | Tetrazepam (psychotropic agent) + Paracetamol (analgesic) for acute MND | vs paracetamol Salzmann et al. 1993 [41] (PELOSO 2007 [7]) | IP pain IP ROM IP GPE |
| Oral Medication | Eperison Hydrochloride (psychotropic agent) for chronic MND | vs placebo Bose et al 1999 [42] (PELOSO 2007 [7]) | IP pain IP ROM |
| Oral Medicine | Chloromezalone (muscle relaxant) for subacute non specific neck pain | vs placebo Berry et al. 1981 [43] (HURWITZ 2008 [44]) | IP sleep |
| Category | Treatments Details | vs Comparison | Quality of Evidence (GRADE*) |
|----------|--------------------|---------------|-------------------------------|
|          | Disorder Characteristic | Primary Authors | Strong | Moderate | Low | Very Low |
| EVIDENCE of BENEFIT – Medical Injections and Oral Medication | | | |
| Oral Medicine | Piroxicam (anti-inflammatory) for chronic non specific neck pain (Note: cervicobrachial pain - went to original article) | vs placebo | Yamamoto et al. 1983 [45] (HURWITZ 2008 [44]) | ST pain, physician perceived improvement |
| Oral Medicine | Indomethacin (anti-inflammatory) for non specific neck pain | vs placebo | Yamamoto et al. 1983 [45] (HURWITZ 2008 [44]) | ST pain, physician perceived improvement |
| Oral Medicine | Tolmetin (anti-inflammatory) for MND, Osteoarthritis | vs naproxen | Ginsbert et al. 1980 [46] (PELOSO 2007 [7]) | IP pain, IP ROM |
| Oral Medicine | Benorylate (analgesic) for subacute to chronic non specific neck pain (Note: across 6 disorder types - 90 patients with degenerative disease, n=20 with cervical spondylosis (had to go to original article to retrieve information) | vs placebo | Berry et al. 1981 [43] (HURWITZ 2008 [44]) | IP pain, IP stiffness, IP sleep, IP ability to work |
| Oral Medicine | Benorylate (analgesic) + Chloromezanone (muscle relaxant) for subacute non specific neck pain | vs placebo | Berry et al. 1981 [43] (HURWITZ 2008 [44]) | IP pain |
| Oral Medicine | Paracetamol (analgesic) + Orphenadrine (anticholinergic) - Norgesic for non specific neck pain | vs placebo | Hoivik et al. 1983 [47] (HURWITZ 2008 [44]; LEAVER 2010 [48]) | ST pain |
| Oral Medicine | Oxycodone Controlled Release (opioid analgesic) for non specific neck pain (acute chronic neck pain flares) | vs placebo | Ma et al. 2008 [449] (TSAKITZIDIS 2009 [22]) | ST pain, frequency of patients' pain episodes, quality of life, quality of sleep |
| EVIDENCE of NO BENEFIT (vs control) or No DIFFERENCE (vs another treatment) - Medical Injections and Oral Medication | Botulinum-A injection a) for chronic MND with or without radiculopathy or headache b) for chronic cervicogenic headache pain and disability c) for chronic myofascial neck and shoulder pain | vs saline | a) Cheshire et al. 1994 [50]; Gobel et al. 2006 [51]; Qjula et al. 2006 [52]; Lew et al. 2008 [24] (LANGEVIN 2011 [26,90]) | a) ST pain (neg M-A) |
| Medical Injection | | | | b) ST, IT pain (neg) ST disability (neg) |
| | | | | c) IT disability (neg) IT GPE (neg) |
## Pharmacological Interventions for Neck Pain

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| Category                        | Treatments Details                                                                 | vs Comparison                  | Quality of Evidence (GRADE*) | Disorder Characteristic | Primary Authors | (REVIEW Reference) |
|---------------------------------|-------------------------------------------------------------------------------------|--------------------------------|------------------------------|------------------------|------------------|---------------------|
|                                 |                                                                                      |                               |                              |                        |                  |                     |
|                                 | EVIDENCE of NO BENEFIT (vs control) or No DIFFERENCE (vs another treatment) - Medical Injections and Oral Medication |
| Medical Injection               | Botulinum–A injection for subacute/chronic WAD                                        | vs placebo                     | ST pain (neg M-A)            | ST pain (neg M-A)      | Braker et al. 2008 [23]; Carroll et al. 2008 [56]; Padberg et al. 2007 [57]; Freund et al. 2000 [58] (LANGEVIN 2011 [26,90]) |
|                                 |                                                                                      |                                |                              | ST disability (neg M-A) |                  |                     |
|                                 |                                                                                      |                                |                              | ST GPE (neg M-A)       |                  |                     |
| Medical Injection               | Nerve block injections Bupivacaine + varying combinations of steroid and sarapin   | vs bupivacaine alone           |                              | ST pain                | Manchikanti et al. 2006 [33]; Manchikanti et al. 2008 [34] (BOSWELL 2007 [35]; FALCO 2009 [36]) |
|                                 | for chronic cervical facet joint pain                                                |                                |                              | LT pain               |                  |                     |
| Medical Injection               | Neurotropic multivitamin plus analgesic for chronic neck disorder                   | vs analgesic                   | IP pain                      | IP GPE (neg)           |                  |                     |
| Medical Injection               | Intra-articular steroid injection for chronic WAD                                   | vs bupivacaine                 |                              | IT pain               |                  |                     |
| Medical Injection               | Intra-cutaneous injection of sterile water for CGH (duration undefined)            | vs saline                      |                              | ST pain               |                  |                     |
|                                 | Subcutaneous injection of CO2 + PT (insufflations) for chronic non-specific neck pain | vs PT                          |                              | IP pain               |                  |                     |
| Opal Medicine                   | Diazepam (psychotropic agent) a) for non-specific neck pain, chronic cervical degeneration | vs placebo                     |                              | c) ST pain and tenderness |                  |                     |
|                                 | b) for subacute MND - with possible radicular symptoms                              | a) Thomas 1991 [64] (PELOSO 2007 [7]; LEAVER 2010 [348] | a) IP pain              | b) ST global evaluation of muscle spasm |
|                                 | c) for acute MND - with spasm                                                       | b) Basmajian et al. 1978 [65] c) Basmajian et al. 1983 [66] (PELOSO 2007 [7]) |
| Opal Medicine                   | Diazepam (psychotropic agent) for chronic non-specific neck pain                   | vs manipulation                |                              |                       |                  |                     |
|                                 |                                                                                      | Sloop et al. 1982 [67] (FURLAN 2011 [68]; GROSS 2010 [69]) |
|                                 |                                                                                      |                               |                              | ST pain and function  |                  |                     |
| Opal Medicine                   | Cyclobenzaprine (psychotropic agent) for subacute MND                               | vs placebo                     |                              |                       |                  |                     |
|                                 |                                                                                      | Basmajian et al. 1978 [65] (PELOSO 2007 [7]) |
| Opal Medicine                   | Cyclobenzaprine (psychotropic agent) for myofascial pain – trapezius                | vs lidocaine infiltration      |                              |                       |                  |                     |
|                                 |                                                                                      | Furtado et al. 2002 [70] (LEITE 2010 [71]) |
| Opal Medicine                   | Phenobarbital (psychotropic agent) for acute MND                                    | vs placebo                     |                              |                       |                  |                     |
|                                 |                                                                                      | Basmajian et al. 1983 [66] (PELOSO 2007 [7]) |
|                                 |                                                                                      |                               |                              |                       |                  |                     |
| Category | Treatments Details | vs Comparison Primary Authors | Quality of Evidence (GRADE*) |
|----------|---------------------|------------------------------|-------------------------------|
| Oral Medicine | Meprobamate (psychotropic agent) for acute neck disorder with radiculopathy | vs placebo Payne et al. 1964 [72] (PELOSO 2007 [7]) | IP pain |
| Oral Medicine | Fluoxetine (psychotropic agent) for chronic WAD | vs amitriptyline Schreiber et al. 2001 [73] (PELOSO 2007 [7]) | IP pain |
| Oral Medicine | Chlorozenone (muscle relaxant) for subacute non specific neck pain | vs benorylate Berry et al. 1981 [43] (HURWITZ 2008 [44]) | ST pain, stiffness, sleep, perceived effectiveness |
| Oral Medicine | Chlorozenone (muscle relaxant) + Benorylate (Analgesic) for subacute non specific neck pain | vs benorylate Berry et al. 1981 [43] (HURWITZ 2008 [44]) | ST pain, stiffness, sleep, perceived effectiveness |
| Oral Medicine | Chlorozenone (muscle relaxant) + Benorylate (Analgesic) for subacute non specific neck pain | vs chlorozenone Berry et al. 1981 [43] (HURWITZ 2008 [44]) | ST pain, stiffness, sleep, perceived effectiveness |
| Oral Medicine | A) Celebrex, Vioxx (NSAIDs), Paracetamol (analgesic) B) Tenoxicam (NSAID) ranitidine (Histamine H2-receptor antagonist) C) Diazepam (psychotropic) for chronic specific neck pain | vs acupuncture A) Giles & Muller 2003 [74] B) Giles & Muller 1999 [75] C) Thomas et al. 1991 [64] (FURLAN 2011 [68]; FURLAN 2012 [76]) | IP and ST pain |
| Oral Medicine | A) Celebrex (NSAID), Vioxx (NSAID), Paracetamol (analgesic) B) Tenoxicam (NSAID) ranitidine (Histamine H2-receptor antagonist) for chronic specific neck pain | vs manipulation A) Giles & Muller 2003 [74] B) Giles & Muller 1999 [75] (FURLAN 2011 [68]; FURLAN 2012 [76]) | IP and ST pain favour manipulation IP and ST disability (NDI score) favour manipulation |
| Oral Medicine | Treatments by GP (analgesics + anti-inflammatory medications) + Education for subacute + chronic MND | vs sham physical therapy Koes et al. 1992 [77] (PELOSO 2007 [7]; HARALDSSON 2006 [78]) | ST, LT severity of main complaint ST, LT physical function |
| Oral Medicine | Celebrex-celacoxin (NSAID), Vioxx-rofecoxib (NSAID), paracetamol (analgesic) for chronic neck pain | vs spinal manipulation Mulle et al. 2005 [79] (GROSS 2010 [69]) | ST pain ST function |
| Oral Medicine | Piroxicam (Anti-inflammatory) for chronic non specific neck pain (Note: cervicobrachial pain - went to original article) | vs indomethacin Yamamoto et al. 1983 [45] (HURWITZ 2008 [44]) | ST pain, physician perceived improvement |
| Oral Medicine | tenoxicam (NSAID) + ranitidine (Histamine H2-receptor antagonist) for chronic MND with degenerative changes | vs acupuncture or manipulation Giles & Muller 1999 [74] (PELOSO 2007 [7]; GROSS 2010 [69]; VERNON 2007 [80]) | IP pain and function |
There is striking lack of trials and evidence for pharmacological therapies commonly used in neck pain. For subacute or chronic WAD, the evidence strongly recommends against the use of botulinum-A to reduce pain, improve disability or global perceived effect after short-term follow-up. For chronic facet joint pain and related disability, the evidence suggests against the use of medial branch block with steroids from short- to long-term follow-up data. For chronic neck pain, the evidence supports the use of only one muscle relaxant (psychotropic agent), eperison hydrochloride. There is limited efficacy with this agent however as it will help one in 37 people achieve immediate pain relief and evidence for longer-term benefits are not available.

**FINAL EVIDENCE-BASED RECOMMENDATIONS**

(SEE TABLE 4)

There is striking lack of trials and evidence for pharmacological therapies commonly used in neck pain. For subacute or chronic WAD, the evidence strongly recommends against the use of botulinum-A to reduce pain, improve disability or global perceived effect after short-term follow-up. For chronic facet joint pain and related disability, the evidence suggests against the use of medial branch block with steroids from short- to long-term follow-up data. For chronic neck pain, the evidence supports the use of only one muscle relaxant (psychotropic agent), eperison hydrochloride. There is limited efficacy with this agent however as it will help one in 37 people achieve immediate pain relief and evidence for longer-term benefits are not available.

**EVIDENCE OF BENEFIT**

This section provides data favouring the use of certain oral medication and medical injections by the GRADE of evidence.

Table 3. Therapies with Conflicting Evidence

| Treatments with Conflicting Evidence | Author (REVIEW) |
|-------------------------------------|-----------------|
| Nerve Block Injections              | Terzi 2002 [91] (prilocaine vs saline) (positive findings) |
|                                     | Inan 2001 [92] (bupivacaine vs perineural injection) (negative findings) |
| analyzed block of greater occipital nerve for neck disorder with cervicogenic headache and radicular symptoms | PELOSO 2007 [7] |
Strong Evidence of Benefit

Based on our assessment, we found no trials meeting criteria for this strength of evidence.

Moderate Evidence of Benefit

Medicinal Injection

There were no medicinal injections that met the criteria for moderate quality evidence of benefit.

Oral Medication

Psychotropic

We found one trial with 215 participants [42] favouring a small benefit [NNT 37, RR 0.68 (95%CI 0.52 to 0.90)] with eperison hydrochloride, a muscle relaxant/psychotropic agent, relative to placebo in patients with chronic mechanical neck disorder at immediate post treatment. There were no reported benefits on pain and range of motion.

| GRADE Symbol | GRADE* and Recommendation | Clinical Importance | Reported Adverse Effect or Side Effects |
|--------------|---------------------------|---------------------|----------------------------------------|
|              |                           | Magnitude of Effect  |                                         |
|              |                           | Duration of Effect   |                                         |

**Strong Evidence of Benefit:**

(Strongly recommend use)

No recommendation.

Evidence of NO Benefit:

(Strongly recommend against use)

- botulinum-A over saline placebo (5 trials, 258 participants) for chronic non-specific neck pain for short-term treatment.

Meta-analysis:

ST Pain: SMDp –0.07
(95% CI –0.36 to 0.21)

Minor, transient and reversible: excessive weakness of injected muscle, arm heaviness and numbness, transient pain or soreness at injection site, flu like symptoms, shift of pain

**Moderate Evidence of NO Benefit:**

(Suggested not to use)

- medial branch block with steroid vs control (1 trials, 120 participants)

LT Pain (NRS): WMD –0.30 (95% CI –0.68 to 0.08)

LT Disability† (NDI): WMD 0.00
(95% CI 1.72 to 1.72)

Transient facial flushing and temporary exacerbation of usual pain

- botulinum-A over placebo (4 trials, 183 participants) for subacute or chronic WAD to reduce pain, disability or global perceived effect at short-term follow-up.

ST Pain: SMDp –0.21
(95% CI –0.57 to 0.15)

ST Disability: SMDp 0.15
(95% CI –0.37 to 0.68)

ST GPE: SMDp 0.15
(95% CI –0.37 to 0.68)

Minor, transient and reversible: excessive weakness of injected muscle, arm heaviness and numbness, transient pain or soreness at injection site, flu like symptoms, shift of pain

| GRADE Symbol | GRADE* and Recommendation | Clinical Importance | Reported Adverse Effect or Side Effects |
|--------------|---------------------------|---------------------|----------------------------------------|
|              |                           | Magnitude of Effect  |                                         |
|              |                           | Duration of Effect   |                                         |

**Key:**

- WAD – whiplash associated disorder
- MND – mechanical neck disorder
- SMDp – Standard Mean Difference pooled
- WMD – weighted mean difference
- RR – relative risk
- NNT – number-needed-to-treat
- 95%CI – 95% confidence interval
- † no significant difference between groups for this outcome
- GPE – global perceived effect
- NR – not reported
- NA – not applicable

**Strong Evidence of Benefit**

Based on our assessment, we found no trials meeting criteria for this strength of evidence.

**Moderate Evidence of Benefit**

**Medicinal Injection**

There were no medicinal injections that met the criteria for moderate quality evidence of benefit.

**Oral Medication**

**Psychotropic**

We found one trial with 215 participants [42] favouring a small benefit [NNT 37, RR 0.68 (95%CI 0.52 to 0.90)] with eperison hydrochloride, a muscle relaxant/psychotropic agent, relative to placebo in patients with chronic mechanical neck disorder at immediate post treatment. There were no reported benefits on pain and range of motion.
Table 5. AMSTAR Rating of Medicine Reviews for Neck Pain

| Author | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|--------|---|---|---|---|---|---|---|---|---|----|----|
| Abdi et al. 2005 [32] | Y | N | Y | Y | Y | Y | Y | Y | NA | N | Y |
| Abdi et al. 2007 [31] | Y | CA | Y | Y | Y | Y | Y | Y | NA | N | N |
| Benyamin et al. 2009 [30] | Y | N | Y | N | N | Y | Y | Y | NA | N | N |
| Boswell et al. 2005 [35] | Y | N | Y | N | N | Y | Y | Y | NA | N | Y |
| Carragee 2008 [61] | Y | N | N | Y | N | N | Y | Y | NA | N | N |
| Conlin et al. 2005 [18] | Y | N | Y | N | N | Y | Y | Y | N | Y | N |
| Falco et al 2009 [36] | Y | Y | Y | N | N | Y | Y | Y | NA | N | N |
| Fu et al. 2009 [87] | Y | Y | Y | N | Y | Y | Y | N | Y | N | N |
| Furlan 2011 [68] | Y | Y | Y | Y | Y | Y | Y | N | N |
| Furlan et al. 2012 [76] | Y | Y | Y | Y | N | Y | Y | Y | Y | N | N |
| Graham et al. 2006 [85] | Y | Y | Y | Y | N | N | Y | Y | N | N |
| Gross et al. 2007 [20] | Y | Y | Y | Y | N | Y | Y | Y | N |
| Gross et al. 2010 [69] | Y | Y | Y | N | Y | Y | Y | Y | N |
| Haraldsson et al. 2006 [78] | Y | Y | Y | Y | Y | Y | Y | Y | N |
| Hurwitz et al. 2008 [44] | Y | N | N | Y | N | Y | Y | Y | NA | N | N |
| Langevin et al. 2011 [26] | Y | Y | Y | Y | Y | Y | Y | Y | N |
| Langevin et al. 2011 [90] | Y | Y | Y | Y | Y | Y | Y | Y | N |
| Leaver et al. 2010 [48] | Y | Y | Y | N | N | Y | Y | Y | N |
| Leite et al. 2009 [71] | Y | Y | Y | Y | N | Y | Y | Y | NA | N | N |
| Peake & Harte 2005 [86] | Y | N | Y | N | N | Y | Y | Y | NA | N | N |
| Peloso et al. 2007 [7] | Y | Y | Y | Y | Y | Y | Y | Y | N |
| Teasell et al. 2010 [38] | Y | N | Y | N | N | Y | Y | Y | NA | N | N |
| Teasell et al. 2010 [39] | Y | N | Y | N | N | Y | Y | Y | NA | N | N |
| Tsakitzidis et al. 2009 [22] | Y | Y | Y | Y | N | Y | Y | Y | NA | N | N |
| Vernon et al. 2007 [80] | Y | Y | Y | N | Y | Y | Y | N | N |
| Vernon & Schneider 2009 [83] | Y | N | Y | N | N | Y | Y | Y | NA | N | N |

Key: Y Yes; N No; NA not applicable; CA can’t assess; AMSTAR Questions:
1. Was an ‘a priori’ design provided? The research question and inclusion criteria should be established before the conduct of the review.
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible.
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? For other types of studies alternative items will be considered.
5. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.
6. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.
9. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).
10. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
Limited data from low to very low GRADE evidence suggests there may be benefit in the use of the following five medicinal injections:

**Paralytic**

1. Botulinum toxin-A plus exercise/medication combination for subacute/chronic WAD [23] or non-specific neck pain for intermediate term pain (meta-analysis [24, 25]).

**Medical Injections**

- **Epidural steroid – Cervical axial or radicular pain**
  - Transforaminal: Malhotra 2009 [93], Guzman 2008 [94], Abdi 2005 [95]
  - AMSTAR Score: 2 - low, 4 - low, 7 - high
  - Adverse Events: Headache, Transient neurological deficits (pain, weakness), Hypersensitivity reaction, Vasovagal response, Nausea, Transient global amnesia, Allergic responses, Seizure, Spinal cord, brainstem or brain edema, Cortical blindness, Epidural or paraspinal hematoma, Peripheral neuropaxia, Dural puncture, Cervical spinal cord or vertebralbasilar, Transient ischemia attack, Death.
  - Frequency: 0 to 22.7% for minor transient adverse events. No values reported for all others.

- **Epidural steroid – Cervical axial or radicular pain**
  - Interlaminar: Abbasi 2007 [96], Guzman 2008 [94], Abdi 2005 [95]
  - AMSTAR Score: 2 - low, 4 - low, 7 - high
  - Adverse Events: Retinal hemorrhage, Allergic reaction, Epidural hematoma, Subdural complications, Dural puncture, Headache neuropathic symptoms, Intracranial hypotension and epidural granuloma, Permanent spinal cord injury, Intravascular uptake of injectate, Pneumocephalus, Venous air embolism, Cervical epidural abscess, Cushing’s syndrome, Death.
  - Frequency: 0 to 17% for minor transient adverse events. No values reported for all others.

- **Stellate ganglion block – Sympathetically maintained pain**
  - Higa 2006 [97]
  - AMSTAR Score: 3 - low
  - Adverse Events: Retropharyngeal hematoma causing airway blockage can lead to death – precipitated by head, neck or chest pain, dyspnea, neck swelling, abnormal sensations in the upper airway.
  - Frequency: Overall rate 14/27 patients (52%), 21/27 (78%) requiring airway management, 1 (3.7%) death.

- **Intraarticular facet joint, medial branch block, radiofrequency neurotomy – Chronic spinal pain 3-6 months in duration**
  - Boswell 2005 [98], Guzman 2008 [94]
  - AMSTAR Score: 5 - low, 4 - low
  - Adverse Events: Dural puncture, spinal cord trauma, infection, spinal anesthesia, chemical meningitis, neural trauma, pneumothorax, radiation exposure, facet capsule rupture, hematoma formation, and steroid side effects, Radiofrequency neurotomy – Cutaneous dysesthesias, Neuritis/neurogenic inflammation, Anesthesia dolorosa, Cutaneous hyperesthesia, pneumoaddox, Deafferent pain.
  - Frequency: Overall rate not reported.

### Table 6. Harms Summary of Findings with AMSTAR Score

| Category          | Treatment Details Disorder Characteristic | Review Reference | AMSTAR Score and Quality | Adverse Events                                                                                                                                             | Frequency                                                                 |
|-------------------|------------------------------------------|------------------|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Medical Injection | Epidural steroid – Cervical axial or radicular pain | Malhotra 2009 [93] | 2 - low                  | Headache, Transient neurological deficits (pain, weakness), Hypersensitivity reaction, Vasovagal response, Nausea, Transient global amnesia, Allergic responses, Seizure, Spinal cord, brainstem or brain edema, Cortical blindness, Epidural or paraspinal hematoma, Peripheral neuropaxia, Dural puncture, Cervical spinal cord or vertebralbasilar, Transient ischemia attack, Death. | 0 to 22.7% for minor transient adverse events. No values reported for all others. |
|                   | Transforaminal                           | Guzman 2008 [94] | 4 - low                  |                                                                                                                                                |                                                                           |
|                   |                                          | Abdi 2005 [95]   | 7 - high                 |                                                                                                                                                |                                                                           |
| Medical Injection | Epidural steroid – Cervical axial or radicular pain | Abbasi 2007 [96] | 2 - low                  | Retinal hemorrhage, Allergic reaction, Epidural hematoma, Subdural complications, Dural puncture, Headache neuropathic symptoms, Intracranial hypotension and epidural granuloma, Permanent spinal cord injury, Intravascular uptake of injectate, Pneumocephalus, Venous air embolism, Cervical epidural abscess, Cushing’s syndrome, Death. | 0 to 17% for minor transient adverse events. No values reported for all others. |
|                   | Interlaminar                             | Guzman 2008 [94] | 4 - low                  |                                                                                                                                                |                                                                           |
|                   |                                          | Abdi 2005 [95]   | 7 - high                 |                                                                                                                                                |                                                                           |
| Medical Injection | Stellate ganglion block – Sympathetically maintained pain | Higa 2006 [97]  | 3 - low                  | Retropharyngeal hematoma causing airway blockage can lead to death – precipitated by head, neck or chest pain, dyspnea, neck swelling, abnormal sensations in the upper airway. | Overall rate 14/27 patients (52%), 21/27 (78%) requiring airway management, 1 (3.7%) death |
| Medical Injection | Intraarticular facet joint, medial branch block, radiofrequency neurotomy – Chronic spinal pain 3-6 months in duration | Boswell 2005 [98] | 5 - low                  | Dural puncture, spinal cord trauma, infection, spinal anesthesia, chemical meningitis, neural trauma, pneumothorax, radiation exposure, facet capsule rupture, hematoma formation, and steroid side effects, Radiofrequency neurotomy – Cutaneous dysesthesias, Neuritis/neurogenic inflammation, Anesthesia dolorosa, Cutaneous hyperesthesia, pneumoaddox, Deafferent pain. | Overall rate not reported |
|                   | Intraarticular facet joint, medial branch block, radiofrequency neurotomy | Guzman 2008 [94] | 4 - low                  |                                                                                                                                                |                                                                           |
Pharmacological Interventions for Neck Pain

**Intramuscular (IM) Analgesic**

2. Intramuscular lidocaine injection with or without stretching (versus placebo [19]; versus dry needling [21]) for chronic non-specific mechanical neck pain for short-term pain.

**Interlaminar Cervical Epidural Steroid**

3. Epidural steroids (plus lidocaine [27, 29]; plus morphine [28]) versus various control injections for chronic neck mechanical neck pain with radiculopathy or radiation into the arm for intermediate-term [29] to long-term pain, function and return to work.

**Intravenous Corticosteroid**

4. Methylprednisolone versus placebo for intermediate-term sick leave and disabling symptoms [17], in an acute emergency room WAD population.

**Subcutaneous Saline**

5. Subcutaneous sterile water injection may be beneficial in reducing pain for chronic neck pain after whiplash [37] based on very low quality evidence.

**Oral Medications**

Limited evidence from low to very low GRADE evidence suggests there may be benefit with the use of the following 10 oral medications:

**Psychotropic/Muscle Relaxant**

1. Cyclobenzaprine plus lysine cloniximate versus lysine cloniximate for subacute nonspecific mechanical neck disorder for immediate post treatment and short-term pain [40].

2. Trazepam plus paracetamol versus paracetamol alone for acute non-specific mechanical neck disorder for immediate post treatment pain, range of motion and global perceived effect [41].

3. Chlormezanone versus placebo for subacute non-specific neck pain for intermediate post treatment sleep [43].

**Anti-Inflammatory**

4. Piroxicam versus placebo for chronic non-specific pain for short-term pain, for physician perceived improvement [45].

5. Indomethacin versus placebo for non-specific neck pain for short-term pain, for physician perceived improvement [45].

6. Tolmetin versus naproxen for non-specific mechanical neck disorder and osteoarthritis for immediate post treatment pain and range of motion [46].

**Analgesic**

7. Benorylate versus placebo for subacute to chronic non-specific neck pain for immediate post treatment pain, stiffness, sleep and ability to work [43].

8. Benorylate plus chlormezanone versus placebo for subacute non-specific neck pain for immediate post treatment pain [43].

9. Norgesic (paracetamol plus orphenadrine) versus placebo for non-specific neck pain for short-term pain [47].

10. Oxycodone controlled release versus placebo for non-specific neck pain for short-term pain, frequency of patients’ pain episodes, quality of life and sleep [49].

**EVIDENCE OF NO BENEFIT**

**Strong Evidence of No Benefit**

**Medical Injection**

Paralytic

For botulinum toxin-A (1 review [26] conducted a meta-analysis of 4 trials, including 183 participants [24, 50, 51, 52]), finding no benefit over placebo for chronic non-specific neck pain at short term follow-up.

**Moderate Evidence**

**Medical Injection**

Paralytic

For botulinum toxin-A, one review [26] conducted a meta-analysis of 4 trials (122 participants [23, 56, 57, 58]) and found no benefit over placebo for patients with subacute/chronic WAD in pain relief, disability or global perceived effect at short-term follow-up.

Corticosteroids

For a medial branch block with steroid added to bupivacaine versus bupivacaine alone (1 trial [33, 34]; 60 participants), we found evidence of small benefits in pain, but not for function for chronic cervical facet joint pain in the short-, intermediate- and long-term [long-term pain: WMD -0.30 (95% CI -0.68 to 0.08)]. This result was not statistically significant and not likely to be clinically important; this trial was performed in a population with severe pain.

**Low or Very Low Evidence of No Benefit**

**Medicinal Injection**

We found limited information based on low to very low GRADE evidence suggesting there is no evidence of benefit for the following 4 medical injections:

**Corticosteroids**

Intra-articular steroid injection versus anaesthetics for chronic WAD for intermediate-term pain [60].

**Paralytic**

1. Botulinum toxin-A versus placebo for chronic cervicogenic headache pain (2 trials 58 participants [53, 54] and disability (1 trial [53]) at short-term and 1 trial [53] at intermediate-term follow-up. Additionally botulinum toxin-A versus placebo (saline) (1 trial [55], 45 participants) was not beneficial in improving disability or global perceived effect for chronic myofascial neck and shoulder pain at intermediate-term follow-up.

**Subcutaneous Insufflation**

2. Subcutaneous insufflation of CO₂ plus physiotherapy versus physiotherapy alone for immediate post treatment pain [63].
Intramuscular Injection Vitamin

3. Intramuscular injection of neurotropic multivitamin plus analgesic versus analgesic alone for chronic neck disorder with radicular symptoms for immediate post treatment pain and global perceived effect [59].

Oral Medication

The authors noted limited information (low to very low GRADE) suggesting no evidence of benefit for the following 17 oral medications:

Psychotropic - Benzodiazepines and Muscle Relaxants

1. Diazepam for acute mechanical neck disorder with spasm [66], subacute mechanical neck disorder with possible radicular symptoms [65], non-specific neck pain and chronic cervical degeneration [64] for immediate post treatment pain [64] and short-term pain, tenderness relief [66] and global evaluation of muscle spasm [65].

2. Diazepam versus manipulation for chronic non-specific neck pain for short-term pain and functional improvement [67].

3. Cyclobenzaprine (versus placebo [65]; versus lidocaine infiltration [70] for subacute MND or trapezius myofascial pain for short-term global evaluation of muscle spasm and global pain and pain at digital compression.

4. Phenobarbital for acute MND for short-term pain and tenderness [66].

5. Meprobamate versus placebo for acute neck disorder with radiculopathy for immediate post treatment pain [72].

6. Fluoxetine versus amitriptyline for chronic WAD for immediate post treatment pain [73].

7. Chlormezanone (versus benorylate); chlormezanone plus benorylate (versus benorylate); chlormezanone plus benorylate (versus chlormezanone) for subacute non-specific neck pain for short-term pain, stiffness, sleep and perceived effectiveness [43].

Anti-Inflammatory Plus Analgesic

1. Celecoxib, rofecoxib, paracetamol [74], tenoxicam [75] and diazepam [64] versus acupuncture for chronic specific neck pain for immediate post treatment and short-term pain.

2. Celecoxib, rofecoxib, paracetamol [43], tenoxicam [75] versus manipulation for chronic specific neck pain for immediate post treatment and short-term pain and disability. (Note: At immediate post treatment and at short-term follow-up, manipulation was favored for pain and disability outcomes).

3. Treatments by a general practitioner (analgesics plus anti-inflammatory medications) plus education versus sham physical therapy for subacute and chronic MND for short-term to long-term severity of main complaint and physical function [78].

4. Celecoxib, rofecoxib, paracetamol versus spinal manipulation for chronic neck pain for short-term pain and function [80].

5. Piroxicam versus indomethacin for chronic non-specific neck pain for short-term pain and physician perceived improvement [45].

6. Ibuprofen plus manipulation versus manipulation for chronic neck disorder with headache and radiculopathy for immediate post treatment pain [82].

7. NSAIDs for chronic specific neck pain (versus acupuncture [83]), chronic MND and neck disorder with radicular signs (versus continuous traction and exercise [86]) for pain relief immediately post treatment. (Note: At immediate post treatment, acupuncture was favored for the pain outcome).

8. NSAIDs (plus placebo cervical traction and postural advice [86]; plus sham acupuncture [83]) versus manual cervical traction, exercise and postural advice [86]; acupuncture [83] for chronic cervical spondylisis with pain in neck and arms of root distribution and neck pain for immediate post treatment pain, range of motion and physician’s assessment of the severity of the conditions. (Note: Pain reduction favored acupuncture at immediate post treatment).

Analgesic

Glaphenine versus paracetamol for acute MND for immediate post treatment pain and range of motion [88].

Other

Melatonin versus placebo for chronic MND or WAD for immediate post treatment pain, sleep and health status [89].

Adverse Events

Medicinal Injections

This section first discusses medicinal injections and then medicines. In the reviews themselves that informed on efficacy, we found minor, transient and reversible side effects following injections, including increased pain reporting for several hours to several days post injection. However a valid estimate of clinically important, uncommon, and rare adverse events cannot be made from these trials due to limited reporting in the original trials and in the reviews. With botulinum toxin-A injection, excessive weakness of the injected muscle, arm heaviness and numbness, transient pain or soreness at injection site, flu like symptoms and shift of pain occurred [7]. For bupivacaine nerve block injection, transient facial flushing and temporary exacerbation of usual pain were reported [7] as they were also reported for intra-articular use of betamethasone [60]. Injection pain, allergic reaction and headache were associated with the administration of intramuscular multivitamin plus analgesic [59]. Worsened pain was associated with both epidural steroid and lidocaine injections [7, 27]. Malaise, headache, nausea and vomiting were associated with subcutaneous CO2 used with physical therapy [63].
We also performed searches specific to harms to augment the information found in the reviews. As part of these searches we found evidence of both minor transient and major catastrophic adverse events for injections [93-98]. Table 6 lists the adverse events associated with each procedure. For both transforaminal and interlaminar epidural steroid injections there is a broad list of adverse events, with interlaminar injections appearing to have more serious outcomes, possibly since the technique approaches the spinal cord more directly [99]. The review on stellate ganglion blocks [94] only considered the development of retropharyngeal hematoma and not other adverse events associated with this procedure. Reviews of intraarticular facet joint and medial branch injections adverse events reported mainly major adverse outcomes, with Higa et al. (2006) reporting an adverse outcome of death (1 death or 3.7% of population) [97]. Injections appear to lead to minor adverse events occur in approximately 1 in 5 patients. However limited reporting overall hinders the ability to provide a more precise estimate of injections’ safety.

**Oral Medications**

Based on the treatment reviews, a valid estimate of clinically important, uncommon, and rare adverse events is not possible, due to limited reporting on adverse events. Minor side effects were reported with oral medications in some trials. Sleepiness was associated with taking diazepam [66]; drowsiness, mouth dryness and xerostomia were associated with taking cyclobenzaprin [65, 70]; sleepiness, gastrointestinal upset and skin irritation were associated with taking cyclobenzaprin and lamisine cloniximate [40]; dizziness, fatigue and dry mouth were associated with taking tetrazepam and paracetamol [41]; dizziness and drowsiness were reported for taking phenobarbital [66]; drowsiness, nausea and indigestion were reported for taking meprobamate [72]; fluoxetine was reported to have anticholinergic effects such as dryness and dizziness [73]; dyseptic difficulties, elimination difficulties and drowsiness were associated with taking glafenine [89]; drowsiness, cephalalgia, dyspeptic difficulties, ulcer and vertigo were reported for taking paracetamol [89]; headaches were associated with taking melatonin [89].

Importantly, no systematic reviews presenting the harms of oral medications in the neck pain population were identified, and therefore is speculation whether an events and event rates seen in other populations might also apply to the neck pain population.

**DISCUSSION**

There was more data on evidence of no benefit. In the review by Langevin et al. [26], a meta-analysis of four trials provided a strong quality of evidence demonstrating no benefit for botulinum toxin-A over placebo for subjects with chronic non-specific neck pain for short-term pain. Additionally in the same review by Langevin et al., another meta-analysis of four trials with moderate quality evidence demonstrated no benefit for botulinum toxin-A over placebo for subacute or chronic WAD patients for short-term pain, disability or global perceived effect. Two reports of one trial by Manchikanti et al. [33, 34] did not support the use of nerve block injections with bupivacaine and varying combinations of steroid and sarapin for subjects with cervical facet joint pain for short- and long-term pain.

Although oral medication such as analgesics, anti-inflammatoryatories, antidepressants, opioids, psychotropic, and muscle relaxants are commonly used in clinical practice, there continues to be low to very low quality evidence available for their benefits and risks in neck pain. Furthermore the existing evidence is conflicting, which limits the ability to make clear recommendations. Data on disability, function, and quality of life are rarely reported. Most pharmacological therapies would be expected to produce side effects and their balance of risks and benefits are likely to vary by the condition being treated. We speculate that physicians assume that injections and medications demonstrating efficacy for other musculoskeletal conditions such as in low back pain [100] inform their use in neck pain and that clinical trials are not being conducted or not considered necessary in the neck pain population. However we are not aware of data that suggests treatment benefits seen in the back pain population can be extended to the neck pain population. Given that neck pain is common, potentially disabling and costly to society, and that benefit-risk may well vary by condition, high quality studies are still needed to understand the benefits and risks in the neck pain population. Our qualitative research suggests that the side effects associated with medication use can be very concerning for patients and patients may discontinue medications related to these concerns [101]. Specifically patient's worried about how medications would interfere with their ability to participate in normal life roles [101]. Further, patients in our qualitative study indicated that they prefer that physicians present all treatment options and not confine their recommendations to prescriptions of medications alone [101].

For medicinal injections, the therapies with the most supporting evidence continue to be IV methylprednisolone for acute whiplash, IM-lidocaine for chronic MND, and epidural methylprednisolone with lidocaine injection for radiculopathy. It remains unclear if all corticosteroids or local anesthetics are equally effective or if there is a dose response for these therapies. Replication in larger, high quality trials is needed for these injections. If subsequent trials were positive, efforts to promote widespread adoption would be indicated. Anti-inflammatory drugs warrant further study particularly since several of them such as ibuprofen and naproxen may be available over the counter without a prescription; we note that they are also frequently used as co-intervention with other physiotherapy management approaches. Oral psychotropic agents classified as muscle relaxants, such as cyclobenzaprin, diazepam, and...
tetrazepam continue to require further study to clarify their benefits and harms. There were no studies of tricyclic antidepressants and one very low quality trial on opiate analgesics in chronic neck pain. In this regard, little has changed since the 1996 [102] and 2007 [20] systematic reviews.

Another challenge in making more definitive recommendations was the lack of high-quality clinical trials that addressed meaningful outcomes in a standardized way. Many studies focus on pain alone with function being reported to a lesser extent. Even when function is reported, different outcomes are used. Consistent use of pain and disability outcomes would facilitate cross study comparisons and inform future metaanalyses. A number of reporting and design issues in neck pain clinical trials have been detailed in Goldsmith et al. [103]. There are design features that would improve the quality of future clinical trials in neck pain. In particular, future research should ensure adherence to CONSORT guidelines, look beyond the basic two group design (active vs placebo or active vs active) that is commonly used and the should consistently report standardized impairment and disability outcomes [104]. A core set of patient reported outcomes and key participation indicators (such as return to work) are needed. Further an accurate prospective collection of adverse events is also fundamental. Finally, studies that compare medicines or injections to other commonly used therapies, such as physical therapies and manual therapies are needed to understand whether some therapies should preferentially be recommended.

The ability to generalize our findings across the entirety of the neck pain population is limited from at least four perspectives. First, there are many disorders that can have neck pain as an associated feature, such as migraine, tension type headache and trigeminal neuralgia. A careful differential diagnosis and its reporting are important when describing neck pain patients included in any trial. This report specifically applies to a narrow type of mechanical neck pain with or without cervicogenic headache or radiculopathy. Second, when considering botulinum toxin injections, identification of the dystonic muscle may need EMG guidance to ensure the right region or muscles are injected; this was not the case in the trials included in this review. Third, once neck pain has been identified, the mechanisms underpinning the pain experience need to be identified where possible. Mechanisms underlying peripheral or central neuropathic pain will be treated differently than nociceptive mechanisms such as chemical [inflammatory from tissue (bradykinin, prostaglandin, serotonin), nerve (NGK, neurokinins, noradrenaline), immune cells (macrophages, cytokines)], ischaemic (SP, CGRP) and mechanical. Understanding the pain experience could help to optimize different medical strategies. Finally, understanding why some patients respond and other do not would also allow the most appropriate therapy to be directed to the right patients. Clinical decision rules may then help guide practice.

Our approach to summarizing the literature has several strengths. We used a comprehensive, librarian-assisted search of multiple databases. We used two independent reviewers to determine article relevance and assess review quality using the AMSTAR tool. We used at least two people to verify data extraction. We used a group and an external panel consensus approach to validate the GRADE of evidence and recommendations. We avoided the professional bias inherent in having a single professional group evaluate its own literature. The largest limitation is that new trials will have been published following the publication of many of these reviews. Given the state of the literature, one large trial with a low risk of bias could change the direction of benefit (positively or negatively) as well as the magnitude of that benefit. We did consider the potential for selection bias and we examined the grey literature of reviews as part of our search strategy.

The vast majority of trials did not lead to firm recommendation, since few injections and medicines results have been replicated by large, high quality trials. Although we did find some meta-analyses (the highest level of evidence), the quality of studies for neck pain continues to be limited. Adverse effects and associated costs of treatment are widely under-reported and when they are reported are they often in narrative form rather than quantitatively expressed. There is evidence of major catastrophic adverse events with all of the injection procedures. Approximately 1 in 5 patients will experience minor transient adverse events with transforaminal or interlaminar epidural steroid injections. No clear estimate of the overall incidence rate for any injection procedure is available due to a lack of reporting. Although we did not find any specific reviews reporting harms associated with oral medication for neck pain, we can be informed by reviews that report adverse events for other musculoskeletal pain disorders for some guidance.

A few systematic reviews of antidepressant side effects have been conducted and Perrot et al. (2008) note that when prescribed for painful conditions, side-effects occur in 30 to 100% of patients and are often dose-dependent [105]. Reported side effects are dysuria, constipation, dry mouth, drowsiness, eye accommodation disorders, tachycardia, memory disorders and confusion, orthostatic hypotension, dizziness, weight gain, trembling, impotence, nausea, fatigue and serotonergic syndrome. Hauser et al. (2012) provide relative risk estimates for similar mild transient adverse events ranging from 0.94 (0.46, 1.68) for headache to 9.51 (1.22, 74.0) for sexual dysfunction [106].

There is a vast literature informing NSAIDS adverse events although the great majority is related to oral and compared to topical use. Zhang et al. report that gastrointestinal events are 3 to 5 times higher compared to placebo, while Jones et al. report that up to 60% of all NSAID users will experience a GI event [107, 108]. Canadian guidelines for NSAID use reported that the rate of gastrointestinal hemorrhage is 1.5 to 2.0% per year for average risk patients while Jones et al. report a rate of 1.0 to 1.5% [108, 109]. The Osteoarthritis Research Society International (OARSI) guidelines reported that cardiovascular events are comparable in the COX-2 class with the traditional NSAIDS blocking both COX-1 and COX-2 (RR 1.19 95% CI 0.80, 1.75) [107], while Jones et al. argue that selective COX-2 inhibitors and NSAIDs could have different rates [108].
Opiates were considered in a recent systematic review of conservative management for low back pain. Opiate use was associated with a greater risk of headache and nausea, drowsiness, dry mouth, constipation, pruritis, vomiting, anorexia and increased sweating over placebo. The risk differential was low and ranged from 3 to 9% [110]. The OARS guidelines report a relative risk for any adverse event related to opiate use at 1.4 (95% CI 1.3, 1.6) and specifies constipation, nausea, drowsiness, dizziness and vomiting as side effects.

A Cochrane review reported that there was no significant difference in the overall safety of Acetaminophen compared to NSAIDS [111]. Acetaminophen can be associated with GI events but at a lower rate than that of NSAIDS. Acetaminophen can lead to renal failure however with a RR up to 2.5 (95% CI 1.7, 3.6) [90].

CONCLUSION

There is a lack of trials in neck pain for common injections and medications and this leads to an inability to fully inform the proper use of pharmacological therapies. The current state of the evidence appears to favor the muscle relaxant eperison hydrochloride for chronic neck pain. Evidence is emerging against IM botulinum toxin-A injections for chronic mechanical neck disorder or subacute/chronic WAD and against medial branch block with steroids for chronic facet joint pain. Given the limited number of trials and the low level of evidence in those that have been performed, coupled with the frequent and disability nature of neck pain, high quality trials of analgesics, anti-inflammatories, and psychotropic agents are urgently needed.

ABBREVIATIONS

AMSTAR Assessment of the Methodological Quality of Systematic Reviews; CI Confidence Interval; COX Cyclooxygenase; GRADE Grading of Recommendation Assessment, Development, and Evaluation; ICON International Collaboration on Neck; IM intramuscular; IP immediate post; LT long-term; MCID Minimal Clinically Important Difference; MND mechanical neck disorder; NDI Neck Disability Index; NNT Number Needed to Treat; NSAID non-steroidal anti-inflammatory drug; PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT randomized controlled trial, RR relative risk; SMD, Standard Mean Difference (pooled);VAS Visual Analogue Scale; WAD whiplash associated disorder; WMD Weighted Mean Difference.

CONFLICT OF INTEREST

Paul M. Peloso conducts clinical research for Merck, a company that manufactures and markets classes of drugs named in this review, including NSAIDs and antidepressants. This article represents the views of Dr. Peloso and the ICON team and should not be construed to represent the views of Merck.

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APPENDIX 1

Oral Medication and Medical Injections

| Oral Medication: Non-Opiate Analgesics |
|---------------------------------------|
| acetaminophen, paracetamol, paramax, migraflex, metomax |

| Oral Medication: Non-steroidal Anti-inflammatory (NSAID) |
|---------------------------------------------------------|
| ibuprofen, naproxen, meloxicam, celecoxib, acetylsalicylic acid, ASA, carbasalatacumin, diflunisal, accefolenac, accefolenac, diclofenac, indometacin, sulindac, piroxicam, dextibuprofen, dextketoprofen, fenoprofen, flurbiprofen, ketoprofen, tiapro (tiaprofenic acid), metamizol, phenylbutazone, phenazone, propyphenazone, toradol, etoricoxib, nabumeton (nabumetone), parecoxib, valdecoxib, lumiracoxib, rofecoxib |

Topical Medication: NSAID

diclofenac, ibuprofen, diclofenac, salicylic acid, piroxicam, ketoprofen, gibus/ menthol/ salicylic acid/ turpentine oil, gelbinic, nicotinic acid/ salicylic acid, oloeresin/ ioidine/ menthol/ salicylic acid, acetid acid/ turpentine oil, capsicum oloeresin/ nicotinic acid/ salicylic acid, cajuput/camphor/mentha, acetic acid/ammonia/turpentine oil, methol/ salicylic acid, ammonium/ oleic acid, turpentine oil, camphor/ creosote/ eucalyptus, globules/ menthol/ pinus mugo pumilio/ salicylic acid/ thymus vulgar/ turpentine oil, camphor/ menthol/ salicylic acid, diclofenac/ linum usitatissimum/ menthol/ salicylic acid, camphor/ nicotinic acid/ salicylic acid, benzocaine/ salicylamide, benzocaine/ salicylic acid, benzocaine/ nicotinic acid/ salicylic acid, ioidine/ salicylic acid, acetylsalicylic acid/ camphor/ menthol/ salicylic acid |

Oral Medication: Analytical Opiate/Narcotics

codeine, buprenorphine, tramadol, fentanyl, hydromonorphone, morphine, oxycodone/ naloxone, opiate, opium, acetyldihydrocodeine, alfentani, allylproline, alphamethylfentanyl, alphaprodine, benzylmorphine , betaprodine, bezitramide, buprenorphine, butorphanol, bromazine, carfentan (carfentan), conti, dextromoramide , dextropropoxyphone, dezocine, diactylmorphine, diamorphine, dihydrocodeine, dihydromorphine , dihydromorphine , diphenoxylate, dipipanone, enadoline, ethylketazocine, ethylmorphine, etonitazene, etorphine, fentanyl, heroien, hydrocodone, hydromorphin (hydromorphine), hydromorphone , ketazocine, ketobemidone, lefetamine, levmethadon, levmethadyl, levmethadon, levor-phanol, loperamide, meperidin, meptazinol, methadone, methadyl , methylmorphine, morphin (morphine), nalbuphine, narcotic, nicocodeine, nicomorphine, normorphine, noscapin, olnemefentanyl, oripavine, oxycodeone , oxycontine, oxymorphine, papaveretum, papaverin, pentazocine, perocct, peronine, pethidin, phenazoncine, phencyclidine, pholcodine, piritramid (piritramidine), prodine, promedol, propoxyphone, remifentanil, sufentanil, tapentadol, thebaine, tilidine, tramadol, ultracet |

Oral Medication: Muscle Relaxants
baclofen, cyclobenzaprine, eperison hydrochloride, methocarbamol, orphenadrine, tizanidine, chlorzoxazone, metaxalone, meprobamate, zopiclone

**Oral Medication:** Benzodiazepines
diazepam, alprazolam or xanax or xanor or tafil or alpro or frontal,bromazepam or lexotanil or lexotan or lexomial or bromam, chlor Diazepoxide or librum or tropium or risolid or klopopixid, cinolazepam or gerodorm, clonazepam or klonopin or rivotril or ictorivi, cloxazolam or ocalid, clorazepate or traxtene, diazepam or valium or pax or apzepam or stesolid, estazolam or proSom, flunitrazepam or rohypnol or fluscard or flunipam or rona or rohydorm, flurazepam or dalmadorm or dalmane, flutoprazepam or restas, halazepam or paxipam or ketazolam or anox or loprazolam or dominocot, iorazepam or ativan or tempeta or tavor, lorabenz, lorometazepam or loramet or noxamid or pronoctan, medazepam or nohibit, midazolam or dominic or versed or hypnovel or dominod, nimetazepam or erimin, nitrazepam or mogadan or aldorm or pacisyn or dumolid, nordiazepam or madar or stily, oxazepam or seresta or serax or serenid or serepax or sobril, pinazepam or domar or prazepam or lysanxia or centrax or quazepam or doral, temazepam or restoril or normiron or euhypons or tenox, Tetrazepam or Mylostan or Triazolam or Halcion or Rilamir

**Oral Medication:** GABA Derivatives
gabapentin, pregabalin

**Medical Injections:** Corticosteroids
betametson, methylprednisolone, triamcinolone acetamide, triamcinolone, steroid of corticosteroid, prednisone, prednisolone, betamethasone

**Medical Injections:** Analgesics
procaine, lidocaine, pripocaine, benzocaine, bupivacaine, mepivacaine, articaine, tetraacaine, ropivacaine, lignocaine, mexiteline, flecainide, tocainide

**Medical Injections:** Neuromuscular Blocking Agent
Botulinum toxin Type A, botulinum toxin type B

**APPENDIX 2**
Achieving Clinically Meaningful Comparisons Between Studies

Treatment efficacy outcomes of primary interest and most commonly reported were pain intensity (e.g., Visual Analog Scale-VAS, NRS, McGill Pain Questionnaire-MPQ) and disability (e.g., Neck Disability Index – NDI, Northwick Park Neck Pain Questionnaire-NPQ, Pain Disability Index-PDI). The magnitude of effect can be estimated for continuous outcomes - the effect size (SMD; WMD) and for binary outcomes (i.e. yes, no) - NNT to achieve this effect. The degree of clinical importance for the observed differences in pain scores between the treatment groups was specified according to the Updated Method Guidelines of Cochrane Collaboration Back Review Group [12] and tradition effect size (Cohen d) [13] estimation.

| Clinical Importance | Pain Intensity | Function (Self Report) | Effect Size | GPE |
|---------------------|---------------|------------------------|-------------|-----|
| Small (A little better) | WMD < 10% of the VAS scale | Neck Disability Index (NDI) | 0.2 as small | little improvement MID |
| Medium (Somewhat better) | 10% ≤ WMD < 20% of the VAS scale | Neck Disability Index (NDI) | ≥ 0.5 as medium | moderate improvement |
| Large (A lot better) | WMD ≥ 20% of the VAS scale | Neck Disability Index (NDI) | ≥ 0.8 as large | a lot of improvement |

Key: WMD – weighted mean difference, VAS – visual analogue scale, NDI – neck disability index, GPE – global perceived effect

**APPENDIX 3**
Excluded studies are listed for medical injections and oral medications with reason for exclusion in square brackets.
Pharmacological Interventions for Neck Pain

Belachew DA, Schaller BJ, Guta Z. Cervical spondylosis: a literature review with attention to the African population. Arch Med Sci 2007; 3(4): 315-22. [Intervention]

Bromfong T, Nilsson N, Haas M, et al. Non-invasive physical treatments for chronic/recurrent headache. Cochrane Database Syst Rev 2004; (3): CD001878. [Comparison]

Conlin A, Bhogal S, Sequeira K, Teassel R. Treatment of whiplash-associated disorders – part I: Non-invasive interventions. Pain Res Manag 2005 Spring; 10(1): 21-32. [Comparison]

Drescher K, Hardy S, MacLean J, Schindler M, Scott K, Harris SR. Efficacy of postural and neck-stabilization exercises for persons with acute whiplash-associated disorders: a systematic review. Physiother Can 2008; 60(3): 215-23. [Comparison]

Kay TM, Gross A, Goldsmith C, et al. Exercises for mechanical neck disorders. Cochrane Database Syst Rev 2005; 3: CD004250. [Comparison]

Kroeling P, Gross A, Goldsmith CH, et al. Electrotherapy for neck pain (Review). Electrotherapy for neck pain. Cochrane Database Syst Rev 2009; 4: CD004251. [Outcome]

Leininger B, Bromfong T, Evans R, Reiter T. Spinal manipulation or mobilization for radiulopathy: a systematic review. Phys Med Rehabil Clin N Am 2011; 22(1): 105-25. [Comparison]

Miller J, Gross A, D’Sylva J, et al. Manual therapy and exercise for neck pain: a systematic review. Man Ther 2010; 15(4): 334-54. [Intervention]

Nikolaidis I, Foyouss IP, Sandercrock PA, Statham PF. Surgery for cervical radiculopathy or myelopathy. Cochrane Database Syst Rev 2010; 1: CD001466. [Outcome]

Reid SA, Rivett DA. Manual therapy treatment of cervicogenic dizziness: a systematic review. Man Ther 2005; 10(1): 4-13. [Outcome]

Salt E, Wright C, Kelly S, Dean A. A systematic literature review on the effectiveness of non-invasive therapy for cervicobrachial pain. Man Ther 2011; 16(1): 53-65. [Intervention]

Teassel RW, McClure JA, Walton D, et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): Part 2 – interventions for acute WAD. Pain Res Manage 2010; 15(5): 295-304. [Comparison]

Trinh K, Graham N, Gross A, et al. Acupuncture for neck disorders. Spine 2007; 32(2): 236-43. [Intervention]

Verhagen AP, Scholten-Peeters GG, de Bie RA, Bierma-Zeinstra SM. Conservative treatments for whiplash. Cochrane Database Syst Rev 2007; 2: CD003338. [Intervention]

Vernon HT, Humphreys BK, Hagino CA. A systematic review of conservative treatments for acute neck pain not due to whiplash. J Manipulative Physiol Ther 2005; 28(6): 443-8. [Comparison]

Vernon H, Humphreys BK. Manual therapy for neck pain: an overview of randomized clinical trials and systematic reviews. Eur J Med Phys 2007; 43(1): 91-118. [Comparison]

REFERENCES

[1] Croft PR, Lewis M, Papageorgiou AC, et al. Risk factors for neck pain: a longitudinal study in the general population. Pain 2001; 93(3): 317-25.

[2] Hogg-Johnson S, van der Velde G, Carroll LJ, et al. 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 2008; 33(4S): S39-51.

[3] Chevan A, Riddel DL. Factors Associated With Care Seeking From Physicians, Physical Therapists, or Chiropractors by Persons With Spinal Pain: A Population-Based Study. J Orthop Sports Phys Ther 2011; 41(7): 467-76.

[4] Chou R, McDonagh M, Nakamoto E, et al. Comparative Effectiveness and Safety of Analgesics for Osteoarthritis: An Update of the 2006 Report. Comparative Effectiveness Review No. 38. Prepared by Oregon Evidence-Based Practice Center under Contract No. HHSA 290-2007-10057-I. Rockville, MD: Agency for Healthcare Research and Quality; October 2011. AHRQ Publication No. 11(12)-EHC076-EF. Available at: http://www.effectivehealthcare.ahrq.gov/reports/analgesicsupdate.cfm.

[5] Canadian Guidelines for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain. April 30 2010. National Opioid Use Guideline Group. Available at: http://www.nationalpaincentre.mcmaster.ca/opioid.

[6] Gilron I, Bailey JM, Tu D, et al, Morphine, gabapentin, or their combination for neuropathic pain. N Engl J Med 2005; 352: 1324-34.

[7] Pepeleo P, Gross A, Handorine T, et al. Medical and injection therapies for mechanical neck disorders (Review). Cochrane Database Syst Rev 2007; (3): CD000319.

[8] Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 2009; 62(10): 1013-20.

[9] Balsam H, Helfand M, Schuenemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4): 401-6.

[10] Santaguida L, MacDermid J, Gross A, et al. ICON Methodology. Orthopaed Online J 2013, (accepted).

[11] Whitchell EP, Lin JS, Chou R, Shekelle P, Robinson KA. Using existing systematic reviews in complex systematic reviews. Ann Intern Med 2008; 148: 776-82.

[12] Furlan AD, Pnennick V, Bombardier C, van TM. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976). 2009; 34: 1929-41.

[13] Cohen J. Statistical power analysis for the behavioural sciences. Hillsdale NJ: Lawrence Erlbaum Associates 1988.

[14] MacDermid JC, Walton DM, Avery S, et al. Measurement properties of the neck disability index: a systematic review. J Orthop Sports Phys Ther 2009; 39(5): 400-17.

[15] Cillins SL, Moore RA, McQuay HJ. The visual analogue pain intensity scale: what is moderate pain in millimetres? Pain 1997; 72: 95-7.

[16] Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 2009; 6(6): e1000097.

[17] Pettersson K, Toolanen G. High-dose methylprednisolone prevents extensive skin leaf after whiplash injury. Spine 1998; 23: 984-9.

[18] Conlin A, Bhogal S, Sequeira K, Teassel R. Treatment of whiplash-associated disorders - Part I: Medical and surgical interventions. Pain Res Manag 2005; 10(1): 33-40.

[19] Eseney M, Caglar N, Aldemir T. Treatment of myofascial pain. Am J Phys Med Rehabil 2000; 79(1): 48-52.

[20] Gross AR, Goldsmith CH, Hoving JL, et al. Conservative management of mechanical neck disorders: a systematic review. J Rheumatol 2007; 34(5): 1083-102.

[21] Hong CZ. Lidocaine injection versus dry needling to myofascial trigger point: the importance of the local twitch response. Am J Phys Med Rehabil 1994; 73(4): 256-63.

[22] Tsakritzis G, Remmen R, Peremans L, et al. Non-specific neck pain: diagnosis and treatment. Good Clinical Practice (GCP). KCE Reports 119C. D/2009/10.273/56.Brussels: Belgian Health Care Knowledge Centre (KCE). 2009.

[23] Braker C, Yariv S, Adler R, Badamy S, Eisenberg E. The analgesic effect of botulinum-toxin A on postwhiplash neck pain. Clin J Pain 2008; 24(5): 1083-102.

[24] Lew HL, Lee EH, Castaneda A, Klima R, Date E. Therapeutic use of botulinum toxin type A in treating neck and upper-back pain of myofascial origin: a pilot study. Arch Phys Med Rehabil 2008; 89: 75-80.

[25] Ferrante FM, Beam L, Rotherock R, King L. Evidence against trigger point injection technique for the treatment of cervicothoracic myofascial pain with botulinum toxin type A. Anesthesiology 2005; 103: 377-83.

[26] Langevin P, Lowcock J, Weber J, et al. Botulinum Toxin Intramuscular Injections for Neck Pain: A Systematic Review and Metaanalysis. J Rheumatol 2011; 38: 203-14.

[27] Stea A, Ovdia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. Acta Anaesthesiol Scand 1993; 37: 562-6.

[28] Castagnera L, Mauvretes P, Pointillart V, Vital JM, Erny P, Senegas J. Long term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. Pain 1994; 58: 239-43.

[29] Pasqualeu A, Varrassi G, Bracchi A, et al. Epidural local anesthetic plus corticosteroid for the treatment of cervical brachial radicular pain: Single injection versus continuous infusion. Clin J Pain 2007; 23: 551-7.

[30] Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. Pain Physician 2009; 12(1): 137-57.
Leaver AM, Refshauge KM, Maher CG, McAuley JH. Conservative management of chronic spinal pain: a systematic review. Pain Physician 2007; 10(1): 229-53.

Abdi S, Datta S, Wargo BW, et al. Systematic review of diagnostic utility and therapeutic effectiveness of cervical facet joint interventions. Pain Physician 2009; 12(2): 323-44.

Byrn C, Olsson I, Falkheden L, et al. Subcutaneous sterile water injections for chronic neck and shoulder pain following whiplash injuries. Lancet 1993; 341: 449-52.

Teasell RW, McClure JA, Walton D, et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): Part 4 - non-invasive interventions for chronic WAD. Pain Res Manag 2010; 15(5): 313-22.

Teasell RW, McClure JA, Walton D, et al. A research synthesis of therapeutic interventions for whiplash-associated disorder (WAD): Part 5 - surgical and injection-based interventions for chronic WAD. Pain Res Manag 2010; 15(5): 323-34.

Nasswetter G, de los Santos AR, Marti ML, Girolamo GD. [Asociacion Chrolenzina en afeciones dolorosas del raquis con contractura muscular. Lysine Chlonixinate Association with Cyclobenzaprine in painful conditions of the spine with muscle spasm. Presse Med Argent 1998; 85: 507-14.

Salzmann VE, Wiedemann O, Loffler L, Sperber H. [Tetrazepam in the treatment of acute zervikalsyndrome, dopple-blind pilotstudie zum vergleich von Tetraepam und placebo.]

Tetrazepam in the treatment of acute zervikalsyndrome, dopple-blind randomized pilot study for comparison of Tetraepam and placebo. Fortschr Med 1993; 34: 544-8.

Bose K. The efficacy and safety of piroxicam vs naproxen in the treatment of cervical and lumbar osteoarthritis. Curr Ther Res 1980; 26(5): 622-9.

Hoivik HO, Moe N. Effect of a combination of orphenadrine/paracetamol tablets (‘Norspic’) on myalgia: a double-blind comparison with placebo in general practice. Curr Med Res Clin Opin 1983; 8: 531-5.

Leaver AM, Refshauge KM, Maher CG, McKeay JH. Conservative interventions provide short-term relief for non-specific neck pain: a systematic review. J Physiother 2010; 56: 73-85.

Ma K, Jiang W, Zhou Q, Du DP. The efficacy of oxycodone for management of acute pain episodes in chronic neck pain patients. Int J Clin Pract 2008; 62(2): 241-7.

Cheshire WP, Abrahall SW, Mann JD. Botulinum toxin in the treatment of myofascial pain syndrome. Pain 1994; 59: 69.

Gobel H, Heinze A, Reichel G, Hefter H, Benecke R. Efficacy and safety of a single botulinum type A toxin complex treatment (Dysport) for the relief of upper back myofascial pain syndrome: Results of a randomized double-blind placebo-controlled multicentre study. Pain 2006; 125: 82-8.

Ojala T, Arokoski JP, Partanen J. The effect of small doses of botulinum toxin A on neck-shoulder myofascial pain syndrome: a double-blind, randomized, and controlled crossover trial. Clin J Pain 2006; 22: 90-6.

Schneider P, Moraru E, Vigil M, et al. Physical therapy and adjunctive botulinum toxin type A in the treatment of cervical headache: a double-blind, randomised placebo controlled study. J Headache Pain 2002; 3: 139-43.

Freund BJ, Schwartz M. Treatment of chronic cervical-associated headache with Botulinum Toxin-A: A pilot study. Headache 2000; 40: 231-6.

Wheeler AH, Guolksian P, Grett S. Botulinum toxin A for the treatment of chronic neck pain. Pain 2001; 94: 255-60.

Carroll A, Barnes M, Cornish S. A prospective randomized placebo-controlled study of the role of botulinum toxin in whiplash-associated disorder. Clin Rehabil 2008; 22: 513-9.

Padberg M, de Bruijn SF, Tavy DL. Neck pain in chronic whiplash syndrome treated with botulinum toxin. A double-blind, placebo-controlled clinical trial. J Neurol 2007; 254: 290-5.

Freund BJ, Schwartz M. Treatment of whiplash associated neck pain with botulinum toxin-A: a pilot study. J Rheumatol 2000; 27: 481-4.

Dennert VR, Munzenberg KJ, Haase W. [Zur therapie der ZervikoBrachialgie, Controllierter klinischer vergleich einer hochdosierten kombination neurotopter Vitamine mit einem Analgetikum.] For therapy of Cervico-brachialgia, controlled comparative clinical high-dose combination of neurotropic vitamins and an Analgeticum. Fortschr Med 1976; 94(10): 505-8.

Barnsley L, Lord SM, Wallis BJ, et al. Lack of effect of intraarticular corticosteroids for chronic pain in the cervical zygapophysial joints. New Engl J Med 1994; 330: 1047-50.

Carragee EJ, Hurwitz EL, Cheng I, et al. Treatment of neck pain: injections and surgical interventions: results of the Bone and Joint Decade 2000-2010 Task Force on Neck Pain and Its Associated Disorders. Spine 2008; 33(45): S153-69.

Sand T, Bovim G, Held G. Intraarticular sterile water injections do not relieve pain in cervicogenic headache. Acta Neuro Scand 1992; 86: 526-8.

Basmajian JV. Cyclicbenzaprin Hydrochloride Effect on Skeletal Muscle Spasm in the Lumbar Region and Neck: Two Double-Blind Controlled Clinical and Laboratory Studies. Arch Phys Med Rehabil 1978; 59(2): 58-63.

Basmajian JV. Reflex cervical muscle spasm: Treatment by Diazepam, Phenobarbital or placebo. Arch Phys Med Rehabil 1983; 64: 121-4.

Sloop SP, Smith DS, Goldenberg E, Core C. Manipulation for chronic neck pain: a double-blind controlled study. Spine 1982; 7(6): 532-5.

Durian A, Yazdi F, Tseratosvade A, et al. Complementary and Alternative Therapies for Back Pain II. Evidence Report/Technology Assessment No. 194. (Prepared by the University of Ottawa Evidence-based Practice Center under Contract No. 290-2007-10059-J (EPCIII). AHRQ Publication No. 10(11)E007. Rockville, MD: Agency for Healthcare Research and Quality, September 2010.

Gross A, Miller J, D’Sylva J, et al. Manipulation or Mobilisation for Neck Pain. Cochrane Database Syst Rev 2010; 1: CD004249.

Furtado RNV, Carazzato S, Farias CA, Chamilien TR, Masiero D. Myofascial syndrome: comparison between infiltration of trigger points treatment and oral medication (cyclobenzaprine) [Sindrome miofascial: comparacao entre o tratamento com infiltração de trigger points e medicação oral (ciclobenzaprine)]. Acta Fisiatrca 2002; 9(3): 117-26.

Leite FM, Atallah AN, El Dib R, et al. Cyclobenzaprine for the treatment of myofascial pain in adults. Cochrane Database Syst Rev 2009; 3: CD006830.

Payne RW, Sorenson EJ, Smalley TK, Brandt EN. Diazepam, meperamide and placebo in musculoskeletal disorders. JAMA 1964; 188(3): 157-60.

Schreiber S, Svetiana V, Shavelzon V, Pick CG, Zahavi E, Shyr Y. A randomized trial of fluoxetine versus amitriptyline in musculoskeletal pain. Isr J Psychiatry Relat Sci 2001; 38(2): 88-94.

Giles LG, Muller R. Chronic spinal pain: a randomized clinical trial comparing medication, acupuncture, and spinal manipulation. Spine 2003; 28(14): 1490-502.
