Medicinal and Injection Therapies for Mechanical Neck Disorders: A Cochrane Systematic Review

PAUL M. PELOSO, ANITA R. GROSS, TED A. HAINES, KIEN TRINH, CHARLES H. GOLDSMITH, PETER AKER, and the Cervical Overview Group

ABSTRACT. ***Objective***. To systematically review randomized trials on medicines and injections used to improve pain, function/disability, and patient satisfaction in adults with mechanical neck disorders (MND) with or without associated headache or radicular findings.

Methods. We searched CENTRAL (Issue 4, 2002), and MEDLINE, EMBASE, MANTIS, CINHAL from their start to March 2003. Two authors independently selected articles, abstracted data, and assessed methodological quality using the Jadad criteria. When clinical heterogeneity was absent, we combined studies using random-effects metaanalysis models.

Results. Thirty-two selected trials had an overall methodological quality of mean 3.2/5. For acute whiplash, administering intravenous methylprednisolone within 8 hours reduced pain at one week [SMD –0.90 (95% CI –1.57 to –0.24)], and sick leave but not pain at 6 months compared to placebo. For chronic MND at short-term followup, intramuscular injection of lidocaine was superior to placebo [SMD 1.36 (95% CI –1.93 to –0.80)]. In chronic MND with radicular findings, epidural methylprednisolone and lidocaine reduced neck pain [SMD –1.46 (95% CI –2.16 to –0.76)] and improved function at one-year followup compared to the intramuscular route. In subacute/chronic MND, we found conflicting evidence for oral psychotropic agents. In chronic MND with or without radicular findings or headache, there was moderate evidence from 5 high quality trials showing that botulinum toxin (Botox A) intramuscular injections were not better than saline in improving pain [SMD pooled –0.39 (95% CI –1.25 to 0.47)], disability, or global perceived effect.

Conclusion. Intramuscular injection of lidocaine for chronic MND and intravenous injection of methylprednisolone for acute whiplash were effective treatments. There was limited evidence of effectiveness of epidural injection of methylprednisolone and lidocaine for chronic MND with radicular findings. Muscle relaxants and nonsteroidal antiinflammatory drugs have unclear benefits. There was moderate evidence that Botox-A intramuscular injections for chronic MND were not better than saline. (J Rheumatol 2006;33:957–67)

Key Indexing Terms:
METAANALYSIS SYSTEMATIC REVIEW NECK MEDICATION INJECTIONS

From Amgen Inc., Thousand Oaks, California, USA; and the Departments of Epidemiology and Biostatistics and Occupational Health and Safety, Schools of Rehabilitation Sciences and Medicine, McMaster University, Hamilton, Ontario, Canada.

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P.M. Peloso, MD, MSc, Amgen Inc.; A.R. Gross, MSc; T.A. Haines, MSc; K. Trinh, PhD (Candidate); C.H. Goldsmith, PhD, Departments of Epidemiology and Biostatistics and Occupational Health and Safety, Schools of Rehabilitation Sciences and Medicine, McMaster University; P. Aker, MSc, private practice, Belleville, Canada.

Cervical Overview Group: T. Kay, MSc; N. Graham, BScPT; P. Kroeling, MD; G. Bronfort, PhD; P. Santaguida, PhD; B. Haraldsson, RMT; C. Myers, PhD; J. Hoving, PhD; J. Ezzo, PhD; A. Morien, PhD; A.M. Eady, MLS. *An interdisciplinary and international working group interested in conducting and maintaining system reviews on conservative management for mechanical neck disorders.*

Address reprint requests to Dr. P.M. Peloso, Global Development Leader, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320. E-mail: ppeloso@adelphia.net

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Background

Twenty-six to 71% of the population will experience neck pain[1-4]. At any moment, 9% of men and 12% of women have neck complaints[5]. The annual incidence in primary care in the UK is 12.1 cases per 1000 person-years[6]; in The Netherlands this is 2% of general practice[7]. In a significant minority, pain persists[8,9]. Up to 15% of patients have associated disability, with 5% citing severe disability[10].

Neck pain is costly[11]. About 15% of hospital physiotherapy and 30% of chiropractic visits are for neck pain[12,13]. Industrial neck-related disorders may cause absenteeism as commonly as low back pain[1,14,15]. In Quebec, 7% of compensation claims are neck-related[16]. Motor vehicle crashes leave 24% to 50% of subjects with persistent symptoms at 12 months[17,18].

Treatments for neck pain are varied[19], as are the perceptions of benefits[20], with medications playing an important role. Yet critical reviews of the evidence-basis for medicinal therapies are lacking, while expert reviews predominate[21,22]. Are all types of medicines equally safe and effective? This is a critical issue for patients, physicians, and policy makers.

Objectives

We wanted to determine what medicines are effective in adults with mechanical neck disorders (MND), whether these medicines were delivered by oral, intravenous (IV), intramuscular (IM), or intraarticular (IA) routes. Outcomes evaluated were pain, measures of performance (i.e., function, activity of daily living, disability), employment status, range of motion, and patient satisfaction/patient global perceived effects.

We also studied factors that influenced the magnitude of treatment effects, particularly methodological quality, patient characteristics (i.e., symptom duration), nature and mechanisms of neck pain (i.e., disorder subtype), type of medication used (i.e., analgesic, etc.), and the route of delivery (i.e., oral, injection, etc.).

Criteria for Considering Studies for this Review

Types of studies. We included randomized controlled trials (RCT) or quasi-randomized controlled trials (Q-RCT), in full text or abstract form, published or unpublished. A Q-RCT is a controlled clinical trial that uses a method of allocation subject to bias, such as, odd-even numbers, day of week, patient record, or social security number.

Types of participants. We included adults (18 years of age or older) with acute (less than 30 days), subacute (30 days to 90 days), or chronic (longer than 90 days) neck disorders categorized as: mechanical neck disorder (MND), including whiplash associated disorders (WAD category I and II)[16,23], described as having myofascial neck pain, and degenerative changes[24]; neck disorder with headache (NDH)[25-27]; and neck disorders with radicular findings (NDR), including WAD category III[16,23].

We excluded studies if they investigated neck disorders with: definite or possible long tract signs (e.g., myelopathies); neck pain caused by other pathological/neurological entities (e.g., rheumatoid arthritis, ankylosing spondylitis, spasmodic torticollis, fractures, and dislocations[24]); headache associated with neck pain but not of cervical origin, coexisting headache when either neck pain was not dominant or the headache was not provoked by neck movements or sustained neck postures, or "mixed" headache[27].

Types of interventions. We included any study where medicine was used. Medicines could be delivered by oral, IV, IM, IA, subcutaneous, or intrathecal routes and classed as analgesics, anesthetics, nonsteroidal antiinflammatory drugs (NSAID), muscle relaxants, opioids, corticosteroids, or botulinum toxin A (Botox A).

Types of outcome measures. Our primary outcomes of interest were: pain reports, improvement in pain (subjective reports of pain), pain tenderness and pain threshold (examiner measured pain); measures of performance such as function (e.g., activities of daily living), disability related to neck pain; work status; range of motion of the cervical spine; patient global perceived effect; and patient satisfaction. The timing of the outcomes assessment was recorded.

Search Strategy for Identification of Studies

The following computerized bibliographic databases were searched without language restrictions by a research librarian for medical, chiropractic, and allied health literature: Cochrane Register of Controlled Trials (CENTRAL – Cochrane Library Issue 4, 2002), MEDLINE (January 1966 to March 2003), EMBASE (January 1980 to March 2003), Manual Alternative and Natural Therapy (1985 to March 2003), Cumulative Index to Nursing and Allied Health Literature (January 1982 to March 2003), and Index to Chiropractic Literature (1980 to March 2003). Reference screening and communication with the Cochrane Back Group co-ordinator, personal communications with identified experts, and personal files supplemented the above electronic searches. Medical Subject Headings (MeSH) and key words included terms related to anatomic, disorder or syndrome, treatment, and methodological terms consistent with the Cochrane Back Group advice.

METHODS

Study selection. Pairs of authors with expertise in medicine, physiotherapy, chiropractic, massage therapy, statistics, and clinical epidemiology independently identified citations and selected studies and reached consensus. We assessed agreement using quadratic weighted kappa statistics (Cicchetti weights[28]). A third author resolved disagreements.

Data abstraction. Two authors also independently abstracted data. We wrote the primary author of the trial if pain data were not reported in a form suitable for quantitative analysis or data on neck pain were not separately reported from other pain conditions. If the author could not be contacted, or if the information was no longer available and partial data were available from the publication, values were imputed where possible[29-31]. Where values could not be imputed from the data available, the author's report of significance was reported in tabular form. We also extracted data on adverse events from the studies. Adverse events were those reported or deemed important by the primary trial authors, and could not be specified in advance by us.

Data analysis and synthesis. For continuous data, we calculated standardized mean differences (SMD) [95% confidence interval (95% CI)] using a random-effects model. Calculation of weighted mean difference was planned but not carried out due to the presence of diverse outcomes across trials. To measure a clinically important effect size, we applied the Cohen criteria[32]: 0.20 represents a small effect size, 0.50 a medium one, and 0.80 or greater, a large one. A 10-mm change in pain on a 100-point pain scale (10%) is probably the minimum clinically significant difference for pain scores, as suggested by Farrar[33] in other pain trials and by Felson[34] in rheumatoid arthritis trials. A change of 5 units on the Neck Pain Disability Index is likely the minimum clinically important difference for neck pain, as suggested by Stratford[35]. When continuous outcomes reported medians, effect sizes

were calculated according to Kendal[36]. We calculated relative risks (RR) for dichotomous outcomes. Calculation of the number needed to treat and treatment advantages were planned for primary findings when a clear positive effect was seen. This was not carried out due to a paucity of trials demonstrating strong evidence of benefit (see Gross[31] for mathematical definitions). Power analyses were conducted for articles reporting nonsignificant findings and are available from the authors.

Prior to creating a pooled effect measure, a multidisciplinary team examined possible sources of clinical heterogeneity by considering: methodological study quality; population differences in age and gender; duration of symptoms (i.e., acute versus chronic); subtype of MND (i.e., neck disorder with radicular findings, whiplash injury, etc.); intervention type by drug class (i.e., analgesic, anesthetic, NSAID, etc.); method of medication delivery (i.e., oral versus IV versus IM versus IA); outcomes [i.e., subject reports of pain and pain relief, range of motion, other measures of performance (i.e., activities of daily living, disability, function), or employment status].

When study pooling was clinically sensible, we tested statistical heterogeneity using the chi-squared method. This tests whether the observed variation among studies is greater than that expected by chance. The more significant the results (the smaller the p value), the more likely that the observed differences were not due to chance. RevMan 4.2 was used to calculate statistical homogeneity. We calculated a pooled SMD or RR using a random-effects model and the RevMan 4.2 program. Sensitivity analysis or meta-regression for the factors symptom duration, methodological quality, and subtype of neck disorder were planned but were not carried out due to insufficient data in many categories. We could not examine for publication bias using funnel plots and for language bias as there were too few studies in any one category. We provide summaries of the groups studied, interventions used, outcomes assessed, adverse effects of treatments, and cost of care.

To further summarize our findings, we used the following "levels of evidence"[37,38] of benefit, or of no benefit relative to the comparison treatment: Strong evidence denotes consistent findings in multiple high quality randomized controlled trials; moderate evidence denotes findings in a single, high quality randomized controlled trial or consistent findings in multiple low quality trials; limited evidence indicates a single low quality randomized trial; unclear evidence denotes inconsistent or contradictory results in multiple randomized trials; no evidence indicates that no studies were identified.

The term "strong evidence of no benefit" was used for trials or metaanalyses large enough to be negative, with a low risk of false-negative conclusions (e.g., power of 80% or greater; sample size of about 70 or greater per arm). The needed sample size per arm was based on rheumatoid arthritis trial criteria for clinically important change[39], since we are aware of no criterion for neck pain trials specifically.

In order to reach conclusions on treatment effectiveness, we considered: size of the treatment effect, expressed both as statistical significance and clinical importance of both the primary studies and the combined effects; if metaanalysis was appropriate; replicability of the effect across multiple trials; and study quality.

In the absence of metaanalyzable data, conclusions were informed by the trials' descriptive elements, methodologic quality, number of trials with consistent findings, plausibility of the results, the strength of the associations in the primary trials, and required consensus among the review team.

Description of Studies

We included 32 medication trials as follows: 16 studies of mechanical neck disorder (MND): acute[40-45], chronic[46-56], mixed[57], and symptom duration not reported[58]; 6 studies of headache of cervical origin (NDH): chronic[44,59-63] and symptom duration not reported[64,65]; 15 studies of neck disorder with radicular signs and symptoms (NDR): acute[43,45], subacute[66], chronic[44,51,55,59,60-62,67-69], mixed[70], and symptom duration not reported[71]; 3 studies of whiplash associated disorders (WAD) that included acute[43] and chronic[52,54]; and 6 studies of degenerative changes, including chronic[50,51], mixed[42,46,70], and not reported[41].

Further details on treatments, reported results, SMD, and RR are shown in Table 1. Figure 1 is a qualitative summary of all medications and injections versus either placebo or control at end of study followup. Agreement between pairs of independent authors from diverse professional backgrounds on study selection for inclusion was excellent, with an estimated kappa (Cicchetti weights) of Kw = 0.76 (SD 0.09).

Three non-English trials are being translated and are awaiting assessment[72-74]. We excluded 70 RCT based on the type of participant (86%) (i.e., generalized arthritis, torticollis not related to MND, other disorders), intervention inappropriate (6%) (i.e., a diagnostic block study), outcome not stratified for neck pain (10%), or design reasons (1%) (i.e., unclear if trial was an RCT). The remaining excluded studies were clearly not RCT. Language bias was thought unlikely as 14 non-English studies were screened for selection: 6 German, 1 French, 2 Italian, 1 Spanish, 2 Japanese, 1 Polish, and 1 Serbian.

Methodological quality of included studies. We assessed methodologic quality using 2 independent authors and a consensus process. Methodological quality was graded using the validated Jadad[75] criteria (maximum score 5, high quality trials score 3 or greater; see Table 2 for criteria and for results). The trial-quality Jadad score ranged from 1/5 to 5/5. The mean number of Jadad criteria met was 3.2/5. Therefore, on average, the methodological quality of these studies was considered high. All studies but one were described as randomized. A large proportion of the studies failed to describe allocation concealment (25/32) and appropriateness of double-blinding (16/32). In contrast, only 7 of the 32 studies lacked an adequate description of withdrawals and dropouts.

Table 1. Characteristics of included studies and their main outcomes.

Author/ Participant	Intervention	Main Outcomes
Barnsley 1994[41] N(A/R): 41/42 Chronic MND	Corticosteroid vs Anaesthetic Duration treatment: 1 session; Duration follow-up: 9 months	PAIN [time to return (days) to 50% of pretreatment pain] Report Results: no significant difference; SMD -0.02(95% CI Random: -0.64 to 0.59)
Basmajian 1978[76] N(A/R): ?/22 Subacute MND with possible radicular symptoms	Cyclobenzaprine HCl (C) vs Diazepam (D vs Placebo (Pl) Duration treatment: 2 weeks (14 to 18 days); Duration follow-up: none	GLOBAL EVALUATION OF MUSCLE SPASM (medical; change score reported; 1 absent to 5 severe) Report Results: no significant difference SMD(D vs Pl) -0.00(95% CI Random: -1.01 to 1.01) SMD(C vs Pl) -1.05(95% CI Random: -2.15 to 0.06) SMD(C vs D) -1.04(95% CI Random: -2.18 to 0.10)
Basmajian 1983[46] N(A/R): 33 to 35/40 Acute MND with "spasm"	Diazepam (D) vs Phenobarbital (Ph) vs Placebo (Pl) Duration treatment: 4 days; Duration follow-up: 1 hour	PAIN INTENSITY (on active movement; 0, none to 4, very marked) Reported Results: no significant difference SMD(D vs Pl) 0.18(95% CI Random: -0.64 to 1.00) SMD(Ph vsPl) 0.29(95% CI Random: -0.56 to 1.13) SMD(D vs Ph) 0.08(95% CI Random: -0.93 to 0.78)
Bose 1999[70] N(A/R)=157/215 MND, NDR, OA	Eperisone hydrochloride (Myonal) vs Matching Placebo Duration treatment: 6 weeks; Duration follow-up: none	PAIN INTENSITY Reported Results: significant, favouring Eperisone RR 0.68(95% CI Random: 0.52 to 0.90)
Brockow 2001[46] N(A/R): 57/49 Chronic MND 82/140 OA	Subcutaneous Carbon Dioxide Insufflation vs Standardized Physical Therapy Duration treatment: 12 days; Duration follow-up: none	PAIN INTENSITY (VAS, 0 to 100 mm) unable to separate neck from low back data Reported Results: not significant
Cheshire 1994[67] N(A/R): 6/6 Chronic NDR (myofascial pain)	Botox A vs Placebo (Pl) Duration treatment: 2 sessions; Duration follow-up: 8 weeks	PAIN INTENSITY (VAS, 0 to100mm) Reported Results: significant, favouring Botox *SMD: -0.62(95% CI Random: -1.79 to 0.59) *SD were estimated using the observed effect size and the level of statistical significance reported, under the assumption of no order effect
Choffray 1987[42] N(A/R): 33/40 Acute MND exacerbation, OA	High bio-availability glaphenine vs Paracetamol Duration treatment: 15 days; Duration follow-up: none	PAIN INTENSITY (0 absent to 3 severe) Reported Results: not significant SMD -0.33(95% CI Random: -1.02 to 0.36)
Dennert 1976[68] N(A/R): ?/60 Chronic NDR	Neurotropic vitamins vs control (analgesic) Duration treatment: 9 days; Duration follow-up: none	PAIN [pain on pressure to the cervical plexus and to paravertebral muscles, rebound pain, scale: strong (++); light (+); no change (0)] Reported Results: not significant for pain on pressure to cervical plexus; significant favouring index treatment for pain on pressure to paravertebral muscles RR(cervical plexus pain): 0.81(95% CI Random: 0.58 to 1.12) RR(paravertebral muscle pain): 0.76(95% CI Random: 0.51 to 1.13) RR(rebound pain): 0.90(95% CI Random: 0.71 to 1.14) PATIENT PERCEIVED EFFECT [distinct improvement (++), some improvement (+), no change (0)] Reported Results: not significant RR: 0.90(95% CI Random: 0.71 to 1.14)
Dostal 1978[59] N(A/R): 32/32 Chronic NDH & NDR	Ibuprofen vs Control (manipulation) Duration treatment: 28 days; Duration follow-up: none	PAIN INTENSITY (1 no pain to 9 maximum pain) Reported Results: not significant RR: 0.69(95% CI Random: 0.42 to 1.13)
Esenyel 2000[47] N(A/R): 90/108 Chronic MND (myofascial pain)	Lidocaine vs Control (exercise) vs Ultrasound (US) Duration treatment: Lidocaine 1 session; US 10 sessions; Cntl 10 sessions; Duration follow-up: 3 months	PAIN INTENSITY (VAS 0 to10) Reported Results: significant, favouring Lidocaine over Cntl; not significant for Lidocaine versus US SMD(Lidocaine vs Cntl): -0.14(95% CI Random: -1.93 to -0.80) SMD(Lidocaine vs US): 0.04(95% CI Random: -0.46 to 0.55)
Ferrante 1998[48] N(A/R): 23/23 Chronic MND (myofacial pain)	Sphenopalatine ganglion block (SPGB) vs Placebo Duration treatment: 1 session; Duration follow-up: 1 week	PAIN INTENSITY (VAS 0-100) Reported Results: SPGB not significantly different from placebo and less effective than trigger point injection
Freund 2000[60] N(A/R)=26/30 Chronic NDH and/or NDR	Botulinum Toxin Type A (BTX-A) vs Placebo (saline) Duration treatment: 1 day; Duration follow-up: 4 weeks	PAIN INTENSITY (combined scores for headache, neck, shoulder VAS 0 to 10) Reported Results: significant improvement from baseline in treatment group but not placebo group; Our analysis however, showed no significant difference between the groups SMD: -0.08(95% CI Random: -0.85 to 0.69) DISABILITY (Vernon-Mior Index) Reported Results: not significant SMD: 0.47(95% CI Random: -0.31 to 1.26)
Giles 1999[50] N(A/R): 98/157 for all spinal patients; 62/? for neck subgroup Chronic MND, OA	Medication (med) va Acupuncture (acup) vs Manipulation (manip) Duration treatment: 3 to 4 weeks; Duration follow-up: none	PAIN (neck pain change scores, VAS 0 to 10) Reported Results: not clear SMD(Med vs Manip): 0.35(95% CI: -0.35 to 1.05) SMD(Med vs Acup): 0.17(95% CI: -1.59 to 0.94) FUNCTION (neck disability index, 0 to 50) Reported Results: not clear SMD(Med vs Manip): 0.92(95% CI: 0.10 to 1.74) SMD(Med v Acup): 0.44(95% CI: -0.49 to 1.36)
Ginsberg 1980[49] N(A/R): 48/50 MND, OA	Tolmetin vs Naproxen Duration treatment: 2 months; Duration follow-up: none	PAIN on passive movement (0 to 4); unable to separate low back from neck data Reported Results: significant favouring Tolmetin
Heikkila 2000[69] N(A/R)=14/14 Chronic NDR	NSAID vs No therapy (Cntl) vs Acupuncture (A) vs Manipulation (M) Duration treatment: 1 to 2 weeks; Duration follow-up: none	PAIN INTENSITY (VAS 0 to 100) Reported Results: significant, favouring ketoprofen and acupuncture
Hong 1994[61] N(A/R): 41/58 Chronic MND +/-	Lidocaine injection vs dry needling Duration treatment: 1 day; Duration follow-up: 2 weeks	PAIN INTENSITY (0-10) Reported Results: significant, favouring Lidocaine SMD post treatment: -0.59(95% CI Random: -1.24 to 0.06)

Table 1. Continued

NDH & NDR (myofacial pain)		SMD @ 2w follow-up: -3.46(95% CI Random: -4.46 to -2.46)
Inan 2001[62] N(A/R): 14/14 NDH & NDR	Greater Occipital Nerve Block vs C2/C3 Blockade Duration treatment: 2 weeks, 3 sessions; Duration follow-up: 2 months	PAIN INTENSITY (VAS 0 to 10) Reported Results: not significant SMD: 0.36(95% CI Random: -0.38 to 1.10)
Koes 1992[57] N(A/R): 58/64 (12 weeks) Subacute and chronic MND	General Practitioner (GP) vs Manual Therapy (MT) vs Physical Therapy (PT) vs Placebo Duration treatment: 9 weeks; Duration follow-up: 12 weeks (6- and 12-months data not extractable)	SEVERITY OF MAIN COMPLAINT [10 point scale] Reported Results: MT and PT better than GP and placebo SMD(GP vs PL): 0.60(95% CI Random: -0.21 to 1.40) SMD(GP vs MT): 0.50(95% CI Random: -0.28 to 1.28) SMD(GP vs PL): 0.00(95% CI Random: -0.69 to 0.70) PHYSICAL FUNCTION [10 point scale] Reported Results: significant SMD(GP vs PL): 0.89(95% CI Random: -0.06 to 1.72) SMD(GP vs MT): 0.91(95% CI Random: -0.08 to 1.74) SMD(GP vs PL): 0.16(95% CI Random: -0.55 to 0.86)
Nasswetter 1998[58] N(A/R): ?/55 MND (cervical pain syndrome)	Lysine cloniximate (LC) vs Lysine cloniximate & Cyclobenzoprine (LC&C) Duration treatment: 4 days; Duration follow-up: 2 weeks	PAIN INTENSITY (0 to 10) Reported Results: significant favouring Lysine cloniximate SMD post treatment: -0.59(95% CI Random: -1.24 to 0.06) SMD @ 2w follow-up: -3.46(95% CI Random: -4.46 to -2.46)
Payne 1964[71] N(A/R): ?/54 NDR; duration disorder NR	Diazepam vs Meprobamate vs Placebo (lactose-placebo) t Duration treatment: 2 days; Duration follow-up: none	PAIN Reported Results: not significant MORNING STIFFNESS Reported Results: not significant
Petterson 1998[43] N(A/R): 39/40 Acute WAD II, III	Methylprednisolone vs Placebo Duration treatment: 1 day; Duration follow-up: 6 months	PAIN INTENSITY (VAS 0 to 10) Reported Results: not significant SMD: -0.46(95% CI Random: -1.10 to 0.18)
Rubenthaler 2000[44] N(A/R): 57/57 Chronic MND, NDR & NDH	Mepivacaine vs NaCl Duration treatment: 3 days; Duration follow-up: 2 week	GLOBAL PERCEIVED EFFECT (1 to 4) Reported Results: not significant RR 2.12 (95% CI Random: 0.85 to 5.33)
Salzmann 1993[45] N(A/R): 20/20 Acute MND, OA, +/- NDR	Tetrazepam & Paracetamol (Tetra) vs Placebo & Paracetamol Duration treatment: 7 days; Duration follow-up: none	PAIN INTENSITY (1 none to 5 severe) Reported Results: significant, favouring Tetrasepam SMD: -1.22(95% CI Random: -2.20 to -0.25) GLOBAL PERCEIVED EFFECT (1 none to 5 very good) Reported Results: significant, favouring Tetrazepam SMD: -1.22(95% CI Random: -2.20 to -0.25)
Sand 1992[64] N(A/R): 20/20 NDH, duration disorder NR	Sterile Water vs Isotonic Saline Duration treatment: 1 session; Duration follow-up: 13 days	PAIN INTENSITY (VAS 0 to 100) Reported Results: not significant SMD: -0.09(95% CI Random: -0.96 to 0.79)
Schnider 2002[63] N(A/R): 32/33 Chronic NDH	Botulium Type A & Standard PT vs Placebo & Standardized PT Duration treatment: 1 session; Duration follow-up: 16 weeks	PAIN INTENSITY (VAS 0 to 100) Reported Results: not significant SMD: 0.00(95% CI Random: -0.69 to 0.69)
Schreiber 2001[42] N(A/R): 35/40 Chronic WAD	Fluoxetine vs Amitriptyline Duration treatment: daily for 6 weeks; Duration follow-up: none	PAIN RELIEF (Likert scale) unable to separate low back from neck data Reported Results: not significant
Stav 1993[41] N(A/R): 42/50 Chronic MND, NDR & OA	Epidural methylprednisolone (MP) & lidocaine vs Placebo Duration treatment: 4 weeks; Duration follow-up: 1 year	PAIN RELIEF (VAS 0 to 100) Reported Results: significant, favouring epidural group SMD: -1.46(95% CI Random: -2.16 to -0.76) RETURN TO WORK Reported Results: significant, favouring epidural group RR: 0.49(95% CI Random: 0.29 to 0.82)
Terzi 2002[65] N(A/R): 20/20 NDH, duration of disorder NR	Prilocaine vs Placebo Duration treatment: 1 session; Duration follow-up: 30 minutes	PAIN INTENSITY (VAS 0 to 10) Reported Results: significant, favouring prolocaine SMD: -3.60(95% CI Random: -5.12 to -2.07)
Thomas 1991[53] N(A/R): 132/132 Chronic MND, OA	Diazepam vs Placebo vs Acupuncture (Acu) Duration treatment: 1 session; Duration follow-up: 2 hours	PAIN INTENSITY (VAS 0 to 10) Reported Results: not significant SMD(D vs Pl): -0.11(95% CI Random: -0.53 to 0.30) SMD(D vs Acu): -0.20(95% CI Random: -0.62 to 0.22)
vanWieringen 2001[54] N(A/R): 71/81 Chronic WAD	Melatonin vs Placebo Duration treatment: 4 weeks; Duration follow-up: none	HEALTH & WELL BEING (pain, sleep, SF36) Reported Results: not significant
Wheeler 1998[55] N(A/R): 22/22 Chronic MND +/- NDR (myofascial)	Botulinum Toxin Type A (BTX-A) 50 units vs Botulinum Toxin Type A (BTX-A) 100 units Duration treatment: 1 session; Duration follow-up: 4 months	NECK PAIN AND DISABILITY Reported Results: not significant GLOBAL PERCEIVED EFFECT Reported Results: not significant
Wheeler 2001[56] N(A/R): 45/50 Chronic MND	Botulinum Toxin Type A (BTX-A) vs Placebo (saline) Duration treatment: 1 session; Duration follow-up: 16 weeks	NECK PAIN AND DISABILITY Reported Results: not significant SMD: -0.43(95% CI Random: -0.17 to 1.02) GLOBAL PERCEIVED EFFECT Reported Results: not significant SMD: 0.16(95% CI Random: -0.75 to -0.42)

KEY: MND mechanical neck disorder; NDH neck disorder with headache; NDR neck disorder with radicular findings; WAD whiplash associated disorder; N A/R sample number analyzed / randomized; I Index treatment; C Comparison treatment; CO-I: Co-intervention; VAS visual analogue scale; SMD standard mean difference; WMD weighted mean difference; CI confidence interval; NNT number needed to treat; NR not reported

RESULTS

We have briefly summarized our findings by subtype disorder in the following section and detailed trial findings by level of evidence and drug class in the later section.

- For acute whiplash associated disorder, a single trial of IV methylprednisolone given within 8 hours of injury was superior to placebo, with short-term improvement in pain and reduced longterm sick leave.
- For chronic mechanical neck disorder or neck disorder with radiation, oral psychotropic agents gave mixed results.

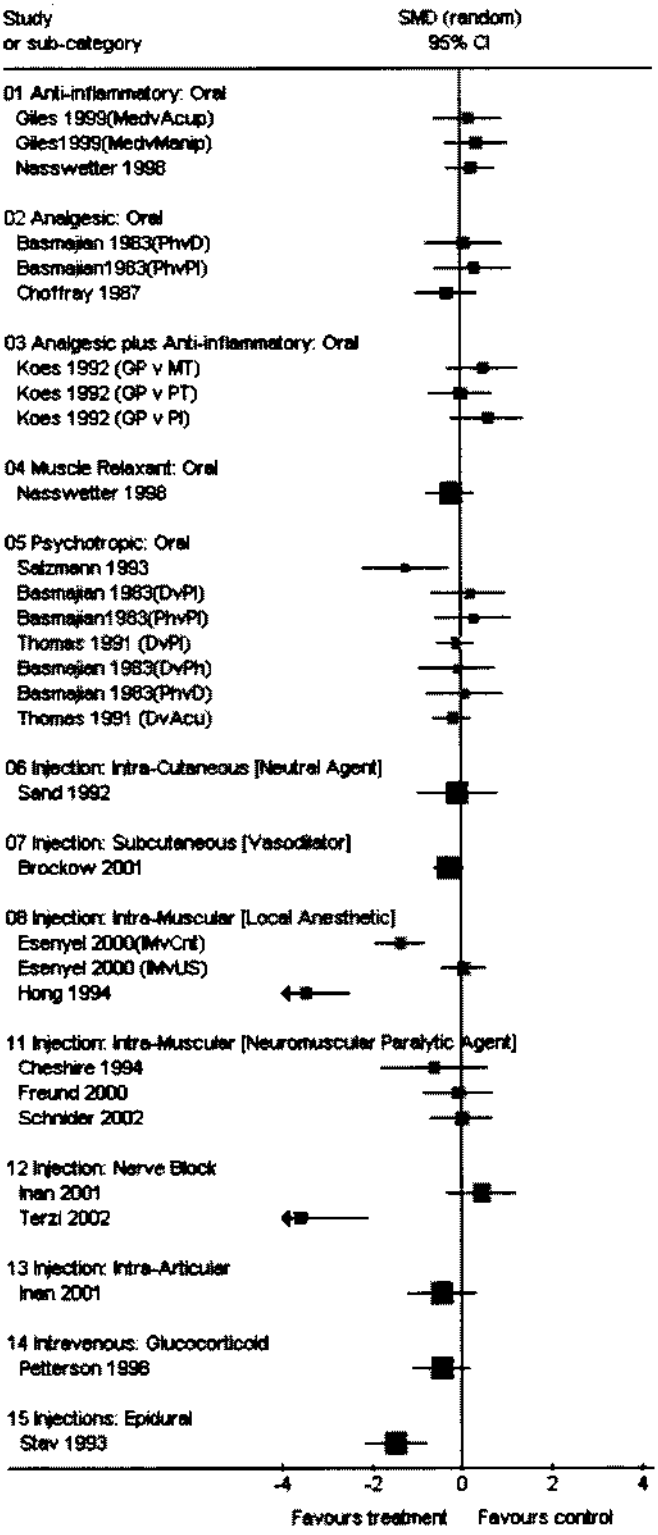

Figure 1. Qualitative summary of medications and medical injections versus a placebo or control for the outcome pain intensity and at end of study followup points.

Diazepam and phenobarbital did not demonstrate effectiveness, whereas cyclobenzaprine trials gave contradictory findings. Single trials of tetrazepam and eperisone hydrochloride were positive.

- NSAID did not demonstrate effectiveness for chronic neck pain.
- For chronic neck pain with radiation, a single study showed that epidural methylprednisolone and lidocaine improved pain and function at one year.
- For chronic mechanical neck disorder, 2 trials gave evidence that IM injection of lidocaine provides short-term benefit.
- For chronic neck disorders with or without radicular findings or headache, Botox A had no advantage over saline injection, based on 5 trials and one metaanalysis.

Strong evidence of benefit. We found no studies meeting our strong evidence of benefit criteria. That is, we found no high quality randomized trials that were replicated, showing benefit for any medications or injections. Therefore, we were unable to calculate number-needed-to-treat and treatment advantage for any high quality intervention. Similarly, sensitivity analyses for symptom duration and neck disorder subtype were not possible due to insufficient data. Primary studies of a given treatment frequently examined mixed disorder types, of variable duration. Subgroups related to intervention type and administration route could not be established.

Moderate evidence of benefit. We found moderate evidence of benefit for the following:

IM Injection of Local Anesthetic (2 trials, 166 people): IM injection of lidocaine was superior to dry needling, leading to pain improvements at one day and 2 weeks [SMD –3.46 (95% CI –4.46 to –2.46)], in one trial[61] of chronic MND ("myofascial pain"). IM lidocaine plus neck stretches were superior to IM saline plus neck stretches [SMD –1.36 (95% CI –1.93 to –0.80)] for chronic MND ("myofascial pain") at 3 months[47], although lidocaine and stretches were not superior to ultrasound and neck stretches.

IV Glucocorticoid (1 trial, 40 people): One high quality study showed that in acute whiplash of less than 8 hours' duration, IV methylprednisolone, 30 mg/kg as a single bolus, followed by a 5.3 mg/kg infusion over 23 hours, led to reduced pain at one week and reduced sick leave but not pain, at 6 months [SMD –0.90 (95% CI –1.57 to –0.24)], compared to placebo[43].

Limited evidence of benefit. We classified the results from one trial as showing limited evidence of benefit:

Epidural Injections (1 trial, 50 people): Epidural injections with methylprednisolone and lidocaine were superior to IM methylprednisolone and lidocaine for chronic neck disorder with radiation. The trial showed improved pain and function measures at 4 weeks and one year [pain: SMD –1.46 (95% CI –2.16 to –0.76); function: RR 0.49 (95% CI 0.29 to 0.82)] 51.

Unclear evidence. We found numerous studies showing unclear evidence of benefit:

Table 2. Methodological quality and outcome for each trial.

Author/Year	Methodological Quality (Jadad Criteria[75])							
	1a	1b	1c	2a	2b	2c	3	T
Barnsley 1994[41]	1	0	0	1	1	0	1	4
Basmajian 1978[66]	1	0	0	1	1	0	0	3
Basmajian1983[40]	1	1	0	1	1	0	0	4
Bose 1999[70]	1	0	0	1	1	0	1	4
Brockow 2001[46]	1	1	0	0	0	0	1	3
Cheshire 1994[67]	1	0	0	1	1	0	1	4
Choffray 1987[42]	0	0	0	1	0	0	0	1
Dennert 1976[68]	1	1	0	1	1	0	1	5
Dostal 1978[59]	1	0	0	1	1	0	1	4
Esenyel 2000[47]	1	0	0	0	0	0	0	1
Ferrante 1998[48]	1	0	0	1	1	0	0	3
Freund 2000[60]	1	1	0	1	1	0	1	5
Giles 1999[50]	1	0	0	0	0	0	1	2
Ginsberg 1980[49]	1	0	0	1	0	0	1	3
Heikkila 2000[69]	1	0	0	0	0	0	1	2
Hong 1994[61]	1	0	0	1	1	0	0	3
Inan 2001[62]	1	0	0	0	0	0	1	2
Koes 1992[57]	1	1	0	1	0	0	1	4
Nasswetter 1998[58]	1	0	0	1	0	0	1	3
Payne 1964[71]	1	1	0	1	1	0	1	5
Pettersson 1998[43]	1	1	0	1	1	0	1	5
Rubenthaler 2000[44]	1	0	0	1	0	0	0	2
Salzman 1993[45]	1	0	0	1	0	0	1	3
Sand 1992[64]	1	0	0	1	0	0	1	3
Schnider 2002[63]	1	0	0	1	0	0	1	3
Schreiber 2001[52]	1	0	0	0	0	0	1	2
Stav 1993[51]	1	0	0	0	0	0	1	2
Terzi 2002[65]	1	0	0	1	1	0	1	4
Thomas 1991[53]	1	0	0	0	0	0	1	2
van Wieringen 2001[54]	1	0	0	1	1	0	1	4
Wheeler 1998[55]	1	0	0	1	1	0	1	4
Wheeler 2001[56]	1	0	0	1	1	0	1	4

* 1a: Was the study described as randomized? (Score 1 if yes); 1b and 1c: Was the method of randomization described and appropriate to conceal allocation? (Score 1 if appropriate and –1 if not appropriate); 2a: Was the study described as double-blinded? (Score 1 if yes); 2b and 2c: Was the method of double blinding described and appropriate to maintain double blinding? (Score 1 if appropriate and –1 if not appropriate); 3: Was there a description of how withdrawals and dropouts were handled? (Score 1 if yes).

Oral Psychotropic Agents (8 trials, 578 people): Certain oral psychotropic agents are specifically prescribed in clinical practice as muscle relaxants. For 2 of these agents, cyclobenzaprine (Flexeril®) and diazepam (Valium®), the following trials have been reported.

Cyclobenzaprine (2 trials, 77 people): Nasswetter[58] showed that cyclobenzaprine plus lysinine cloniximate was superior to lysine cloniximate alone for pain in MND at 14 days. Basmajian[66] showed that cyclobenzaprine was not superior to placebo for subacute MND at 14 to 18 days, using a global evaluation of muscle spasm.

Diazepam (3 trials, 194 people): Basmajian[66] showed that diazepam was not superior to placebo for subacute MND at 14 to 18 days for global evaluation of muscle spasm. Basmajian[40] showed diazepam was not significantly better than placebo for acute MND at 4 days. Thomas[53] found no significant benefit of diazepam over placebo at 2 hours, in participants with chronic cervical degeneration.

Tetrazepam (1 trial, 20 people): Another benzodiazepine, tetrazepam, was shown by Salzmann[45] to significantly improve pain, range of motion, and global perceived effect for acute MND at one week, when tetrazepam plus paracetamol were compared to paracetamol.

Other Agents (4 trials, 349 people): Other oral psychotropic agents showed mixed results for short-term pain, global patient evaluation, and mobility. There was evidence of significant short-term improvement in pain and range of motion for eperisone hydrochloride versus placebo for chronic MND at 6 weeks (22 people)[70]. However, Basmajian[40] (22 people) showed that phenobarbital was not significantly better than placebo for pain and tenderness for acute MND at 4 days. Similarly, Payne[71] (40 people) showed that meprobamate was

not significantly better than placebo for pain of NDR at 2 days. Schreiber[52] (40 people) compared fluoxetine to amitriptyline for chronic WAD and found no significant differences in pain at 6 weeks.

Oral Antiinflammatory Agents and Oral Analgesics (4 trials, 198 people): Giles[50] compared tenoxicam plus ranitidine to acupuncture or manipulation for chronic MND with degenerative changes and found no significant difference at 4 weeks. Dostal[59] compared ibuprofen plus manipulation to manipulation in chronic NDH and found no significant differences for pain at 4 weeks. Oral glaphenine did not result in significantly superior pain control compared to paracetamol for acute MND at 15 days, but did result in greater range of motion[42]. Koes[57] evaluated treatments by general practitioners (GP), defined as any combination of analgesics and antiinflammatory medications and education, and demonstrated that at 9 weeks, this combination of GP treatment was not significantly better than sham physical therapy (placebo) for subacute and chronic MND.

IM Injections of Multivitamins (1 trial, 60 people): Dennert[68] showed that IM injections of a multivitamin, Neurotrat, for chronic neck disorder with radiation had no significant advantage at 9 days for pain or global perceived effect, over the analgesic Metamuzol.

Nerve Block Injections (2 trials, 34 people): Using a prilocaine 2% anesthetic block of the greater occipital nerve was significantly better than saline injections for cervicogenic headache for pain[65]. Use of bupivacaine anesthetic to the greater occipital nerve had similar results for pain as a C2/C3 block with bupivacaine for cervicogenic headache with or without radicular findings, at 3 days, 2 weeks, and 2 months, although both groups improved over baseline[63].

Moderate Evidence of No Benefit. We established moderate evidence of no benefit for the following:

Botox A (5 trials, 141 people): For chronic neck disorders with or without radicular findings or headache, we found moderate evidence that there was no benefit for Botox A over saline IM injections across 5 high quality trials. The outcomes of interest per study were as follows: pain[52,67]; pain, disability, and range of motion[60]; and pain, disability, and global perceived effect[26,55]. Our team found that metaanalysis of 3 studies[52,60,67] was clinically and statistically justified for the pain outcome at 4 to 8 weeks post-treatment. This gave a nonsignificant pooled SMD of –0.39 (95% CI –01.25 to 0.47), using a random-effects model. Metaanalysis at several different timepoints led to the same conclusions (See Figure 2).

Intracutaneous Injections (1 trial, 20 people): Intracutaneous injection of sterile water, studied by Sand[64], in neck disorder with headache (duration of disorder not specified), showed no significant advantage over saline for pain and range of motion at one day and 13 days and neither group improved over baseline.

Subcutaneous Injections (1 trial, 57 people): The subcutaneous vasodilator, carbon dioxide, plus standard physical therapy led to no significant change in pain at 12 days compared to physical therapy alone in chronic MND[46].

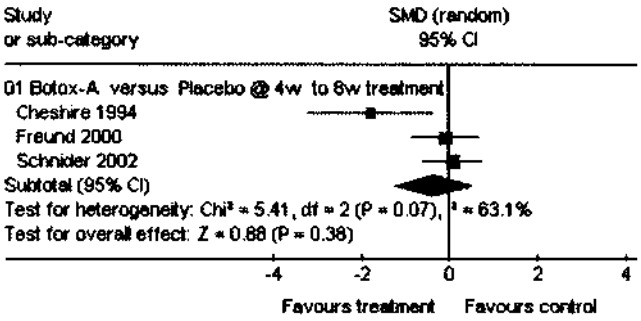

Figure 2. Metaanalysis of botulinum toxin (Botox A) trials.

Melatonin (1 trial, 81 people): Melatonin provided no benefit for sleep, pain, or general health status (Medical Outcome Study Short Form-36) at 4 weeks[54] compared to placebo, in chronic MND and WAD.

Side effects and cost. We found that the side effects described in these studies were minor and transient (Table 2 provides details by author). There were no serious side effects reported. However, most of our studies in this review had small sample size and short-term followup. It would have been unlikely for any uncommon side effect to be detected in any of these trials. For example, NSAID may cause gastrointestinal bleeding with prolonged use in a small number of users. Only 2 studies described the cost of the treatment. The epidural study described the cost as "low cost" but no specific information was given. The Botox A studies quoted a cost of $335 US per 100 units. Our clinical experience suggests that injection to one side of the neck will require at least 100 to 200 units, if not up to 200 units.

DISCUSSION

In general, systematic evaluation of medicines and injections for neck pain yielded disappointing results. High quality positive trials have not been replicated. There is some moderate evidence of benefit, based on a single high quality trial or a small number of methodologically limited trials. Thus, moderate evidence exists for IV methylprednisolone used within 8 hours of injury for acute whiplash and IM lidocaine for chronic MND. There was limited evidence of effectiveness of epidural methylprednisolone and lidocaine for chronic neck disorder with radicular findings. These trials need replication. Oral psychotropic agents gave a mixed picture; further studies should be a priority. Whether tetrazepam is effective is not known, as results come from a single, small trial. There is moderate evidence that Botox A injections are not superior to saline for chronic neck disorders with or without radicular findings or headache.

Drugs commonly used in clinical practice, yet having limited data on benefit, include the NSAID, tricyclic antidepressants, neuroleptic agents, and opioid analgesics. Insufficient

data exist to suggest that these therapies are effective, yet they are all known to have side effects. High quality studies are needed to ensure that more good than harm is being done for patients with neck pain.

This lack of studies in neck pain is in contrast to low-back pain, where there is evidence of benefit for antiinflammatory drugs in acute and chronic low-back pain[76] including studies of the newer cyclooxygenase 2-specific antiinflammatories[77]. Both muscle relaxants[78] and tricyclic antidepressants have been studied for low-back pain and found to be beneficial[79]. There are also randomized trials of opiates in low-back pain[80]. The lack of study of medicines and injections for neck pain is also in contrast to the large literature on physical therapy techniques[81] and spinal mobilization and manipulation[31].

Why would this discrepancy exist? Neck pain is common, occurring in 10% to 30% of the population, with disability in 5%[82], so worthy of study from a "burden of illness" perspective. Do physicians feel that medications and injections used for low-back pain can readily be adopted for neck pain? Research demonstrating that different spinal areas respond similarly to treatments is lacking in this case.

Our approach to summarizing the literature has several strengths. We used a comprehensive, librarian-assisted search and multiple databases. We used teams of healthcare professionals to decide on article relevance and assess quality. We had at least 2 people extracting data, and the principal investigator verified data entry. We used a group consensus approach, coupled with the Sackett and van Tulder hierarchy, to determine the strength of the evidence. We avoided any professional bias inherent in having a single profession evaluate its literature.

Weaknesses of our study rest with limitations in the primary studies. We were unable to make many firm statements about the strength of the evidence, since few therapies have been replicated by large, high quality trials. This also limited our ability to metaanalyze results, and calculate needed-to-treat numbers. Unfortunately, the quality of medicine and injection studies for neck pain does not seem to have improved over time. Adverse effects of treatments and associated costs are largely underreported statistically; when they are, descriptions tend to be narrative rather than quantitative in nature.

The most promising therapies appear to be IV methylprednisolone for acute whiplash and IM lidocaine for chronic MND. It is not clear if all corticosteroids or local anesthetics are equally effective. These trials demand replication in larger, high quality trials. If subsequent trials were positive, efforts to promote widespread adoption would be indicated. Epidural methylprednisolone and lidocaine for chronic neck disorder with radicular findings also appear promising and need further study. Oral psychotropic agents classified as muscle relaxants, such as cyclobenzaprine, diazepam, and tetrazepam require further study to clarify their benefits and harms.

Surprisingly, we found no evidence for acetaminophen and largely negative data for antiinflammatory drugs in neck pain, either acute or chronic. In many of the physiotherapeutic trials, acetaminophen and antiinflammatory drugs were allowed as a cointervention for all the treatment arms. Therefore, unlike the low-back pain literature, evaluation of the benefit of acetaminophen and antiinflammatory drugs alone was not possible. There were no studies of tricyclic antidepressants or opiate analgesics in chronic neck pain. In this regard, little has changed since our 1996 systematic review[83,84].

The majority of the studies focused on pain and function as their outcomes. However, there were varying numbers of measurement tools used to assess these outcomes, and a number of these tools were not validated. Future research should also focus on other, more objective outcomes such as return to work or return to regular activity.

Finally, clinicians are also interested in how a therapy compares to other commonly used therapies. Studies comparing medicines and injections to physical therapy techniques or manual therapy, and whether synergistic effects occur, are needed.

Reviewers' Conclusions

Implications for practice. There is moderate evidence for the benefit of IV methylprednisolone given within 8 hours of acute whiplash from a single trial. Lidocaine injection into myofascial trigger points appears effective in 2 trials. There is limited evidence for epidural methylprednisolone and lidocaine in chronic neck disorder with radicular findings. There is mixed evidence for oral psychotropic agents; the evidence on NSAID and analgesics was largely negative from a limited number of studies. There is moderate evidence that Botox A is not superior to saline injection for chronic MND. Poor methodological quality, insufficient sample size, and lack of trial replication make definitive conclusions impossible for most medicines.

Implications for research. There is a strong imperative for methodologically rigorous studies of all medicinal and injection therapies for mechanical neck pain, as no high quality, consistent evidence was found for any treatment strategy.

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