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Systematic review

Adverse events associated with the use of cervical manipulation and mobilization for the treatment of neck pain in adults: A systematic review

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A B S T R A C T

Adverse events (AE) are a concern for practitioners utilizing cervical manipulation or mobilization. While efficacious, these techniques are associated with rare but serious adverse events. Five bibliographic databases (PubMed, CINAHL, PEDro, AMED, EMBASE) and the gray literature were searched from 1998 to 2009 for any AE associated with cervical manipulation or mobilization for neck pain. Randomized controlled trials (RCTs), prospective or cross-sectional observational studies were included. Two independent reviewers conducted study selection, method quality assessment and data abstraction. Pooled relative risks (RR) were calculated. Study quality was assessed using the Cochrane system, a modified Critical Appraisal Skills Program form and the McHarm scale to assess the reporting of harms. Seventeen of 76 identified citations resulted in no major AE. Two pooled estimates for minor AE found transient neurological symptoms [RR 1.96 (95% CI: 1.09–3.54) $p < 0.05$]; and increased neck pain [RR 1.23 (95% CI: 0.85–1.77) $p > .05$]. Forty-four studies (58%) were excluded for not reporting AE. No definitive conclusions can be made due to a small number of studies, weak association, moderate study quality, and notable ascertainment bias. Improved reporting of AE in manual therapy trials as recommended by the CONSORT statement extension on harms reporting is warranted.

1. Introduction

Neck pain is a commonly experienced musculoskeletal disorder that affects adults globally (Linton et al., 1998; Cote et al., 2004; Hogg-Johnson et al., 2008). In the United States, costs related to care for spinal pain have risen 65% from 1997 to 2005 (Martin et al., 2008). The international prevalence of neck pain related to work injuries ranges from 27.1% to 47.8% (Cote et al., 2008). A recent study reported that more than 58% of people with neck pain post motor vehicle accident were work-disabled (Buitenhuis et al., 2009). It is commonly known that practitioners, such as chiropractors, osteopaths and physiotherapists, treat patients with neck pain and these practitioners utilize manual therapy (MT) techniques. These manual techniques include spinal manipulation, mobilization and those applied to the soft tissues. There has been much attention drawn to cervical spine manipulation (CSM) and its association with serious outcomes such as stroke and death (Rothwell et al., 2001; Smith et al., 2003; Cassidy et al., 2008). It has only been since 2001, that the first case control studies (Rothwell et al., 2001; Smith et al., 2003; Cassidy et al., 2008) looking at the association between stroke and chiropractic manipulation have been published. There are however several reports of more benign outcomes that are overshadowed (Cagnie et al., 2004; Rubinstein et al., 2007; Thiel et al., 2007). In contrast, there is a paucity of reports of adverse events (AE) related to mobilization techniques. In 2007, two large cohort studies, also involving chiropractic patients (Rubinstein et al., 2007; Thiel et al., 2007) have been published adding to the evidence base that less serious events are the more commonly occurring ones. An accurate risk estimate for the more serious adverse events has been difficult to obtain. Many have tried to provide an incidence rate, ranging from 1 in 100,000 (Rivett and Reid, 1998) to 1 in several million, (Haldeman et al., 2002) but the methods for these calculations are often flawed. Despite these rare events, focus remains on these serious events relative to the minor or moderate events.

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Regardless of this focus, adverse outcomes in MT have been without standardized definitions. It is only recently that the first paper to propose a framework for defining adverse events was published (Carnes et al., 2010) specific to MT. The authors provide a hierarchical system that define and categorize the range of possible adverse events by considering the severity and duration of the event as well as the context in which it occurred. This information is then used to categorize the event as mild, moderate or major. Further testing of their proposed system is needed. Without standardization in terminology and reporting, it is quite possible that much of the reporting that has occurred within MT studies, is prone to misclassification errors and is difficult to summarize findings across studies. Furthermore, it is likely that this deficit contributes to the challenge of quantifying an accurate incidence rate for all adverse events.

To accurately assess the risk of adverse outcomes related to the techniques of cervical manipulation and mobilization we must evaluate the risk of all events. This must be weighed against the benefit as evidenced in the increasing literature base of efficacy trials of manual therapy for neck disorders. The current evidence includes high quality studies supporting a multimodal treatment approach (Gross et al., 2007). Until recently, the evidence for adverse events associated with CSM has been dominated by case reports and retrospective case series or surveys from neurologists (Hurwitz et al., 1996; Di Fabio, 1999; Ernst, 2002). This bias may lead to over reporting of serious and catastrophic adverse events compared to minor and moderate events. This level of evidence, while possibly establishing temporal and biologic plausibility arguments, is plagued by numerous biases such as measurement or selection bias. Further there has been an emphasis on examining adverse events occurring in the chiropractic profession (Haneline et al., 2003; Gouveia et al., 2009) while other practitioners such as osteopaths and physiotherapists have been evaluated less frequently. The goal of this systematic review is to synthesize the literature that has reported adverse events related to both cervical manipulation and mobilization techniques across professions at the highest possible level of evidence.

2. Methods

2.1. Study identification

The following databases were searched from 1998 to February 1, 2009: MEDLINE, CINAHL, EMBASE, AMED, PeDro, the trial registries of the Cochrane group, the World Health Organization and the US National Institutes of Health based www.clinicaltrials.gov. Subject headings (MeSH) and key words included anatomical terms, disorder or syndrome terms, treatment terms, and methodological terms consistent with those advised by the Cochrane Back Group.

The specific search strategy is available upon request from the authors. No language restrictions were applied. In an attempt to search for unpublished studies, hand searching of the following conference proceedings occurred: the International Federation of Manipulative therapists (IFOMT) 2000–2008, the World Federation of Chiropractors, 1998–2008. As well, researchers in MT, identified by previous studies, were emailed and enquiries were made about unpublished or ongoing trials. At least two independent reviewers were involved in all stages of the review. Selection of eligible studies was determined using three categories, yes, no or unsure for the relevant criteria. Disagreements were resolved by consensus.

2.1.1. Study selection

The following inclusion criteria were used for studies for this review.

2.1.2. Type of studies

Randomized and quasi-randomized controlled trials, along with prospective cohorts, case series or cross-sectional surveys were included. The observational studies established primary outcomes of adverse events related to cervical manipulation or mobilization. All were either published or unpublished. All retrospective studies were excluded. The evaluations of retrospective studies have previously been reported in the literature (Hurwitz et al., 1996; Di Fabio, 1999; Ernst, 2001, 2002, 2007; Mann and Refshauge, 2001). Conclusions from these reviews have been problematic due to the level of study designs and the quality of reporting. It was felt that including them in this review would not make any new contribution.

2.1.3. Type of participants

The participants were adults with the following:

- Neck pain without radicular findings, including neck pain without specific cause, whiplash associated disorder (WAD) categories I and II (Spitzer et al., 1987, 1995; Guzman et al., 2008), myofascial pain syndrome, and neck pain associated with degenerative changes (Schumacher et al., 1993).
- Cervicogenic headache (Olesen, 1988; Sjaastad et al., 1990; Olesen and Gobel, 1997);
- Neck disorders with radicular findings (Rubinstein et al., 2007), including degenerative joint or disc disease with spinal stenosis, spondylolisthesis, or discogenic radiculopathy; WAD category III (Spitzer et al., 1987, 1995)

Studies were excluded if they investigated neck disorders with the following specific causes:

- definite or possible long tract signs (e.g. myelopathies);
- neck pain caused by other pathological entities (Schumacher et al., 1993);
- headache not of cervical origin but associated with the neck;
- co-existing headache when either neck pain was not dominant or the headache was not provoked by neck movements or sustained neck postures; or
- 'mixed' headache including more than one headache classification

2.1.4. Type of intervention

1) Cervical manipulation was defined as a high velocity, low amplitude force applied to the cervical vertebrae and 2) Cervical mobilization was defined as lower velocity manual forces applied with varying amplitude to the cervical vertebrae or any neuromuscular-based soft tissue techniques (such as muscle energy or proprioceptive neuromuscular facilitation). These studies could have MT used alone or in combination with other treatments.

2.1.5. Type of comparison

Placebo, wait list/no treatment control group, active treatment control (e.g. manipulation and exercise vs. exercise) or inactive treatment (e.g. sham ultrasound) were included.

2.1.6. Type of outcome

The primary outcome was any adverse events (or lack of events) following treatment with MT. The adverse events were initially grouped into *major* – death, stroke or permanent neurological deficits and *minor*– transient neurological symptoms, increased neck pain/stiffness, headache, radiating pain, fatigue or other. Reported adverse events were abstracted from eligible studies into categories previously recorded 'as' common side effects to spinal manipulation (Cagnie et al., 2004). ‘Stroke’ and ‘other’ categories were added to allow for any event to be recorded.

During title and abstract screening, it was suspected that adverse events would generally not be reported in the abstracts of randomized controlled trials (RCTs). Therefore, if the other inclusion criteria were met, but the outcome was not reported in the abstract then the study qualified for full text screening. Study selection was determined using three categories, yes, no or unsure for the relevant criteria. At least two independent reviewers were involved in the selection process. Disagreements were resolved by consensus or discussion with a third reviewer.

Agreement was measured by the quadratic weighted Kappa (Fleiss and Cohen, 1973). Authors were emailed for clarification where necessary regarding detail of the population, intervention or outcome.

2.2. Data abstraction and analysis

Data abstraction occurred with two independent reviewers using standardized forms that had been pilot tested. If dropouts were lost for reasons related to symptomatology, such as increased pain, the authors were emailed for clarification. If the reason for dropouts was unknown or unrelated to symptoms, no further action was taken. Data analysis was performed using Revman 5.0 (The Nordic Cochrane Centre, 2008). The adverse events outcomes were extracted. The events were treated as present or absent and the intent was to estimate relative risk ratios, with 95% confidence intervals. In studies where only frequencies were provided and no further data was obtained after contacting the authors, risk ratios could not be constructed. Selection of studies for pooling of the data considered the clinical characteristics of studies including disorder type, duration of the disorder, and the intervention. A priori it was decided that statistical heterogeneity (differences between study outcomes) would be investigated using the Chi-squared test and I^2 test and considered positive at $p < .05$ and $>40\%$ respectively.

2.3. Assessment of study quality

Two independent reviewers undertook the validity assessment. Disagreements were resolved by discussion with a third reviewer and consensus reached. Authors were contacted where necessary to clarify the reporting of methods. The RCTs were assessed using the Cochrane risk of bias tool (maximum score 12, high score greater than 6) and the McHarm quality assessment (Santaguida et al., 2004) for the reporting of harms in efficacy trials (maximum score 14, high score greater than 9). The observational studies were assessed using a modified form from the Critical Skills Appraisal Programme (Critical Appraisal Skills Programme, 2004) (maximum score 10, high score greater than 6). For all three tools, studies were categorized into low, moderate or high risk of bias (Higgins and Green, 2008).

2.4. Summary of findings

A summary of findings table was developed for important outcomes. We assessed the quality of the body of the evidence using the GRADE approach (Guyatt et al., 2008; Higgins and Green, 2008). Domains that may decrease the quality of the evidence are as follows: 1) the study design, 2) risk of bias, 3) consistency of results, 4) directness (generalizability), 5) precision (sufficient data), and 6) reporting of the results for studies that measure one particular outcome. Domains that may increase the quality of the evidence are 1) large magnitude of effect; 2) all residual confounding would have reduced the observed effect, and 3) a dose–response gradient is evident. High quality was defined as studies with low risk of bias that provided consistent, direct and precise results for the outcome. The GRADE rating was downgraded by a level for each of the domains not met or increased by factors, such as, a large effect; all plausible confounding would reduce a demonstrated effect and dose–response gradient.

1. *High quality of evidence*: Further research is very unlikely to change our confidence in the estimate of effect. There are consistent findings among 75% of RCTs with low risk of bias that are generalizable to populations typical in clinical practice. There are sufficient data, with narrow confidence intervals. There are no known or suspected reporting biases.
2. *Moderate quality of evidence*: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
3. *Low quality of evidence*: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
4. *Very low quality of evidence*: We are very uncertain about the estimate.

3. Results

3.1. Study selection

Seventy six articles were reviewed in full text of which 59 were excluded as follows: a) 44 did not report adverse events, b) 21 did not meet the intervention definitions, c) 8 presented combined data for the whole spine or data that was unclear that could not be used, d) two were abstracts, e) one was a commentary not a proper study, f) one paper was an economic analysis, g) one had an inappropriate population, h) two were not RCTs. Our search resulted in the selection of 14 RCTs and three observational studies (see Fig. 1). No major AE were reported in any study. The weighted Kappa (Fleiss and Cohen, 1973) for the selection phase was excellent Kw = 0.89, 95% CI (0.82–0.95).

3.2. Description of studies

Duration of neck pain in the studies was reported as follows: five studies had chronic populations (Bronfort et al., 2001; Haas et al., 2004; Dziedzic et al., 2005; Chen et al., 2007; Zhi et al., 2008), one was acute and subacute (Evans et al., 2003), four were subacute and chronic (Hoving et al., 2002; Jull et al., 2002; Mayor et al., 2008; Strunk and Hondras, 2008), five were mixed (Haas et al., 2003; Hurwitz et al., 2004; McReynolds and Sheridan, 2005; Rubinstein et al., 2007; Kanlayanaphotporn et al., 2009) and two were not specified (Cagnie et al., 2004; Thiel et al., 2007). Types of disorders were as follows: three cervicogenic headache (Jull et al., 2002; Haas et al., 2004; Chen et al., 2007), 6 mechanical neck pain (Bronfort et al., 2001; Cagnie et al., 2004; Mayor et al., 2008; Strunk et al., 2008; Zhi et al., 2008; Kanlayanaphotporn et al., 2009), two nonspecific neck pain (Hoving et al., 2002; Dziedzic et al., 2005), and 6 were not specified (Evans et al., 2003; Haas et al., 2003; Hurwitz et al., 2004; McReynolds and Sheridan, 2005; Rubinstein et al., 2007; Thiel et al., 2007).

3.3. Methodological quality

Table 1 lists the risk of bias in the 14 RCT studies that were retrieved. Overall randomization was well done in 13 studies. Allocation concealment and adequate data reporting also rated well with 10 and 12 studies respectively, meeting criteria. Blinding is difficult to achieve in manual therapy trials although two studies were able to do so adequately. Haas et al. (2003) used different

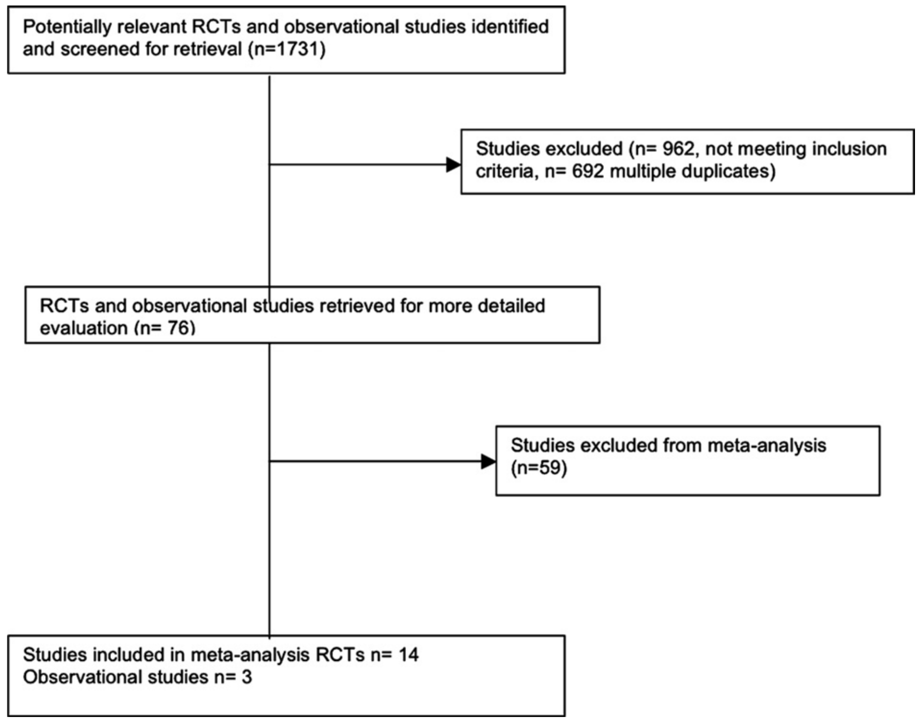

Fig. 1. Flow diagram of search and selection process.

chiropractors for assessment and treatment. Participants and treatment providers were blinded to the findings of the assessors. Kanlayanaphotporn et al. (2009) used two different therapists and an assessor. This allowed for different people to be involved and blinded at different stages such as baseline data collection, patient screening, treatment and outcome data collection. Each therapist was blinded to the findings of the other. Selective reporting and other biases faired more poorly with only 6 and 8 studies meeting criteria respectively.

On the whole the RCTs performance on the McHarm ranged from moderate to high risk of bias (see Table 1). The observational studies performed from low to moderate. The three observational studies were specifically designed to capture harm data and it is therefore not surprising that they were more complete in their reporting of harms. Observational study quality using the modified CASP form produced varying results across the three studies. Rubinstein et al. (2007) rated the highest of the group and Thiel et al. (2007) lowest (see Table 1). Generally, observational studies represent a lower grade of evidence but are able to increase their weighting when the studies show large effect sizes and a strong dose–response relationship (Guyatt et al., 2008). Areas of concern in these three observational studies were related to the effects from confounding factors, specifying the details of the measurement of exposure to manipulation, and insufficient length of follow-up. Generally, confounding factors were identified within studies, but not accounted for in the statistical analyses. With the exception of Rubinstein et al. (2007) it is unknown if manipulation was the only treatment given or whether other techniques were employed. Follow-up in Rubinstein et al. (2007) was longer at three months, but was far less in the other studies at 48 h and between two to six weeks. Observational studies have inherent biases in their design due to a lack of randomization and are best suited to capture data on harms (Guyatt et al., 2002). These three studies in combination provide evidence of similar results and consistent conclusions for the occurrence of minor and moderate adverse events related to CSM.

In the studies using multimodal treatments, it was assumed that there was an interaction effect in the combination of manipulation and mobilization with exercise. This did not allow for pooling with study arms using manual therapy alone. This interaction is supported by the Cochrane review of Gross et al. (2004) that found that there was greater efficacy with a multimodal approach than one using just manipulation or mobilization in isolation. If an interaction between MT and exercise is occurring to increase efficacy, it is possible that it also impacts on adverse events. Therefore pooling estimates from studies using pure manipulation or mobilization with those combining MT with exercise is not warranted. Other studies using multimodal treatments were not pooled due to heterogeneity in the combinations of manual therapy or in the comparison intervention (such as TENS or intramuscular injection). Two studies only were eligible for pooling, as they reported similar adverse events, used similar manual therapy techniques, and were administered in subjects with mechanical neck disorders. Both also had similar comparators against other MT techniques. Table 1 details the characteristics of all included studies. Results are listed by type of intervention, comparison, and outcome.

3.4. *Effects of interventions*

3.4.1. *Studies with single modal treatment*

Two studies were found using only neck manipulation with comparisons to other neck mobilization or spinal manipulation elsewhere in the spine. Haas et al. (2003) compared CSM applied to a specific identified level of restriction to CSM applied to a random level. This study was not included in the meta-analysis of AE due to the nature of the comparison and limited clinical relevance. One study by Kanlayanaphotporn et al. (2009) was similar in methods to Haas et al. (2003) but used mobilization instead of manipulation for treatment. The findings within this study showed no occurrence of adverse events. These two studies varied greatly in both risk of bias and harms reporting.

Table 1
Study characteristics.

Study	Participants	Intervention	Comparison	Any adverse outcomes	Treatment phase length	Practitioner PT = Physiotherapist, CH = Chiropractor, OP = Osteopath	Study design	a. Risk of bias b. McHarm
Bronfort et al., 2001	Chronic (>12 weeks) mechanical neck pain	SMT, light massage for 15 min with 45 min of sham microcurrent	a. SMT and low-tech exercise b. High tech exercise	RR 0.83 95% CI (0.39–1.76); $p > 0.05$	11 weeks	CH	RCT	a. low b. high
Cagnie et al., 2004	Duration not specified; mechanical neck pain	SMT, uncertain if other treatment occurred	none	Frequencies ranging from 13.4–54.4% of neuro & radiating symptoms, ⇑ neck pain, headache, fatigue and other	1 visit	CH, PT, OP	Case series	a. high b. moderate
Chen et al., 2007	Chronic cervicogenic headache	SMT combined with massage, traction and other soft tissue techniques	Transcutaneous electrical nerve stimulation (TENS);	None occurred	20 days; each treatment given on alternate days	Traditional Chinese Medicine	RCT	a. high b. high
Dziedzic et al., 2005	Chronic, nonspecific neck pain	SMT, mobs, passive or active movements, advice, exercise	a. Pulsed short wave diathermy, advice, exercise b. advice, exercise	None occurred	6 weeks; 8–20 min sessions	PT	RCT	a. low b. high
Evans et al., 2003	Neck pain < 12 weeks	SMT, light massage, advice	a. medical care (medication, advice) b. Self-care education (2–45 min sessions with PT	Frequencies ranging from 10–90% of neuro symptoms, ⇑ neck pain, headache, and other	12 weeks, frequency determined by CH	CH	RCT	a. moderate b. high
Haas et al., 2003	Neck pain of varying length	SMT specific to identified level of restriction	SMT to 'sham' generated level	RR = 1.13 95% CI (0.47–2.69); $p > 0.05$	1 visit	CH	RCT	a. low b. high
Haas et al., 2004	Chronic, cervicogenic headache,	SMT once a week, +/−2 modalities	a. SMT 3 times/week, +/−2 modalities b. SMT 4 times/week, +/−2 modalities	None occurred	3 weeks	CH	RCT	a. low b. high
Hoving et al., 2002	Nonspecific neck pain > 2 weeks	Mobs, soft tissue techniques, exercise; 45 min once per week	a. PT − exercise, traction, stretching, massage, modalities; twice per week for up to 12 visits b. General practitioner − advice, medication; 10 min visits every 2 weeks	Frequencies ranging from 5.7 to 28.3% of neuro & radiating symptoms, ⇑ neck pain, and headache.	6 weeks	PT	RCT	a. low b. high
Hurwitz et al., 2004	Neck pain of varying length	SMT to neck and/or upper thoracic	a. SMT, heat b. SMT, EMS, c. SMT heat, EMS d. Mobs to neck and/or upper thoracic e. Mobs, heat f. Mobs, EMS g. Mobs heat, EMS	RR = 1.31 95% CI (1.12–1.52); $p < 0.05$	2 weeks	CH	RCT	a. moderate b. high

Jull et al., 2002	Cervicogenic headache – ≥2 mos–10 yrs	SMT, mobs	a. SMT, mobs, exercise b. Exercise c. no treatment	RR = 2.69, 95% CI (0.74–9.85), $p > .05$	6 weeks; 8–12 visits	PT	RCT	a. low b. high
Kanlayanaphotporn et al., 2009	Mechanical neck pain ≥ 1 week	Mobs specific to identified level of restriction	Mobs randomly applied to level	None occurred	1 visit	PT	RCT	a. low b. moderate
Mayor et al., 2008	Mechanical neck pain, subacute and chronic	Mobs, stretching, trigger point massage, pnf	TENS, 80 Hz, 150 microns	RR = 0.40, 95% CI (0.11–1.45); $p > 0.05$	4 weeks – 3 visits per week	PT	RCT	a. moderate b. high
McReynolds and Sheridan, 2005	Neck pain of varying length	SMT, soft tissue techniques, muscle energy	Intramuscular injection	RR = 0.13 95% CI (0.02–0.94); $p < 0.05$	I visit	OP	RCT	a. moderate b. high
Rubinstein et al., 2007	Neck pain of varying length	SMT, mobs, exercise, modalities, other techniques	None	Frequencies ranging from 2.6 to 25.9% of neuro symptoms, ⇑ neck pain, headache, fatigue and other.	3 visits	CH	Case series	a. low b. low
Strunk and Hondras, 2008	Mechanical neck pain ≥ 4 weeks	SMT	SMT to thorax, muscle energy	RR = 1.50 95% CI, (0.18–12.5); $p > 0.05$	2 weeks; 4 visits	CH	RCT	a. moderate b. moderate
Thiel et al., 2007	Not specified	SMT, uncertain if other treatment occurred	None	Frequencies ranging from 0.7 to 1.7% of neuro & radiating symptoms, ⇑ neck pain, headache and other.	2 visits within a 6 week time frame	CH	Case series	a. high b. low
Zhi et al., 2008	Chronic mechanical neck pain (spondylosis) ≥ 12 weeks	SMT (4 times every other day), acupotomy (once per week for 2 weeks)	Traction (4 times every other day)	None occurred	1 visit	Unable to ascertain	RCT	a. high b. high

3.4.1.1. Manipulation vs. true control. No trials were found that reported on adverse events.

3.4.1.2. Transient neurological symptoms.

- Manipulation vs. Comparison

Meta-analysis for AE experiencing transient neurological symptoms showed a pooled relative risks, RR = 1.96, 95% CI (1.09, 3.54) $p < .05$ (Fig. 2). These two trials provide moderate evidence that this association exists for up to 2 weeks post treatment. Alternatively this can also be expressed as 194 events per 1000 patients compared to 99 events per 1000 patients in the control group. This is supported by an RR < 2. The use of a continuity correction with the Mantel Hansel method for zero cell counts has been shown to be the least biased method (Sweeting et al., 2004). In the Strunk and Hondras, 2008 trial however, the small sample size is a significant limitation of this study. Caution must be used however as the GRADE of evidence of these two trials is low (Table 2).

3.4.1.3. Increased neck pain.

- *Manipulation vs. Comparison*

Fig. 3 provides strong evidence that neck manipulation or mobilization does not result in an increase in neck pain RR = 1.25, 95% CI (0.84, 1.87) $p > .05$. Alternatively, this can be expressed as 253 events per 1000 patients compared to 206 events per 1000 patients in the control group. A non-significant result combined with an RR just over one, questions the association of the intervention with this reaction. However, the limitations of the Strunk study and the low GRADE rating remain, affecting confidence in the estimate.

3.5. Studies using multimodal treatments

Ten trials were found using a multimodal approach. Four reported the occurrence of no adverse events. Two studies had active controls that used advice and exercise and exercise respectively. The remaining studies had comparator treatments that included traction, TENS, intramuscular injection, exercise, pulsed short wave diathermy, self-care, medical care, physiotherapy without manual treatment, and traction. Two studies reported only frequencies and did not allow the construction of an RR. With the exception of McReynolds and Sheridan, 2005 all trials had non-significant findings. They are presented below. See Table 1 for the estimates of the remaining studies.

3.5.1. Headache

One trial (Jull et al., 2002) with a factorial design and low risk of bias compared manipulation and mobilization to a control. The risk ratio was large, but was non-significant and has a wide confidence interval RR = 10.5 (95% CI: 0.60–185.58) $p > .05$. Also the combination of manipulation and mobilization does not allow for the result to be linked to either technique in isolation. Two further arms showed no significant findings: 1) Manipulation, mobilization vs. exercise RR = 1.77 (95% CI: 0.45, 7.01) $p > .05$; 2) Manipulation, mobilization and exercise vs. exercise RR = 1.06 (95% CI: 0.23, 5.01) $p > .05$.

3.5.2. Radiating symptoms

One study with high risk of bias provides evidence that cervical manipulation and mobilization has a protective effect when compared to intramuscular injection (McReynolds and Sheridan, 2005) (RR 0.13, 95% CI: 0.02–0.94), $p < .05$. Although the result is statistically significant, the RR is very small and it is a stand alone study.

We were unable to pool any of the estimates from these multimodal trials due to mixed manual interventions and individual comparisons. For individual study quality see Table 1. A GRADE level was not assigned to these studies.

3.6. Studies reporting the occurrence of no adverse events

The following comparison trials reported no occurrences of adverse events. Only studies using manual therapy against various comparisons were found.

- Chen et al. (2007) – Manipulation and Soft tissue techniques vs. TENS
- Dziedzic et al. (2005) – Advice and exercise vs. Advice, exercise, manipulation, and mobilization vs. Advice, exercise and pulsed short wave diathermy
- Haas et al. (2004) – Manipulation and soft tissue techniques once/week vs. Manipulation and soft tissue techniques 3x/week vs. Manipulation and soft tissue techniques 4x/week.
- Kanlayanaphotporn et al. (2009) – Mobilization specific vs. Mobilization random.
- Zhi et al. (2008) – Manipulation and Acupotomy vs. Traction.

4. Discussion

This is the first systematic review evaluating the evidence for the presence of adverse events associated with cervical manipulation or mobilization from RCTs. The inclusion of RCTs synthesizes evidence about the risk of adverse events that until now has been reported from lower level studies. Another review has recently been published examining RCTs for reports of harms in medicine (Pitrou et al., 2009). While it is acknowledged that an RCT is not primarily used to detect adverse events, especially those that are rare, the strength of meta-analysis with sufficient data cannot be disregarded. Observational studies are more appropriate to detect harms if the research question is focused on the collection of harms data (Guyatt et al., 2002). The combination of the rarity with which serious adverse events are thought to occur and a lack of standard definitions or outcome measures brings into question the confidence we have in most study data that has been collected to date. In

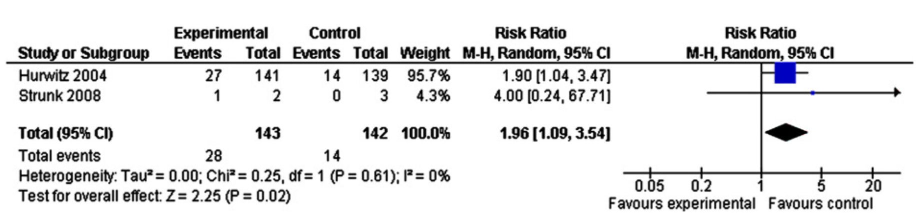

Fig. 2. Manipulation vs manipulation or mobilization: outcome – transient neurological symptoms.

Table 2
Summary of findings.

Cervical manipulation or mobilization for the treatment of neck pain in adults compared to an alternate application of manipulation or mobilization in the neck or elsewhere in the spine					
Patient or population: adults with neck pain *Settings*: in outpatient orthopaedic settings *Intervention*: Cervical manipulation and/or mobilization[b]					
Outcomes	Illustrative comparative risks[a] (95% CI) Assumed risk Control	 Corresponding risk Cervical manipulation and/or mobilization	Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)
Major/catastrophic adverse events					
No studies reporting this outcome	–	–	Not estimable	0 (0)	–
Minor adverse events – transient neurological symptoms					
Patient self report Follow-up: 1–14 days	99 per 1000	194 per 1000 (108–350)	RR 1.96 (1.09–3.54)	285 (2 studies)	⊕⊕⊝⊝ low[c,d]
Minor adverse events – Increased neck pain					
Patient self report Follow-up: 1–14 days	206 per 1000	253 per 1000 (175–365)	RR 1.23 (0.85–1.77)	389 (2 studies)	⊕⊕⊝⊝ low[c,d]

CI: Confidence interval; RR: Risk ratio.
[a] The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
[b] All of the trials included in the meta-analysis used cervical manipulation or mobilization in isolation. The studies that were pooled all used comparisons with manual therapy and do not allow analysis of the intervention vs. no treatment.
[c] It was unclear whether one of the studies was free of other biases.
[d] One of the studies was a pilot and had very small sample size.

addition, previous studies have indicated that patients overestimate rare mortality related risks and underestimate common risk (Hakes and Viscusi, 2004). Although the estimate for serious adverse events is not well reported and therefore relatively unknown in this area, it is clear that more common, less serious adverse events are occurring relatively more frequently. Since this is the case, RCTs can be effectively used to capture the more mild to moderate events. This data, along with evidence of benefit can be used to assess estimates for the risk benefit assessment in this area. Thus we feel that the use of prospective data was warranted and will add to the knowledge base.

Our review did not address the question of power and found minor to moderate, more common adverse events of which there was an average occurrence of 16.3% across studies. The first study to look at the adequacy of the statistical power of RCTs to detect severe, less common adverse events was published (Tsang et al., 2009). They reported a range of power from 0.07 to 0.90 studying a variety of conditions. Future systematic reviews evaluating AE in general, can adequately assess power of these studies to detect adverse events but will require improved reporting of 1) adverse events and 2) treatment techniques and clinical parameters in a transparent, standardized way. Furthermore standardized definitions of adverse events are required. A framework for this has been proposed (Carnes et al., 2010) and is based on "consensus". They used a heterogenous group of experts ranging from manual therapy practitioners to physicians, psychologists and pharmacists. Patients were not involved. Three rounds of a Delphi process were conducted with each building on the previous, namely construct definition, classification of events within the constructs and the effect of severity and duration. One aspect that could be considered along side severity and duration is the onset of symptoms. This will speak directly to the temporality of the event and potentially provide strength for the argument of causation. Consideration of this framework for future studies will be a step towards properly capturing and classifying all events. However, testing of this framework is required. If successful, it is suggested that this along with consideration of patient input could serve to provide the basis for development of standardized questionnaires for both the clinician and patients participating in studies. Since RCTs are generally not designed to answer questions of harm, we feel it would be most appropriate to design two versions of the measures, a shorter version for use as a secondary measure in RCTs and a longer more detailed version for use in observational studies where harm is the primary research question.

We were able to meta-analyze results from two studies for two different outcomes of minor adverse events. The comparisons in both cases were against different types of MT. Therefore, the estimates can only be applied to scenarios where the clinician is considering using mobilization instead of manipulation or considering manipulating a different area of the spine. The latter choice, particularly in the thorax, is supported by an increasing body of evidence as an alternative treatment approach to manipulating the cervical spine (Fernandez-De-Las-Penas et al., 2004; Cleland et al., 2005, 2007; Gonzalez-Iglesias et al., 2009). Pooling of estimates

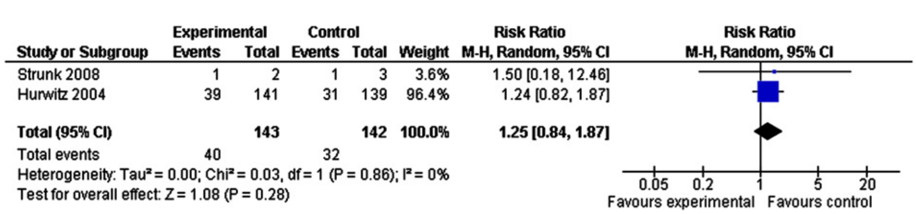

Fig. 3. Manipulation vs manipulation or mobilization: outcome – increased neck pain.

was limited by the clinical heterogeneity of studies with respect to interventions and comparators. Overall these estimates provide moderate quality evidence due to a lack of precision (as per GRADE), and uncertainty related to biases such as selective outcome reporting, differences between groups at baseline and the effect of co-interventions. There was only one study with comparison of the intervention against no treatment (Jull et al., 2002) and three with an active control (Bronfort et al., 2001; Jull et al., 2002; Dziedzic et al., 2005). Similarly, the heterogeneity within the multimodal studies regarding intervention and comparisons precluded any pooling of data. Considering that 44 of 76 studies were excluded because they did not report any information regarding adverse events is a reflection of the poor standards within this area. Our results suggest that ascertainment bias may compromise the credibility of current studies. More trials are required to report on adverse events if meta-analysis is to be useful for obtaining a summary estimate of minor adverse events.

No catastrophic outcomes were reported in any of the eligible studies. This includes Thiel et al. (2007), which reported the performance of 50,276 cervical manipulations. The details of the MT treatments provided in this study were not well reported. We cannot be certain whether other treatment techniques were also utilized and therefore the estimates are confounded by non MT adjunct treatments. In addition, this study had a short but very thorough follow-up. This study supports the theory that the occurrence of catastrophic events is quite rare.

The most important finding of this systematic review is the identification of the need for more stringent reporting of adverse events in MT efficacy trials. The use of the McHarm clearly demonstrated deficits in the reporting of harms in MT RCTs despite the 2004 CONSORT statement extension on harms reporting. Half of our RCTs were published in 2005 or later. This also encompasses the implementation of standardized definitions as only the observational studies provided any definitions of what would constitute an adverse event. Interestingly in the majority of eligible studies, increased neck pain and headaches were the two most commonly captured adverse events. These are often primary outcomes for efficacy studies (with the exception that there is a decrease in symptoms). Neck pain is typically measured on a continuum and is prone to fluctuation (Tomlinson et al., 2005). If studies are to continue to report increased neck pain as an adverse event, there should be a consensus as to the threshold where the degree of increase in neck pain is deemed adverse. Definitions of AE need to address aspects beyond an increase in symptoms. Severity, duration and onset will help make these differentiations possible.

The very issues identified by this review requiring improvement, have also introduced bias into our results. Even with less ascertainment bias of AE, we cannot be fully confident that the symptoms that are currently being reported as adverse are as such. Information bias is present in both the classification and measurement of these events. Without a priori standardized definitions, particularly of the more commonly reported treatment related symptoms, we cannot be confident that these minor and moderate events are being accurately captured; nor can we compare across different studies. Without a standardized and validated measure, we cannot always be confident that all events are being captured. In addition, we must consider the impact of differences in the frequency of adverse events, which are always less than the expected frequency of the primary outcome; sample size calculation based on rare events will yield very large numbers. If sample size is based on outcomes of benefit, there is likely an underpowering within RCTs to detect statistical differences in the frequency of adverse events between groups; this in turn will result in type II errors (Tsang et al., 2009).

The results of this systematic review are unlikely to impact clinical practice, as no strong evidence links the occurrence of adverse events to the treatment and therefore conclusions of clinical relevance are limited. The following implications for future research should be considered. There is a need for more trials comparing cervical manipulation and/or mobilization in isolation (single modal treatment) to allow for uncontaminated effect estimates pertaining solely to these manual interventions. This is in direct contrast to the evidence for efficacy, which supports a multimodal approach; however, multimodal studies are likely to be more representative of real clinical practice than single modal. There is clearly value for future research in AE to use both types of interventions. If trials start to incorporate the capturing of AE in their study design and adopt the CONSORT Statement extension on harms reporting guidelines, valuable information on mild to moderate adverse events can be added to this area. We are not suggesting that RCTs are the study of choice to detect harms. In general, large scale observational studies are the most appropriate to detect adverse events and are likely the only way that serious adverse events will be captured. Such studies should be conducted across manual therapy professions not just chiropractic. Manual therapy practitioners using these interventions should consider using the framework of Carnes et al. (2010) as a starting point.

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