CERVICAL SPINE MANIPULATION: A RAPID LITERATURE REVIEW

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Please note that this Rapid Literature Review is a summary of information from other sources, not a representation of the policy position of Manitoba Health, Seniors, and Active Living or the Manitoba Health Professions Advisory Council.

Prepared for the Manitoba Health Professions Advisory Council

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Executive Summary

INTRODUCTION

Neck manipulation or adjustment is a manual treatment where a vertebral joint in the cervical spine—comprised of the 7 vertebrae C1 to C7—is moved by using high-velocity, low-amplitude (HVLA) thrusts that cannot be resisted by the patient. These HVLA thrusts are applied over an individual, restricted joint beyond its physiological limit of motion but within its anatomical limit. The goal of neck manipulation, referred to throughout this report as cervical spine manipulation (CSM), is to restore optimal motion, function, and/or reduce pain. CSM is occasionally utilized by physiotherapists, massage therapists, naturopaths, osteopaths, and physicians, and is the hallmark treatment of chiropractors; however the use of CSM is controversial. This paper aims to thoroughly synthesize evidence from the academic literature regarding the potential risks and benefits of cervical spine manipulation utilizing a rapid literature review method.

METHODS

Individual peer-reviewed articles published between January 1990 and November 2016 concerning the safety and efficacy of cervical spine manipulation were identified through MEDLINE (PubMed), EMBASE, and the Cochrane Library.

KEY FINDINGS

- A total of 159 references were identified and cited in this review: 86 case reports/ case series, 37 reviews of the literature, 9 randomized controlled trials, 6 surveys/qualitative studies, 5 case-control studies, 2 retrospective studies, 2 prospective studies and 12 others.
- Serious adverse events following CSM seem to be rare, whereas minor adverse events occur frequently.
- Minor adverse events can include transient neurological symptoms, increased neck pain or stiffness, headache, tiredness and fatigue, dizziness or imbalance, extremity weakness, ringing in the ears, depression or anxiety, nausea or vomiting, blurred or impaired vision, and confusion or disorientation.
- Serious adverse events following CSM can include the following: cerebrovascular injury such as cervical artery dissection, ischemic stroke, or transient ischemic attacks; neurological injury such as damage to nerves or spinal cord (including the dura mater); and musculoskeletal injury including injury to cervical vertebral discs (including herniation, protrusion, or prolapse), vertebrae fracture or subluxation (dislocation), spinal edema, or issues with the paravertebral muscles.

- Rates of incidence of all serious adverse events following CSM range from 1 in 10,000 to 1 in several million cervical spine manipulations, however the literature generally agrees that serious adverse events are likely underreported.
- The best available estimate of incidence of vertebral artery dissection of occlusion attributable to CSM is approximately 1.3 cases for every 100,000 persons <45 years of age receiving CSM within 1 week of manipulative therapy. The current best incidence estimate for vertebral dissection-caused stroke associated with CSM is 0.97 residents per 100,000.
- While CSM is used by manual therapists for a large variety of indications including neck, upper back, and shoulder/arm pain, as well as headaches, the evidence seems to support CSM as a treatment of headache and neck pain only. However, whether CSM provides more benefit than spinal mobilization is still contentious.
- A number of factors may make certain types of patients at higher risk for experiencing an adverse cerebrovascular event after CSM, including vertebral artery abnormalities or insufficiency, atherosclerotic or other vascular disease, hypertension, connective tissue disorders, receiving multiple manipulations in the last 4 weeks, receiving a first CSM treatment, visiting a primary care physician, and younger age. Patients whom have experience prior cervical trauma or neck pain may be at particularly higher risk of experiencing an adverse cerebrovascular event after CSM.

CONCLUSION

The current debate around CSM is notably polarized. Many authors stated that the risk of CSM does not outweigh the benefit, while others maintained that CSM is safe—especially in comparison to conventional treatments—and effective for treating certain conditions, particularly neck pain and headache. Because the current state of the literature may not yet be robust enough to inform definitive prohibitory or permissive policies around the application of CSM, an interim approach that balances both perspectives may involve the implementation of a harm-reduction strategy to mitigate potential harms of CSM until the evidence is more concrete. As noted by authors in the literature, approaches might include ensuring manual therapists are providing informed consent before treatment; that patients are provided with resources to aid in early recognition of a serious adverse event; and that regulatory bodies ensure the establishment of consistent definitions of adverse events for effective reporting and surveillance, institute rigorous protocol for identifying high-risk patients, and create detailed guidelines for appropriate application and contraindications of CSM. Most authors indicated that manipulation of the upper cervical spine should be reserved for carefully selected musculoskeletal conditions and that CSM should not be utilized in circumstances where there has not yet been sufficient evidence to establish benefit.

Introduction

Neck manipulation or adjustment is a manual treatment where a vertebral joint in the cervical spine—comprised of the 7 vertebrae C1 to C7—is moved by using high-velocity, low-amplitude (HVLA) thrusts that cannot be resisted by the patient. These HVLA thrusts are applied over an individual, restricted joint beyond its physiological limit of motion but within its anatomical limit. The goal of neck manipulation, also known as cervical spine manipulation (CSM), is to restore optimal motion, function, and/or reduce pain (Stevinson & Ernst, 2002; Biller et al., 2014; Wynd et al., 2013). CSM is occasionally utilized by physiotherapists, massage therapists, naturopaths, osteopaths, and physicians, and is the hallmark treatment of chiropractors (Coulter et al., 1996).

CSM is used by manual therapists for a large variety of indications including but not limited to neck, upper back, and shoulder/arm pain, as well as headaches, however the use of CSM is controversial among health professionals. This is in part due to increasing reports of patients who have experienced serious adverse events following CSM, putting into question the safety of the treatment. In fact, the safety of CSM has been an issue of significant debate since 1907, when the first adverse event was reported (Rivett, 2006). Much of this debate may be attributed to the lack of agreement between incidence reports of adverse events following CSM, which vary widely across sources. Moreover, there exists substantial disagreement as to whether the benefits of CSM outweigh the risks, given that there currently exists limited evidence for the effectiveness of CSM. Consequently, this paper aims to thoroughly synthesize evidence from the academic literature regarding the potential risks and benefits of cervical spine manipulation utilizing a rapid literature review method.

Methods

Individual peer-reviewed articles were identified through MEDLINE (PubMed), EMBASE, and the Cochrane Library. The search was limited to English language sources concerned with human subjects and published between January 1990 and November 2016.

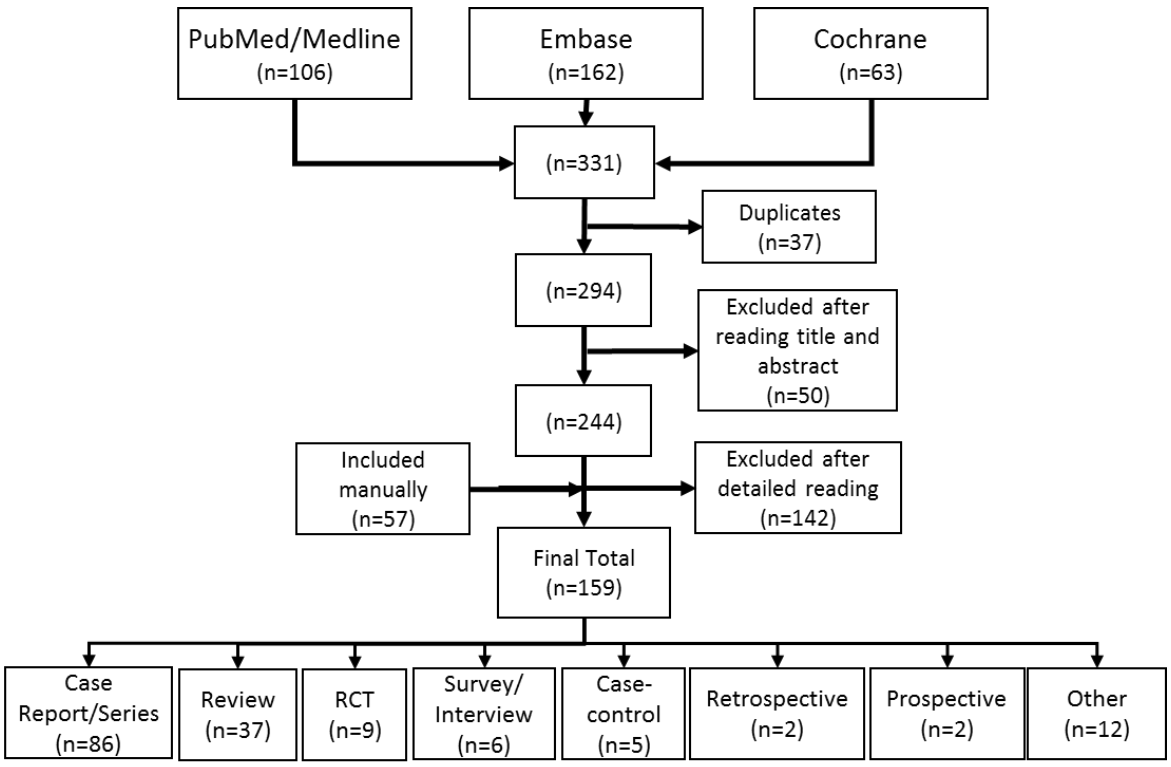
The Medical Subject Heading (MeSH) terms “upper neck manipulation,” “cervical spine manipulation,” “chiropractic adjustment” were used in combination with the following keywords to identify relevant articles and documents for this review: “high velocity”, “low amplitude”, “high neck manipulation”, “chiropractic adjustment”, “chiropractic neck manipulation”, “spinal adjustment”, “spinal manipulation”, “spinal correction”, “vertebral sublaxation”, “upper cervical low force”, “cervical manipulation”, “cervical spine manipulation”, “carotid and vertebral artery dissection”, “arterial dissection”, “vertebrobasilar artery dissection”, “stroke”, “neurological

damage", "educational requirements", "chiropractors", "physicians", "physiotherapists", "osteopaths", "reserved acts", "controlled acts", "risk", "injury", "adverse effects", "complications", "patient safety", "clinical benefit"

All reports which contained data about the benefits and risks associated with cervical spine manipulation were included, regardless of the profession of the therapist or the research methodology used for the report. Articles that did not concern cervical spine manipulation in particular (i.e., investigations of spinal manipulation in general), articles that concerned other typed of manual therapy (i.e., spinal massage, mobilization), dual publications of the same material, articles concerning cases of spinal manipulation for non-therapeutic purposes, and correspondence articles (i.e., Letters to the Editor, Editorials, etc.) were excluded.

Articles were first screened by a reading of the titles and abstracts, and screened again through a thorough review of the full text publication. Figure 1 further illustrates a flowchart for the article selection process for this rapid literature review.

FIGURE 1: SEARCH STRATEGY



Results

A total of 159 references were identified and cited in this updated review: 86 case reports/ case series, 37 reviews of the literature, 9 randomized control trials, 6 surveys/qualitative studies, 5 case-control studies, 2 retrospective studies, 2 prospective studies and 12 others (including cadaveric studies and narrative reviews/overviews from peer-reviewed journals).

The majority of articles obtained concerned case reports of serious adverse events linked to CSM. Case reports are typically reserved for descriptions of medical conditions that are interesting, rare or novel, or associated with serious outcomes (Brighton et al., 2003). The purpose of a case report is to build a foundation for future study or to present information on a given condition where other knowledge is currently limited (Brighton et al., 2003). Case reports and case series are placed at the bottom of the hierarchy of clinical evidence, as they can only provide only anecdotal evidence and contain intrinsic methodological limitations, namely a lack of statistical sampling and an inability to strictly determine causation (Brighton et al., 2003; Burns et al., 2011). Nevertheless, case reports and case series have been instrumental in the recognition of new diseases and adverse outcomes of treatment and can help generate research hypotheses and possible mechanisms of disease (Brighton et al., 2003).

Randomized controlled trials (RCTs) are considered the gold standard for establishing the efficacy or effectiveness of a treatment, and are situated at the top of the hierarchy of clinical evidence—just under systematic reviews and meta-analyses of RCTs (Brighton et al., 2003; Burns, Rohrich, & Chung, 2011). This is because RCT methodology reduces spurious causality and bias (Brighton et al., 2003). 8 of the 9 RCTs found for this review concerned measuring beneficial impacts of CSM, with only 1 attempting to measure possible adverse impacts of CSM on tissue damage, or markers thereof. While RCTs should typically aim to establish potential adverse effects of treatment, all RCTs in this review reported that no serious adverse events occurred through the duration of study.

It is well recognized in the literature that serious adverse events associated with CSM are rare. Thus, in the case with CSM, an RCT is not the best means for establishing clinical evidence around CSM and examining serious adverse events, as rare events may not present during the course of an RCT. Examination of uncommon adverse events using an RCT would require an extremely large sample size, vast financial resources and a substantial time investment (Song & Chung, 2010). Moreover, RCTs usually only inspect one or few variables and may not be able to reflect the full picture of the complexity around CSM (i.e., confounding factors). Consequently, in the case of CSM, several authors in the literature indicated that observational studies—particularly case-

control studies—would be the best means for examining CSM and serious adverse events (Carlesso et al., 2010; Rubinstein et al., 2008; Yin et al., 2014; Wynd et al., 2013).

Whereas an RCT randomizes participants to an exposure (in this case, CSM) or to a control group and then examines outcomes, a case-control study observes subjects in order to determine both their exposure and their outcome status, and the exposure status is thus not determined by the researcher. A case-control study starts instead by identifying a case group that has a particular outcome of interest (i.e., cervical artery dissection, ischemic stroke, radiculopathy) in comparison to a control group without the outcome, and examines possible causal exposures. While case-control studies provide less evidence for causal inference than an RCT, they are appropriate in circumstances where an outcome is rare (Song & Chung, 2010).

ADVERSE EFFECTS OF CERVICAL SPINE MANIPULATION

The results of this rapid literature review confirm that cervical spine manipulation is associated with risk of adverse events. For the purposes of this review, an adverse event is here defined as the sequelae following a CSM with mild, moderate or severe symptoms that have a negative impact on the patient. While the majority of adverse events reported in the literature as associated with cervical spine manipulation were benign and transient, there is still a risk for more serious and life-threatening events. The adverse outcomes of CSM are further discussed in the following sections.

MINOR ADVERSE EVENTS

As noted above, the majority of all adverse events reported to be associated with CSM are typically minor, benign, and transient or self-limiting (Rubinstein, 2008; Gouveia et al., 2009). The minor adverse events associated with CSM include transient neurological symptoms, increased neck pain or stiffness, headache, tiredness and fatigue, dizziness or imbalance, extremity weakness, ringing in the ears, depression or anxiety, nausea or vomiting, blurred or impaired vision, and confusion or disorientation (Hurwitz et al., 2005; Rubinstein, 2008; Stevinson, 2002; Ernst, 2007; Gouveia et al., 2009). The majority of the evidence concerning minor adverse events in the literature pertains to spinal manipulation in general, and data on minor adverse events in reference to CSM in particular is limited.

A meta-analysis of data from multiple randomized controlled trials by Carlesso et al. (2010) found that participants who had received CSM were 1.96 times more likely (RR=1.96; 95% CI (1.09, 3.54); $p < .05$) to experience transient neurological symptoms (i.e., radiating pain or discomfort) for up to 2 weeks post treatment than a comparison. Moreover, the study estimated the incidence of transient neurological symptoms for those receiving CSM to be 194 events per

1000 patients. The authors report that CSM does not result in a significant increase in neck pain (RR=1.25; 95% CI (0.84, 1.87); p > .05). They also purport that the limited number of studies and the design of each study did not allow for analysis of the independent link between CSM and headache, however, their meta-analysis revealed no significant link between headache and CSM combined with cervical spinal mobilization therapy (Carlesso et al., 2010).

A randomized controlled trial by Achalandabaso et al. (2014) which sought to establish whether spinal manipulation was associated with tissue damage markers found that cervical manipulation did not produce significant changes in the creatine phosphokinase (CPK), lactate dehydrogenase (LDH), C-reactive protein (CRP), troponin-I, myoglobin, neuron-specific enolase (NSE), and aldolase blood levels. This trial thus suggests that mechanical strain produced by CSM "seems to be innocuous to the joints and surrounding tissues in healthy subjects." (Achalandabaso et al., 2014; p. 1)

3 RCTs found in this review reported on experiences of minor adverse outcomes of CSM:

- 4.3% of participants experienced minor adverse events (neck soreness and stiffness) from spinal manipulation in an RCT by Boline et al. (1995).
- 16.7% of participants experienced minor adverse events (3 headaches of mild to moderate severity and 1 episode of neck and upper thoracic pain and muscle tension of moderate severity) in an RCT by Goertz et al. (2016)
- 30.4% participants (n=85) had 212 adverse symptoms as a result of spinal manipulation or mobilization (increased neck pain or stiffness reported by 25% of the participants with headache and radiating pain reported less commonly) in an RCT by Hurwitz et al. (2005). Authors did not report on the number of adverse events experienced by the spinal manipulation group independently, but reported that "patients randomized to manipulation were more likely than those randomized to mobilization to have an adverse symptom occurring within 24 hours of treatment (adjusted odds ratio [OR] = 1.44, 95% confidence interval [CI] = 0.83, 2.49)

Sample sizes in these RCTs were small, ranging from 50 to 280 participants, meaning that the reported incidence of minor adverse events following CSM in these RCTs may not be generalizable to reflect actual population-level incidence.

A prospective national survey of U.K. chiropractors by Thiel et al. (2007) that examined treatment outcomes obtained from 19,722 patients found that "minor side effects with a possible neurologic involvement were more common." The highest risk immediately after treatment was fainting/dizziness/light-headedness in, with an incidence of approximately 16 per 1000 treatment consultations. Up to 7 days after treatment, reported risks included headache with an

approximate incidence of 4 per 100; numbness/tingling in upper limbs at approximately 15 per 1000 and fainting/dizziness/light-headedness at approximately 13 per 1000 treatment consultations.

More rigorous evidence on the incidence of minor adverse events following CSM is not currently available; however, it is estimated that about 50% of all chiropractic patients experience such minor adverse effects after treatment (Ernst, 2002) and the frequency of all adverse events following general spinal manipulation is estimated to vary between 33% and 60.9% (Gouveia et al., 2009).

SERIOUS ADVERSE EVENTS

Evidence in the literature suggests that serious adverse events after CSM are rare; however, it is also acknowledged that the incidence of serious adverse events is typically underestimated due to a lack of quality studies as well as underreporting by practitioners (Gouveia et al., 2009; Ernst, 2007). Currently there is a paucity of research around estimates of incidence of serious adverse events. Current estimates vary widely, and range from 1 in 200,000 to 1 in several million cervical spine manipulations (Thiel et al., 2007). The above mentioned prospective national survey by Thiel et al. (2007) indicated no reports of serious adverse events from 28,807 treatment consultations and 50,276 cervical spine manipulations which, as the authors contend, "translates to an estimated risk of a serious adverse event of, at worse1 per 10,000 treatment consultations immediately after cervical spine manipulation, 2 per 10,000 treatment consultations up to 7 days after treatment and 6 per 100,000 cervical spine manipulations.

If serious adverse events are in fact rare after CSM and the goal is to establish CSM as a cause of these adverse events, the best type of study to investigate the risk of CSM would be case-control studies, because subjects are selected from the outset by their outcome status (Song & Chung, 2010). This rapid literature review only found five case-control studies investigating risk of adverse events following CSM, and these concerned risk of stroke only (Dittrich et al., 2007; Cassidy et al., 2008; Rothwell et al., 2001; Engelter et al., 2013; Smith et al., 2003). The majority of evidence in the literature relied upon case reports and case series (n=86 articles), which are classified on the lowest level of evidence in the hierarchy of research designs, due to high level of bias and lack of control of confounding factors (Burns, Rohrich, & Chung, 2012; Brighton et al., 2003). Appendix A details results from each case report/case series article. Serious adverse events associated with CSM in the literature are discussed in depth below and can be characterized by their impact on cerebrovascular, neurological, musculoskeletal systems.

Cerebrovascular

According to the literature, CSM comes with a risk for cerebrovascular complications, which are postulated to be a result of physical trauma—that likely results during the high-velocity, low-amplitude thrusts applied during CSM—to the vasculature that supplies the brain and spinal cord (Paciaroni & Bogousslavsky, 2009). Damage to the cervical vasculature linked to CSM includes arterial dissection (i.e., longitudinal disruptions in an artery's wall) or occlusion (i.e., blockage or closing of the artery) (Paciaroni & Bogousslavsky, 2009). Both arterial dissection and occlusion can lead to dysfunction of part of the brain supplied by the artery, which can be temporary (i.e., in the form of transient ischemic attacks), or more permanent with lasting deficit (i.e., ischemic stroke). (Kim & Schulman, 2009; Debette & Leys, 2009).

Studies pertaining to cerebrovascular events associated with CSM were the most prolific in the literature acquired for this review. In the case report and case series literature, cerebrovascular events comprised 68.0% (n=66) of adverse events in cases associated with CSM. Dissection or occlusion (including thrombosis) of one or more cervical arteries were reported in 38.1% (n=37) of cases, with 26.8% (n=26) of all dissections or occlusions involving one or both of the vertebral arteries and 10.3% (n=10) pertaining to the dissection of the internal carotid artery. 46.4% (n=45) of all cases reporting cerebrovascular adverse events in the literature explicitly stated that the case involved stroke. Other adverse cerebrovascular events included the development of hematomas at the site of manipulations (8.2%, n=8), cerebrospinal fluid collection in the spinal column and/or brain (3.1%, n=3), cerebellar hemorrhage (2.1%, n=2), intracranial hypotension (2.1%, n=2), and transient ischemic attacks (1.0%, n=1). Table 1 summarizes the findings of serious cerebrovascular adverse events in the case report and case series literature.

Table 1: Summary of Adverse Cerebrovascular Events in Case Reports / Case Series

Type of Cerebrovascular Event	**% (n)**
All Adverse Cerebrovascular Events (n=97 cases)	68.0 (66)
Stroke	46.4 (45)
Dissection	34.0 (33)
Vertebral Artery	23.7 (23)
Internal Carotid Artery	9.3 (9)
Not specified	1.0 (1)
Occlusion/Thrombosis	4.1 (4)
Vertebral Artery	3.1 (3)
Retinal artery occlusion	2.1 (2)
Internal Carotid Artery	1.0 (1)

Basilar artery	1.0 (1)
Haematoma	8.2 (8)
Cerebrospinal fluid collection	3.1 (3)
Cerebellar haemorrhage	2.1 (2)
Intracranial hypotension	2.1 (2)
Transient Ischemic Attacks	1.0 (1)

A total of 5 case-control studies were obtained in this rapid literature review and are further described in table format in Appendix B. Smith and associates (2003) used a case-control study design to review patients <60 years of age with cervical artery dissection from 1995 to 2000 at two academic medical centers to determine whether CSM was an independent risk factor for cervical artery dissection. Results showed a 6-fold increase in vertebral artery dissection and stroke/transient ischemic attack (OR, 6.62; 95% CI, 1.4–30.0) even after adjustment for neck pain before the stroke/transient ischemic attack in the multivariate analysis but showed no significant increase in carotid artery dissection (Smith et al., 2003).

Another case-control study by Engelter et al. (2013) found CSM to be significantly associated with cervical artery dissection-caused stroke cases compared with ischemic stroke from other causes (6.9% versus 0.6%; adjusted OR, 11.9; 95% CI, 4.28–33.2) and compared with healthy subjects (Adjusted OR, 3.6; 95% CI, 1.23–10.7). The authors stated that their "findings suggest a clear association between cervical artery dissection and cervical manipulation therapy." (Engelter et al., 2013; p. 1953)

Some of articles in the literature, however, put into question the association of CSM with cervical artery dissection caused stroke. In another small case-control study, Dittrich et al (2007) found that CSM on its own failed to be significantly associated with cervical artery dissection caused stroke; however, mild mechanical stress including CSM less than 24 hours prior to symptom onset was significantly associated with cervical artery dissection-caused stroke (p=0.01). However, the authors postulated that the lack of significance was due to the small sample size in the study (n=94) and resultant low statistical power. A retrospective review of medical legal cases by Haldeman et al. (2002) also concluded that stroke, particularly vertebrobasilar dissection, should be considered a random and unpredictable complication of any neck movement including cervical manipulation. The authors further state:

> "They may occur at any point in the course of treatment with virtually any method of cervical manipulation. The sudden onset of acute and unusual neck and/or head pain may represent a dissection

> in progress and be the reason a patient seeks manipulative therapy that then serves as the final insult to the vessel leading to ischemia." (p. 1098)

This evidence, however, is anecdotal, did not allow for an appropriate control group (such as in an RCT or case-control study) and therefore cannot deduce any concrete conclusions regarding causation (Haldeman et al., 2002).

A case-control, case-crossover study by Cassidy et al. (2009), which analyzed Ontario administrative data regarding hospitalization for vertebral artery dissection-caused stroke strokes found that, for those under 45 years of age, there was an increased association between chiropractic visits and stroke (OR 1.37; 95% CI 1.04–1.91). However, they also found that visiting a primary care physician was similarly associated with an increased risk of vertebral artery dissection-caused stroke both in those under 45 years of age (OR 1.34; 95% CI 0.94–1.87) and 45 years and older (OR 1.52; 95% CI 1.36–1.67) (Cassidy et al., 2009). The authors suggest that patients with undiagnosed vertebral artery dissection are seeking clinical care for headache and neck pain from both primary care physicians and chiropractors before having a vertebral artery dissection-caused stroke, putting into question the presumed causal link between CSM and stroke. However, the aforementioned study by Engelter et al. (2013) found that prior cervical trauma seemed to be an important environmental determinant of cervical arterial dissection, but was not an independent outcome predictor, implying while prior trauma may be associated with artery dissection, it is not necessarily the cause.

The principal involvement of the vertebral artery could be due to the anatomy of this artery which likely predisposes it to damage during CSM, especially at the C1 and C2 vertebrae (Miley et al., 2008). A number of studies estimated the incidence of vertebral artery dissection or occlusion ranged between one in 5000 to one in 5.8 million manipulations (Miley et al., 2008; Haldeman et al., 2002). Vertebral artery dissection overall is considered rare, with an annual incidence of approximately 1 to 1.5 per 100,000 people (Dziewas et al., 2003). Although vertebral artery dissection accounts for only 2% of ischemic stroke in the general population, it is responsible for nearly 20% of stroke in younger patients less than 40 years old (Dziewas et al., 2003) . While the true incidence of CSM-associated vertebral artery dissection or occlusion is unknown—since many cases are probably asymptomatic, or the dissection produces mild symptoms (Cassidy et al., 2009)—the literature states that the best available estimate of incidence is approximately 1.3 cases attributable to CSM for every 100,000 persons <45 years of age receiving CSM within 1 week of manipulative therapy (Miley et al., 2008; Rothwell et al., 2001).

Vertebral artery dissection or occlusion can result in ischemic stroke. The current best incidence estimate for stroke following CSM comes from a population-based study by Lee et al (2006) that found that vertebral artery dissection-caused stroke (i.e., vasobasiliary artery stroke) affected 0.97 residents per 100,000 population between 1987 and 2003. An ecological study by Boyle et al. (2008) using administrative data from Saskatchewan and Ontario on hospitalizations with discharge diagnoses of vertebral artery dissection-caused stroke found the incidence rate was 0.855 per 100,000 person-years for Saskatchewan and 0.750 per 100,000 person-years for Ontario. The authors did not find any association between population-level changes in the incidence of vertebral artery dissection-caused stroke and population-level rates of chiropractic utilization; however, the study design does not allow for inferences to be drawn at the individual level regarding the association between chiropractic utilization and the risk of VBA stroke (Boyle et al., 2008).

A systematic review by Miley et al. (2008) found that vertebral artery dissection-caused stroke patients under 45 years of age were 5 times more likely than controls to have had CSM within 1 week of the event date (OR=5.03, 95% CI, 1.32– 43.87); there was no significant association for those aged 45 years and older. The authors' review concludes that overall, there is weak to moderate evidence to support causation between CSM and vertebral artery dissection and subsequent stroke, especially in those under 45 years of age (Miley et al., 2008).

The majority of the literature on reported adverse cerebrovascular events associated with CSM are due to the impact of the vertebral artery, but the literature also contained case reports that linked CSM with dissection of the internal carotid artery. Nevertheless, a case series by Hanelin et al. (2003) and a recent systematic review by Chung et al. (2015) both indicated that the current medical literature does not support a clear causal relationship between CSM and internal carotid artery dissection. Moreover, Chung et al. (2015) indicated that the incidence of internal carotid artery dissection following CSM is currently unknown, as no epidemiological studies have attempted an estimate as of yet.

Neurological

Neurological adverse events have been reported to be an important risk of CSM in the literature. For the purpose of this review, only neurological adverse events that occurred as a result of injury to the nerves (radiculopathy) or spine (myelopathy) were considered. It is important to note that neurological adverse events in cases of CSM reported in the literature also sometimes involved musculoskeletal injury, such as vertebral disc herniation, prolapse, or fracture, where injuries to the surrounding musculoskeletal tissues were accompanied with neurological symptoms due to associated nerve or spinal injury (Padua et al., 1996; Ciconni et al., 2014; Kraft et al., 2001). No

epidemiological studies on neurological adverse events following CSM exist to date, and thus estimates of incidence currently do not exist.

A 2001 survey of neurologists by Stevinson et al. found 35 cases—reported by 24 of a total of 239 respondents (10%)—of serious neurological complications occurring within 24 hours of cervical spine manipulation, none of which had been previously reported in the literature (Stevinson et al, 2001). However, only 6 of these cases involved radiculopathy (n=3) or myelopathy (n=3).

Radiculopathy—where one or more nerves are damaged—can come with symptoms such as pain, weakness, numbness, or difficulty controlling specific muscles. Of all the case reports examined in this literature review, radiculopathy was reported in a total of 11.3% (n=11) of cases. Types of symptoms reported in the case reports included severe pain, nerve palsy, diaphragmatic paralysis and dyspnea (laboured breathing), and dysphagia (difficulty swallowing).

Myelopathy—which describes any neurologic deficit related to the spinal cord—can be caused by trauma resulting in a spinal cord injury. Symptoms of myelopathy may vary widely depending on the location and severity of the spinal injury. Of all the case reports examined in this literature review, myelopathy was reported in a total of 5.2% (n=5) of cases. Types of symptoms reported in the case reports included transient paralysis (including a case of Brown- Séquard Syndrome) and general neurological symptoms. 4.1% (n=4) of cases also involved a tear to the dura (tissue that lines the outside of the brain), resulting in neurological symptoms such as dizziness or vertigo.

3 cases concerning adverse neurological events also involved musculoskeletal damage, involving disc protrusions or prolapse. Table 2 summarizes the findings of serious neurological adverse events in the case report and case series literature. Overall, data on neurological adverse events following CSM are limited to individual cases and case series. There is no evidence in the literature available at this time to suggest that this condition is necessarily a consequence of CSM.

Table 2: Summary of Adverse Neurological Events in Case Reports / Case Series

Type of Neurological Event	% (n)
All Adverse Neurological Events (n=97 cases)	20.6 (20)
Radiculopathy	11.3 (11)
Myelopathy	5.1 (5)
Dural tear	4.1 (4)
Musculoskeletal & Neurological	4.1 (4)

Musculoskeletal

In the literature, adverse musculoskeletal events have also been reported to be an important risk to CSM; however there is currently no data regarding the incidence or association of musculoskeletal adverse events to CSM. In the literature on case series acquired for this review, adverse musculoskeletal events included injury to cervical vertebral discs (including herniation, protrusion, or prolapse), vertebrae fracture or subluxation (dislocation), spinal edema, or issues with the paravertebral muscles.

Table 3 summarizes the findings of serious adverse musculoskeletal events in the case report and case series literature. Data on adverse musculoskeletal events following CSM are limited to individual cases and case series and currently there is no evidence to suggest that these issues are necessarily a consequence of CSM.

Table 3: Summary of Adverse Musculoskeletal Events in Case Reports / Case Series

Type of Musculoskeletal Event	% (n)
All Adverse Musculoskeletal Events (n=97 cases)	15.5 (15)
Disc herniation	6.2 (6)
Vertebrae fracture/dislocation	3.1 (3)
Disc prolapse	2.1 (2)
Disc protrusion	2.1 (2)
Edema	1.0 (1)
Paravertebral muscles contracture	1.0 (1)
Musculoskeletal & Neurological	5.1 (5)

PREDICTORS OF ADVERSE EVENTS

The literature highlighted a number of risk factors that may increase a patient's susceptibility to experiencing an adverse event following CSM. Firstly, there is some evidence to suggest that prior cervical trauma and pain is an important predictor for experiencing an adverse cerebrovascular event following CSM (Hurwitz et al., 2005; Dittrich et al., 2007; Cassidy et al., 2008; Engelter et al., 2013). Cassidy et al. (2008) hypothesized that increased risks of vertebral artery dissection-caused stroke associated with chiropractic as well as primary care physician visits "is likely due to patients with headache and neck pain from [vertebral artery] dissection seeking care before their stroke." (p. S176) As previously indicated, Engelter et al. (2013) found prior cervical trauma to be an important predictor of cervical artery dissection in patients who had received CSM—particularly in younger patients—but this prior trauma was not independently associated with cervical artery dissection. This finding provides an alternative explanation to claims made by

other authors who argue that it is the prior trauma to the cervical region that causes cervical artery dissection, and not CSM.

Other risk factors highlighted in the literature included vertebral artery abnormalities or insufficiency, atherosclerotic or other vascular disease, hypertension, connective tissue disorders, receiving multiple manipulations in the last 4 weeks, receiving first CSM treatment, visiting a primary care physician, and younger age (Cagnie et al., 2005; Cagnie et al., 2006; Biller et al., 2014; Todd et al., 2015; Cassidy et al., 2008; Rubinstein et al., 2008). Some of the challenges of determining predictive factors include absence of accurate description of the manipulative procedure used, poor follow-up after treatment so that serious complications are not linked to the manipulative procedure, and lack of a national or international vigilance system and standardized reporting definitions to track the adverse events.

Despite the identified risks for an adverse event following CSM, some authors have speculated that such adverse events are predictable and may be attributed to inadequate judgment and examination by manual therapists, as well as insufficient skill or inappropriate use of techniques (Refshauge et al., 2002). Concerns about the risk for serious adverse events following CSM have led several regulatory bodies to develop and recommend guidelines to assist the clinician or manual therapist to identify patients in whom neck manipulation may be contraindicated (Thomas et al., 2008; Puentedura et al., 2012). These contraindications and red flags are noted in Table 4.

Red flag symptoms may indicate the presence of a contraindicated condition. According to Refshauge et al. (2002), CSM should never be performed when absolute contraindications or red flag symptoms are present. Childs et al. (2005) recommend that contraindications and red flags be used in conjunction with sound clinical reasoning as part of an examination scheme to assist in determining if CSM an appropriate and to prevent possible adverse events.

Table 4: Absolute contraindications to performing cervical spine manipulation (CSM)

Absolute Contraindications	Red Flags
• Acute fracture, dislocation • Acute soft tissue injury • Dislocation • Osteoporosis • Ligamentous rupture • Ankylosing spondylitis • Instability • Rheumatoid arthritis • Tumor • Vascular disease • Infection	• Previous diagnosis of vertebrobasilar insufficiency • Facial/intra-oral anesthesia or paresthesia • Visual disturbances • Dizziness/vertigo • Blurred vision • Diplopia • Nausea • Tinnitus • Drop attacks • Dysarthria

• Vertebral artery abnormalities • Acute myelopathy • Connective tissue disease • Recent surgery • Anticoagulant therapy	• Dysphagia • Any symptom listed above aggravated by position or movement of the neck • No change or worsening of symptoms after multiple manipulations

Manual therapists may use different pre-manipulative testing procedures to assess patients for red flags and contraindications (which may include the taking of detailed histories, pre-manipulative or provocative testing of vertebral arteries, and physical examination of patients before application of CSM). However, the clinical utility of the existing assessment procedures is controversial. In a review by Thomas et al. (2008) of pre-manipulative testing techniques, the authors found that the pre-manipulative use of a Doppler velocimeter—a continuous wave ultrasound to assess the integrity of blood supply to the hindbrain and the effects of cervical spine position on vertebral artery blood flow—may provide a more objective assessment of vertebral artery blood flow than other more provocative tests used by manual therapists. However they also stated that sensitivity, specificity, reliability and thus clinical utility of the test has not yet been established.

Rivett et al. (2000) found there were no meaningful significant differences in blood flow in various head positions, when comparing patients exhibiting positive and those with negative responses to pre-manipulative testing. The pre-manipulative test used was shown to be highly reliable in categorizing subjects as positive or negative, however the authors could not determine the validity of the test nor the clinical value (Rivett et al., 1999). Moreover, Thiel et al. (1994) investigated blood flow velocity with duplex Doppler ultrasonography during a provocative pre-manipulative test called the Wallenberg test, involving sustained extension, rotation, and combined extension/rotation of the neck. No subjects demonstrated abnormal flow patterns during testing, and no meaningful significant differences in mean velocity ratios were found between the control group and another group displaying clinical signs and symptoms of vertebrobasilar insufficiency. The investigators contended that the results failed to support the validity of the Wallenberg test in pre-manipulative screening for vertebrobasilar insufficiency. Similar conclusions were drawn by Côté et al. (1996) who evaluated the validity of the Wallenberg test as a pre-manipulative screening procedure by measuring the vascular impedance to blood flow of the vertebral artery. They reported the sensitivity for increased impedance to flow and positive predictive value as 0% and concluded that the extension/rotation test is of questionable value for screening patients at risk of stroke with CSM. Moreover, Haldeman et al. (2002) were unable to recognize characteristics from a patient's history or examination that would indicate increased risk of a cerebrovascular accident following CSM.

Overall, authors highlighted the questionable validity and reliability of current pre-manipulative testing used by manual therapists (Licht et al., 2000; Thomas et al., 2008; Gross & Kay, 2001; Rivett et al., 1999; Côté et al., 1996). Establishing sensitive, specific, reliable and valid methods of assessing patients for red flag symptoms or contraindications could have substantial beneficial impacts. According to a review by Puentedura et al. (2012) of 134 case reports of adverse events following CSM, "if all contraindications and red flags were ruled out, there was potential for a clinician to prevent 44.8% of [adverse events] associated with CSM." (p. 71)

BENEFICIAL EFFECTS OF CERVICAL SPINE MANIPULATION

While the vast majority of evidence in the literature concerns risks of adverse outcomes associated with CSM, a number of studies in the literature reported benefits. While CSM is used by manual therapists for a large variety of indications including neck, upper back, and shoulder/arm pain, as well as headaches (Biller et al., 2014; Assendelft et al., 1996; Gibbon et al., 2001), the evidence seems to support CSM as a treatment of headache and neck pain only. A recent trial attempted to establish an effect of CSM on blood pressure; however, it found that CSM did not lower systolic nor diastolic blood pressure when compared with a sham procedure (Goertz et al., 2016).

Headache

Several systematic reviews have investigated the effectiveness of spinal manipulation in the management of headaches, particularly tension-type, migraine and cervicogenic headache (Astin & Ernst, 2002; Vernon et al., 2009; Posadzki & Ernst, 2011). A randomized controlled trial performed by Jull et al. (2002) found that cervical spinal joint manipulation and specific exercise targeted to deep neck flexor muscles reduced headache frequency and intensity in patients with cervicogenic headache at short and long-term follow-up. A pilot RCT by Haas et al. (2010) aimed to test the effect of CSM dose (number of CSM treatments received) on cervicogenic headache, as well as the efficacy of CSM across dose conditions. This study showed that a positive effect might be obtained in the range of 8–16 sessions for headache relief in cervicogenic headache, although the authors stated that a dose effect cannot be ruled out at this stage.

There is some evidence in the literature for CSM as a treatment of tension-type headaches as well. A study by Boline et al. (1995) found that participants who received CSM had sustained therapeutic benefit at four weeks after cessation of treatment compared to a group who received amitriptyline—a medication used to treat migraine headaches. The quality of this clinical trial, however, is poor due to the design and failure to blind participants (by using a placebo and sham CSM) to the type of treatment received. A more recently published study by Vernon et al. (2009) found that participants treated with CSM had significantly fewer headaches compared to a

control group receiving sham CSM and participants treated with CSM combined with amitriptyline had statistically significantly fewer tension-type headaches than the control group receiving placebo and sham CSM. Nevertheless, the trial was prematurely stopped due to the small sample size, and thus the reliability and statistical of this study is questionable.

Neck Pain

CSM is a common treatment for non-specific neck pain and there is some evidence in the literature to suggest CSM can provide effective pain relief for at least some neck conditions. Gross et al. (2010) conducted a Cochrane Review that assessed if manipulation or mobilization improves pain, function/disability, patient satisfaction, quality of life, and global perceived effect in adults experiencing neck pain with or without cervicogenic headache or radicular findings. The review found that moderate quality evidence showed cervical manipulation and mobilization produced similar effects on pain, function and patient satisfaction at intermediate-term follow up. The same review found that low quality evidence suggested cervical manipulation may provide greater short-term pain relief than a control (Gross et al., 2010).

A recent randomized control trial found that participants treated with neck manipulation did not experience more rapid recovery than those treated with neck mobilization and concluded that because neck manipulation is not appreciably more effective than mobilization, it therefore cannot be justified on the basis of superior effectiveness (Leaver et al., 2010). Where cervical spine manipulation involves a HVLA thrust beyond a joint's physiological limit of motion (which cannot be resisted by the patient), cervical spinal mobilization instead uses low-velocity, small or large amplitude passive movement techniques within the joint's range of motion and the patient's control (Schroeder et al., 2013). Because the evidence suggests that CSM and cervical spinal mobilization may have similar effects on neck pain, cervical spinal mobilization may be the safer choice for manual therapists, as it is less likely to be associated with serious adverse events (Hurwitz et al., 2004; Hurwitz et al., 2005). However, a systematic review by Schroeder et al (2013) concluded that manipulation or mobilization therapy has limited benefit when compared with physical therapy or exercise in both acute and chronic neck-pain patients.

Discussion

The results of this rapid literature review indicate that CSM is frequently associated with minor adverse events and rarely with serious adverse events. The evidence about serious adverse events, however, relies mostly on case reports and case series. The strongest evidence, in the

form of case-control studies, concerns risk for vertebral artery dissection and ischemic stroke following CSM, though further research is still required to solidify this association.

Many authors purported that the risks associated with CSM outweigh the benefits. This conclusion is likely based on the fact that evidence of the effectiveness of CSM is still very limited and the potential benefits of the technique may not offset the risks, especially considering risks can have substantial consequences. Conversely, many authors argued that conventional treatments (including medication and surgery, for example) pose more risk of serious adverse events for patients than CSM. Such comparisons, however, are problematic as conventional treatments are typically subject to strict postmarket surveillance (in the case of medication) and internal review and evidence-based guidelines (in the case of medical intervention) in order to mitigate harm and ensure treatment efficacy. Accordingly, many authors advocated for establishment of standardized definitions for what constitutes an adverse event, as well as a consistent means for reporting and surveillance of CSM harms (Biller et al., 2014; Carlesso et al., 2010).

The literature indicates that some non-cerebrovascular adverse events might be avoidable by heeding contraindications and detecting red flag symptoms for cervical spine manipulation (Stevinson et al., 2002; Assendelft et al., 1996). Cerebrovascular adverse events are more difficult to prevent because they tend to occur in relatively young adults without known abnormalities, and reported risk factors are numerous with little consensus across manual therapists and disciplines as to which risk factors are pertinent (Stevinson & Ernst, 2002; Biller et al., 2014; Todd et al., 2015; Cassidy et al., 2008; Rubinstein et al., 2008). Although there exist screening protocols for high-risk patients, they have not been shown to be sensitive or specific at identifying patients who are at risk of adverse outcomes from CSM and the extent of their utilization by manual therapists is not known (Licht et al., 2000; Thomas et al., 2008; Gross & Kay, 2001; Rivett et al., 1999; Côté et al., 1996). Further research is required to establish valid and reliable protocol for identifying high-risk patients.

Avoiding practitioners who make use of rotatory techniques for cervical manipulation (Stevinson & Ernst, 2002) and using mobilization (low-velocity passive movements) instead of manipulation of the cervical spine (Di Fabio, 1999; Leaver et al., 2010) might lower the risk of vertebral artery damage. Others argue that even minor unwanted effects are an absolute contraindication to future cervical spine manipulation (Vautravers, 2000).

Further research is required to strengthen evidence for efficacy of CSM for treatment of neck pain and headache, as well as for other indications where evidence currently does not exist (i.e., upper back and shoulder/arm pain, high blood pressure, etc.). In addition, research is required in order to establish whether CSM has a causal relationship with non-cerebrovascular adverse events,

such as adverse neurological or musculoskeletal events. In order to dispel controversy, higher quality evidence that takes into account potential confounders (such as a pre-existing arterial injury or dissection) is required to solidify a causal association between CSM and cerebrovascular accidents. Moreover, research on safety and efficacy of CSM in infants and children is extremely limited (Spigelblatt, 2002; Todd et al., 2015; Vohra et al., 2007). Further research is required to establish safety and efficacy of CSM in this group. Overall, the majority of the sources in the literature called for vigorous assessment of risk versus benefit in consideration of using HVLA cervical spine manipulation, which also involve cost-benefit analyses that compare CSM to other standard treatments (Di Fabio, 1999; Rubinstein et al., 2008; Stevinson & Ernst, 2002; Chung et al., 2015; Carlesso et al., 2010; Bryans et al., 2011; Biondi et al., 2015).

This rapid literature review has several limitations. Although the search strategy was thorough, some relevant published articles may have been missed. High levels of under-reporting or recall bias in the case report and case series literature might distort the overall picture generated. Publication bias could have exerted a similar effect. For instance, it is possible that journals of complementary medicine and chiropractic-authored research are unlikely to publish findings which might be considered 'negative'. Moreover, this search was limited to English language sources (except data from non-English case reports published in English language reviews) and thus may not capture the full extent of research conducted in non-English speaking countries. Evidence that did not investigate the specific impact of CSM was excluded, and consequently this review did not discuss literature in which CSM was utilized but not independently examined. Lastly, this review utilized a rapid literature review methodology which did not involve thorough or systematic evaluation of the quality of studies acquired.

In conclusion, serious complications of cervical spine manipulation seem to be rare, whereas less serious adverse events occur frequently. It should be noted that there exists considerable controversy around the safety and efficacy of CSM. While many authors stated that the risk of CSM does not outweigh the benefit, others maintained that CSM is safe (especially in comparison to conventional treatments) and effective for treating certain conditions, particularly neck pain and headache.

The current debate around CSM is notably polarized, with many authors advocating for the abandonment of CSM due to the risk of adverse events and to the lack of evidence around benefit, while others argue that CSM should be considered safe until the evidence around risk is more clearly established. Because the current state of the literature may not yet be robust enough to inform definitive prohibitory or permissive policies around the application of CSM, an interim approach that balances both perspectives may involve the implementation of a harm-reduction strategy to mitigate potential harms of CSM until the evidence is more concrete. As noted by

authors in the literature, this might include mandating authorized manual therapists (particularly chiropractors who perform the majority of CSM treatments) to inform patients of the risks of cervical spine manipulation—in the same way that patients are informed of the risks of conventional medical or surgical procedures or interventions—before consenting to treatment. In addition, they propose that patients who have received CSM should be provided with information to help in the early recognition of a serious adverse event in order to prevent further injury or harm.

Regulatory bodies should consider working to establish consistent definitions of adverse events following CSM to facilitate effective reporting and surveillance; institute rigorous protocol for identifying high-risk patients before application of CSM; and create detailed guidelines for appropriate application and contraindications for CSM. Most authors indicated that manipulation of the upper cervical spine should be reserved for carefully selected musculoskeletal problems that do not respond to such simple measures as time, massage, exercise, mobilization, longitudinal traction, or over-the-counter medication and especially that CSM should not be utilized in circumstances where there has not yet been sufficient evidence to establish benefit.

Appendix A: Case Reports

Reference	Therapist	Patient (Indication for seeking CSM)	Adverse event	Outcome	Type of Event
Alimi et al. (1996)	Not specified	48-year-old woman (neck pain)	Dissection of right intracranial artery causing Wallenberg's syndrome	Persistent neurological deficit	Cerebrovascular: Dissection, ICA, Stroke
Alimi et al. (1996)	Chiropractor	47-year-old man	Intimal tear of right vertebral artery causing transitory neurological deficits	Bypass surgery, complete recovery	Cerebrovascular: Dissection, VBA, Transient Ischemic Attacks
Beck et al. (2003)	Chiropractor	40-year-old woman	Wallenberg's syndrome	No details provided	Cerebrovascular: Stroke
Beran et al. (2000)	Chiropractor	27-year old woman (shoulder stiffness)	Vertebral artery dissection causing stroke. Symptoms started after a 48-hour delay	Minimal persistent neurological deficit	Cerebrovascular: Dissection, VBA, Stroke
Beran et al. (2000)	Chiropractor	37-year old man (headache)	Vertebral artery dissection causing multiple infarcts. Symptoms started immediately after CSM	Persistent diplopia and ataxia	Cerebrovascular: Dissection, VBA, Stroke
Cerimagic et al. (2007)	Not specified	46-year-old man (neck pain & cervicogenic headaches)	Right vertebral artery occlusion (from the V2 segment distally); stroke (extensive right cerebellar infarction)	Residual stroke sequelae	Cerebrovascular: Occlusion, VBA, Stroke
Chakraverty et al. (2011)	Chiropractor	50-year-old man	Neurological symptoms a few hours after manipulation; spinal cord injury (intramedullary high signal on the right side of the cord was shown at the C2 and C3 levels)	No details provided	Neurological: Myelopathy
Chen et al. (2005)	Chiropractor	72-year-old man (neck pain)	Haematoma of ligamentum flavum at the level of C3-C4 with hemiparesis	Complete recovery after laminectomy	Cerebrovascular: Hematoma
Chung (2002)	'Bonesetter'	46-year-old man	Cervical cord oedema followed by tetraplegia	Residual deficits	Neurological: Myelopathy
Ciconni et al. (2014)	Osteopath	33-year-old woman (neck pain)	Cervico-brachial neuralgia at C6–TI level and sensory-motor deficit in the right arm following day after CSM; lateral body oscillations, contracture of the paravertebral muscles and disc protrusion	No details provided	Musculoskeletal & Neurological: Paravertebral muscles contracture, Disc protrusion, Radiculopathy
Colloca &	Chiropractor	49-year-old woman	None	General subjective	None

Polkinghorn (2003)		with Ehlers-Danlos Syndrome (chronic spine and extremity joint pain)		improvement in neck and back pain and headaches	
Colloca & Polkinghorn (2003)	Chiropractor	43-year-old man with Ehlers-Danlos Syndrome (chronic head, neck, and back pain and bilateral knee pain and secondary complaints of left arm pain and weakness)	None	Improvement in cervical range of motion and self-reported pain and disability	None
Cortazzo & Tom (1998)	Chiropractor	36-year-old man (neck & shoulder pain)	Vertebral artery dissection causing stroke.	Good clinical improvement and resolution of dissection	Cerebrovascular: Dissection, VBA, Stroke
Dandamudi et al. (2013)	Chiropractor	63-year-old male (neck pain)	Left-arm numbness and weakness 30 minutes after CSM; acute ischemic stroke in the right posterior frontal and parietal cortex.	No details provided	Cerebrovascular: Stroke
Devereaux (2000)	Chiropractor	34-year old woman (neck pain)	Vertebral artery dissection causing occipital lobe infarction and hemianopsia. Symptoms started within minutes of CSM	Persistent visual field disturbances	Cerebrovascular: Dissection, VBA, Stroke
Donzis & Factor (1997)	Chiropractor	39-year-old woman	Acute infarction of the ventromedial aspect of the inferior right occipital lobe causing stroke with left peripheral visual field loss. Symptoms started immediately after CSM	Residual stroke sequelae	Cerebrovascular: Stroke
Frisoni & Anzola (1991)	Chiropractor	42-year-old man (torticollis)	Stroke; Horner's syndrome	Residual deficit, facial paresis and pain	Cerebrovascular: Stroke
Frisoni & Anzola (1991)	Chiropractor	39-year-old woman	Vertebrobasilar stroke; Horner's syndrome, C1 vertebral artery dissection	Residual deficit, mild vertigo, decreased sensitivity in face and left limbs, incoordination in lower left limb	Cerebrovascular: Dissection, VBA, Stroke

Frisoni & Anzola (1991)	Chiropractor	49-year-old woman	Vertebrobasilar stroke; cerebellar hemorrhage	Complete recovery after hospitalisation	Cerebrovascular: Stroke
Gamer et al. (2002)	Not specified	37-year-old man	Dissection of carotid artery followed by Horner Syndrome	Not mentioned	Cerebrovascular: Dissection, ICA, Stroke
Garner & Case (1996)	Chiropractor	59-year-old patient	Emboli released from arteriosclerotic internal carotid artery causing partial loss of vision	Permanent visual field defects	Cerebrovascular: Dissection, ICA
Gouveia et al. (2007)	Chiropractor	41-year-old woman (neck pain)	Vertebro-basilar stroke 48 hours after CSM; Horner's syndrome	Residual stroke sequelae	Cerebrovascular: Stroke
Gouveia et al. (2007)	Chiropractor	34-year-old man (neck pain)	Cervical epidural haematoma with C5–C6 level of algic hypostesy and tetraparesis	Emergency laminectomies of C3–C6 with removal of the haematoma were performed, leading to a full recovery	Cerebrovascular: Epidural hematoma, Tetraparesis
Haynes (1994)	Chiropractor	36-year-old woman	Dissecting aneurysm of vertebral artery, thrombo-embolism	No information provided	Cerebrovascular: Dissection, VBA
Heiner (2009)	Chiropractor	38-year-old woman, pregnant	Epidural hematoma extending from the level of the foramen magnum to the C4 level with associated mass effect upon the spinal cord	Residual deficit, mild paresthesias	Cerebrovascular: Epidural hematoma
Hillier & Gross (1998)	Chiropractor	38-year-old woman (neck pain)	Cervical injury causing profuse vomiting, vertigo and Horner's syndrome. Symptoms started 30 min after CSM	No details provided	Neurological: Radiculopathy
Hsieh et al. (2010)	Chiropractor	61-year-old woman (chronic neck soreness and right shoulder pain)	Ventrally herniated disc at the C3/C4 level, which instigated the compression and edema of the spinal cord	Complete recovery	Musculoskeletal: Disc herniation
Izquiedo-Casas et al. (2004)	Chiropractor	37-year-old woman	Dissection of vertebral artery followed by Tetraparesis	Fibrinolysis resulted in complete recanalization of the artery	Cerebrovascular: Dissection, VBA, Tetraparesis
Jacobi et al. (2001)	Physiotherapist	3-month-old girl	Bleeding into adventitia of both vertebral arteries causing ischemia of caudal brainstem with subarachnoid haemorrhage	Death	Cerebrovascular: Stroke
Jay et al. (2003)	Chiropractor	26-year-old woman	Bilateral dissection of vertebral arteries	No details provided	Cerebrovascular:

		(headache and sinusitis)	followed by bilateral occipital-parietal haemorrhagic infarction and visual impairment		Dissection, VBA, Stroke
Jeret & Bluth (2000)	Chiropractor	31-year old woman	Left vertebral artery dissection causing cerebellar infarction	Complete recovery	Cerebrovascular: Dissection, VBA, Stroke
Jeret & Bluth (2000)	Chiropractor	64-year-old man	Dissection of left internal carotid artery causing parietal stroke	No details provided	Cerebrovascular: Dissection, ICA, Stroke
Jeret & Bluth (2000)	Not specified	51-year-old man	Right internal carotid artery dissection causing subcortical stroke	Significant recovery after surgery	Cerebrovascular: Dissection, ICA, Stroke
Jeret (2001)	Chiropractor	34-year-old man (whiplash injury, non-radiating neck pain)	Dural tear causing persistent positional dizziness	Complete recovery	Neurological: Dural tear
Jones et al. (1999)	Chiropractor	Woman-age not indicated	Infarct in left inferior cortex causing right superior homonymous quadrantanopia	Persistent abnormalities	Cerebrovascular: Stroke
Jumper et al. (1996)	Chiropractor	87-year-old man	Retinal artery occlusion. CSM probably released emboli from arteriosclerotic carotid artery	No details provided	Cerebrovascular: Retinal artery occlusion/embolism, Stroke
Ke et al. (2016)	Chiropractor	36-year-old man (neck pain)	Bilateral vertebral artery dissection, pontine infarction, and mild intervertebral disc hernia of C3/C4, C4/C5	Residual stroke sequelae	Cerebrovascular: Dissection, VBA, Stroke
Klougart et al. (1996)	Chiropractor	34-year-old man	Unclear	Death	Unclear
Ko et al (2006)	Doctor of Oriental Medicine	55-year-old man (neck pain)	Retropharyngeal haematoma/aggravation of symptoms; several hours after CSM	Complete recovery after hospitalisation	Cerebrovascular: Haematoma, retropharyngeal
Ko et al (2006)	Doctor of Oriental Medicine	51-year-old woman (neck pain)	Herniated disc (C5/6, 6/7)/both upper extremity pain, sensory deficit and headache; immediate after CSM	Not mentioned	Musculoskeletal: Disc herniation
Kong et al. (2000)	Doctor of Oriental Medicine	32-year-old woman (neck and back pain)	CSF leakage at lower cervical or upper thoracic area (dural tear)/orthostatic headache, nausea and severe dizziness; immediate after CSM	Complete recovery after bed rest	Cerebrovascular & Neurological: Cerebrospinal fluid collection, Dural tear
Kraft et al. (2001)	Orthopaedic surgeon	43-year-old man (tinnitus)	Intracapsular/intraosseous oedema of the facet joints C2/C3, with lesions of the nerve root at C3 causing severe neck pain	No details provided	Musculoskeletal & Neurological: Oedema, Radiculopathy
Kusenov et al.	Chiropractor	29-year-old woman	C5-C6 ventral cervical cerebrospinal fluid	No details provided	Cerebrovascular:

(2013)			collection		Cerebrospinal fluid collection
Lee et al. (2000)	Non-licenced practitioner	30-year-old woman (neck pain)	Stroke (Rt posterolateral medulla oblongata and cerebellum infarction)/transient loss of consciousness vertigo, ataxia, Lt hemiparesis; immediate after CSM	Residual stroke sequelae	Cerebrovascular: Stroke
Leon-Sanches et al. (2008)	Chiropractor	27-year-old woman	Acute vertebral artery thrombosis with infarct in the left cerebellar hemisphere	Death	Cerebrovascular: Thrombosis, VBA, Stroke
Leweke et al. (1999)	Chiropractor	34-year-old woman (neck pain)	Dissection of both vertebral arteries causing cerebellar infarction and stroke. Symptoms developed hours after therapy	Residual neurological deficit	Cerebrovascular: Dissection, VBA, Stroke
Licht et al. (2003)	General practitioner	39-year-old man (neck pain)	Large infarction in the left cerebellar hemisphere (presumably due to arterial dissection)	Complete recovery	Cerebrovascular: Dissection, Stroke
Lipper et al (1998)	Chiropractor — CSM with high velocity thrust	58-year-old woman (neck pain)	Contusion of upper spinal cord causing Brown–Séquard syndrome. Symptoms started immediately after therapy	Residual neurological deficit	Neurological: Myelopathy
Menendez-Gonzalez et al. (2003)	Chiropractor	33-year-old patient	Dissection of vertebral artery followed by Wallenberg's syndrome	No details provided	Cerebrovascular: Dissection, VBA, Stroke
Michaud (2002)	Chiropractor	42-year-old woman	Wallenburg syndrome, vertebral artery dissection, stroke (lateral medullary infarct)	No details provided	Cerebrovascular: Dissection, VBA, Stroke
Mikkelson et al. (2015)	Chiropractor	37-year old woman	Basilar artery occlusion, stroke (ischemic lesions in the right cerebellar hemisphere)	Minor residual deficits, sensory and cognitive	Cerebrovascular: BA occlusion, Stroke
Misra et al. (2001)	"Untrained person" (barber)	30-year-old man	Vertebral artery insufficiency (temporary loss of consciousness) immediately following CSM, possibly caused by extramedullary, intradural mass compressing spinal cord at C1/C2 and pressing against the VBA.	Permanent neurological deficit	Cerebrovascular: VBA occlusion
Morelli et al. (2006)	Chiropractor	49-year-old man (neck main)	Intracranial hypotension, dural leakage	Complete recovery	Cerebrovascular & Neurological: Dural leakage, Intracranial hypotension
Nadgir et al. (2003)	Chiropractor	34-year-old man	Bilateral internal carotid and vertebral artery dissection	Residual left-side hemianaesthesia	Cerebrovascular: Dissection, VBA,

				and dysaesthesia	Dissection, ICA
Oehler et al. (2003)	Chiropractor	31-year-old woman (headache)	Bilateral dissections of vertebral arteries	No details provided	Cerebrovascular: Dissection, VBA
Oware et al. (1995)	Chiropractor	36-year-old man (low back pain)	Long thoracic nerve palsy with motor axon degeneration causing paraesthesiae, pain and reduced mobility of right arm	No details provided	Neurological: Radiculopathy
Padua et al. (1996)	Chiropractor	67-year-old man (neck pain)	Prolapse of discs C5/C6 and C6/C7 causing radiculopathy. Symptoms developed either during or shortly after CSM	Gradual improvement	Musculoskeletal & Neurological: Disc prolapse, Radiculopathy
Padua et al. (1996)	Not specified	60-year-old man	Disc herniation at C4/C5. Symptoms developed either during or shortly after CSM	Full recovery	Musculoskeletal: Disc herniation
Padua et al. (1996)	Chiropractor	56-year-old man (neck pain)	Protrusion of discs C4/C5, C5/C6 and C6/C7 causing cervical myelopathy. Symptoms developed either during or shortly after CSM	Surgery, gait remained ataxic	Musculoskeletal & Neurological: Disc protrusion, Myelopathy
Padua et al. (1996)	Chiropractor	62-year-old man (neck pain)	Stenoses of spinal canal at C3, C5/C6, C7 causing cervical myelopathy. Symptoms developed either during or shortly after CSM	Surgery, permanent neurological deficit	Neurological: Myelopathy
Parenti et al. (1999)	Chiropractor	50-year-old woman (neck pain)	Left intracranial vertebral artery and carotid artery dissection causing stroke. Symptoms started " a few minutes" after CSM	Gradual improvement	Cerebrovascular: Dissection, VBA & ICA, Stroke
Park et al. (1997)	Acupressure therapist	26-year-old man (headache)	Stroke (extensive infarction of the pons and the Lt cerebellar hemisphere)/loss of consciousness, vertigo; immediate after CSM	Residual stroke sequelae	Cerebrovascular: Stroke
Park et al. (2001)	Non-licenced practitioner	29-year-old woman (neck and shoulder pain)	Atlanto-axial subluxation/pain worsened, headache, neck ROM limitation; immediate after CSM	Complete recovery after hospitalisation	Musculoskeletal: Atlanto-axial subluxation, Limited range of motion in neck
Parwar et al.(2001)	Chiropractor	44-year-old man (strained shoulder muscle)	Dissection of right internal carotid artery causing Horner's syndrome. There was also a subtle dissection of the right vertebral artery	No details provided	Cerebrovascular: Dissection, ICA, Stroke
Peters et al. (1995)	Chiropractor	29-year-old woman (neck pain, vertigo)	Dissection of internal carotid artery causing stroke with somnolence. Acute dissection confirmed by autopsy CT	Death	Cerebrovascular: Dissection, ICA, Stroke
Quintana et al. (2002)	'Native American healer'	62-year-old woman	Dissection of left vertebral artery, infarction of middle left cerebellar hemisphere and vermis	Residual deficit at five months	Cerebrovascular: Dissection, VBA, Stroke
Raskind and	Chiropractor	47-year-old woman	Cerebellar haemorrheae	No information	Cerebrovascular:

North (1990)				provided	Cerebellar haemorrhage
Saxler & Barden (2004)	Chiropractor	27-year-old woman	Epidural haematoma extending from cervical to sacral spine	Complete recovery	Cerebrovascular: Haematoma, epidural
Schmitz et al. (2005)	General medical practitioner	37-year-old patient	Displaced odontoid fracture in the presence of an aneurismal bone cyst	Complete recovery after surgery	Musculoskeletal: Fracture, vertebrae
Schram et al. (2001)	Chiropractor	47-year-old man (neck and shoulder pain)	Phrenic nerve injury, diaphragmatic paralysis, severe dyspnoea	Residual deficit, breathing difficulties	Neurological: Radiculopathy
Sedat et al. (2002)	Chiropractor	42-year-old woman (neck pain)	Dissection of extra-cranial port of the right posterior inferior cerebellar artery	Residual headache and stiffness on discharge from hospital	Cerebrovascular: Dissection, Cerebrallar artery, Stroke
Segal et al. (1996)	Chiropractor	33-year-old woman (neck pain)	Spinal epidural haematoma. Symptoms started 15 minutes after CSM	Haematoma was surgically removed, full recovery	Cerebrovascular: Haematoma, spinal epidural
Siegel et al. (2001)	Chiropractor	33-year-old woman (headache)	Vertebral artery dissection followed by pontine infarct	Permanent, severe neurological deficit	Cerebrovascular: Dissection, VBA, Stroke
Simnad (1997)	Chiropractor	45-year-old woman (tension headache)	Dissection of carotid artery causing complete ophthalmoplegia. Unusual case of previously asymptomatic posterior communicating artery aneurysm	Surgical intervention, full recovery	Cerebrovascular: Dissection, ICA, Stroke
Sivakumaran & Wilsher (1995)	Not specified	65-year-old man (neck pain)	Diaphragmatic palsy (patient remained symptom-free) — a chance finding on routine x-ray	Not applicable	Neurological: Radiculopathy
Sivakumaran & Wilsher (1995)	Chiropractor	49-year-old woman (arthritic pain)	Diaphragmatic palsy causing chronic dyspnoea.	No details provided	Neurological: Radiculopathy
Stevinson et al. (2001)	Chiropractor	46-year-old man	Subdural haematoma	Full recovery after surgery	Cerebrovascular: Haematoma, subdural
Stevinson et al. (2001)	Not specified	Woman-age not indicated	Vertebral artery dissection causing occlusion and stroke with cerebral oedema. Symptoms developed within 4 hours of CSM. Eight further cases of stroke described	Surgical decompression, removal of part of cerebellum, permanent neurological deficit	Cerebrovascular: Dissection, VBA, Stroke
Stevinson et al. (2001)	Chiropractor	46-year-old man	Subdural haematoma. Symptoms developed immediately after CSM	Surgical intervention, full	Cerebrovascular: Haematoma, subdural

				recovery	
Stevinson et al. (2001)	Not specified	42-year-old woman	Prolapse of disc at level C5/C6.	Major residual deficits	Musculoskeletal: Disc prolapse
Stevinson et al. (2001)	Osteopath	32-year-old woman	Radiculopathy at level C6/C7/C8. Symptoms began within 12 hours of CSM	Minor residual deficit	Neurological: Radiculopathy
Suh et al. (2005)	Chiropractor	36-year-old woman (neck and shoulder pain)	Intracranial hypotension	Complete recovery after epidural blood patch	Cerebrovascular: Intracranial hypotension
Sullivan (1992)	Chiropractor	41-year-old woman	Haemorrhage in ventricular system, 8 h	No information provided	Cerebrovascular: Cerebellar haemorrhage
Tinel et al. (2008)	Non-medical practitioner (not specified)	39-year-old woman	Dissection of the left vertebral artery associated with a thrombosis of the vertebra-basilar trunk and a hypoplastic right vertebral artery; stroke (cerebral ischemia of the left cerebellum with extension to the left side of the brainstem)	Residual stroke sequelae	Cerebrovascular: Dissection, VBA, Stroke
Tome´ et al. (2004)	Chiropractor	40-year-old patient	Multiple cervical disc herniation	No details provided	Musculoskeletal: Disc herniation
Trendel et al. (2014)	No details provided	51-year-old man	Acute severe neck pain and dysphagia	Complete recovery	Neurological: Radiculopathy
Tseng et al. (2002)	Not specified	37-year-old man (shoulder pain)	Disc herniation at C4–C5	Complete recovery	Musculoskeletal: Disc herniation
Tseng et al. (2002)	Not specified	38-year-old man (upper back pain)	Disc herniation at C6–C7	Complete recovery	Musculoskeletal: Disc herniation
Tsuboi (2001)	Shiatsu practitioner	80-year-old man (neck and shoulder stiffness)	Retinal artery embolism causing partial loss of vision. Treatment mainly forceful neck massage (it is arguable whether this constitutes CSM)	Permanent ocular effects	Cerebrovascular: Retinal artery occlusion, embolism, Stroke
Wang et al. (1995)	Not specified	32-year-old man	Dissection of right vertebral artery causing basilar artery infarction and stroke	Mild residual neurological deficit	Cerebrovascular: Dissection, VBA, Stroke
Watanabe et al. (1996)	Chiropractor	39-year-old woman	Ischaemic lesion in medulla oblongata causing stroke. Symptoms developed 5 hours after CSM	No details provided	Cerebrovascular: Stroke
Weinstein & Cantu (1991)	Chiropractor	29-year-old man (persistent neck pain)	Stroke (vertebra-basiliar insufficiency)	Complete recovery	Cerebrovascular: Stroke
Wilson et al. (2015)	Chiropractor	32-year-old woman	C5/6 central disc protrusion, ventral epidural cerebrospinal fluid collection from C6 to T7; intracranial hypotension	Complete recovery	Musculoskeletal & Cerebrovascular: Cerebrospinal fluid

					collection, Intracranial hypotension
Wojcik et al. (2003)	Chiropractor	46-year-old woman (neck pain)	Dural tear	Complete recovery	Neurological: Dural tear
Yokota et al. (2003)	Chiropractor	38-year-old man	Dissection of left vertebral artery followed by Dejerine syndrome	No details provided	Cerebrovascular: Dissection, VBA, Stroke
Yoon et al. (2001)	Non-licenced practitioner	18-year-old woman (shoulder pain)	Fracture (C5 body)/neck pain, rotation limitation; immediate after CSM	Complete recovery after hospitalisation	Musculoskeletal: Fracture, vertebrae
Yoshida et al. (2000)	Chiropractor	57-year-old man	Vertebral arteriovenous fistula at C1 level causing radiculopathy of right arm. Vertebral artery dissection due to CSM the most likely cause	Surgical obliteration of fistula, rapid improvement	Neurological: Radiculopathy

Appendix B: Case-Control

Author	Methodology	Population	Measured Events
Cassidy et al (2008)	Population-based case-control and case-crossover study	**Cases:** All residents of Ontario (109 020 875 person-years over 9 y) with posterior circulation strokes admitted to Ontario, Canada, hospitals, identified from discharge and databases. 818 posterior circulation strokes per 100 million person-years. 3164 controls matched to cases. **Case-controls:** 4 age- and sex-matched controls randomly selected from the Registered Persons Database (listing of all healthcare numbers for Ontario)	**Age <45 y** Posterior circulation stroke within 1 wk of any visit • DC: OR, 2.41 (95% CI, 0.98–5.95) • PCP: OR, 2.90 (95% CI, 1.64–5.13) Posterior circulation stroke within 1 wk of headache of cervical DC visit • DC: OR, 3.11 (95% CI, 1.16–8.35) • PCP: OR, 20.00 (95% CI, 4.38–91.28) **Age >45 y** Posterior circulation stroke within 1 wk of any visit • DC: OR, 0.30 (95% CI, 0.12–0.77) • PCP: OR, 2.30 (95% CI, 2.85.3.85) Posterior circulation stroke within 1 wk of headache of cervical DC visit • DC: OR 1.18 (95% CI, 0.16–1.66) • PCP: OR 6.99 (95% CI, 3.93–12.44)
Engelter et al (2013)	Multicenter case-control study (Cervical Artery Dissection and Ischemic Stroke Patients) study in 18 centers in 8 countries designed to assess determinants of CD	**Cases:** 966 cases of CD **Controls:** 651 age- and sex-matched non–CD-IS); 280 healthy subjects.	Any trauma: OR, 7.6 (95% CI, 5.6–10.2) vs non–CD-IS, OR, 3.7 (95% CI, 2.4–5.56) vs healthy subjects CSM: OR, 11.9 (95% CI, 4.28–33.2) vs non–CD-IS, OR, 3.6 (95% CI, 1.23–10.7) vs healthy subjects
Dittrich et al (2007)	Small, single-centre case-control study	Cases: 47 patients with cervical artery dissection cause stroke Controls: 47 patients with stroke of another cause	CSM < 30 days OR, 2.3 (95% CI 0.7–7.2, p=0.16) vs non—CD-IS: NS Mild mechanical stress <24 hours including CSM and cervical artery dissection (p=0.01)

Rothwell et al (2003)	Population-based nested case-control design	All Ontario people admitted to acute care facility with a diagnosis of posterior circulation stroke from January 1993–December 1998	**Age <45 y** • Posterior circulation stroke within 1 wk of DC visit: OR 5.03 (95% CI, 1.32–43.87) • Number of cervical chiropractic visits previous month (≥3 visits): OR, 4.98 (95% CI, 1.34–18.57) **Age >45 y** • Posterior circulations stroke within 1 wk of DC visit: OR, 0.64 (95% CI, 0.25–1.67) • Number of cervical chiropractic visits previous month (≥3 visits): OR, 1.60 (95% CI, 0.31–8.25)
Smith et al (2003)	Institutional database query nested-case control study design	Combined databases of 2 California academic stroke centers for all patients with acute ischemic stroke or TIA from 1995–2000. 1107 cohort, 151 dissections, 306 other identified strokes randomly selected as controls, age and sex matched. Final study group: 51 CAD and 100 controls selected	**Pain before stroke/TIA** • All dissections (n=51): OR, 4.6 (95% CI, 2.1–10) • VAD (n=25): OR 3.8 (95% CI, 1.3–11) • ICAD (n=26): OR 4.7 (95% CI, 1.7–13) **SMT within 30 d** • All dissections (n=51): NS • VAD (n=25): 6.6 (95% CI, 1.4–30) • ICAD (n=26): NS

CD indicates cervical artery dissection; **CI**, confidence interval; **CSM**, cervical spine manipulation; **DC**, doctor of chiropractic; **ICAD**, internal carotid artery dissection; **non–CD-IS**, ischemia from other causes; **NS**, not significant; **OR**, odds ratio; **PCP**, primary care physician; **SMT**, spinal manipulative therapy; **TIA**, transient ischemic attack; and **VAD**, vertebral artery dissection.

Appendix C: Randomized Controlled Trials

Author	Methodology	Population	Experimental Intervention	Control Intervention	Primary Outcome Measure	Main Result
Achalandabaso et al. (2014)	Randomized repeated-measures controlled trial with 3 groups; 3 × 3 mixed-model ANOVA	40 healthy students	CSM (one treatment); SM (one treatment)	Sham spinal manipulation treatment	Tissue damage markers: creatine phosphokinase (CPK), lactate dehydrogenase (LDH), C-reactive protein (CRP), troponin-I, myoglobin, neuron-specific enolase (NSE), and aldolase	Neither cervical manipulation nor thoracic manipulation produced significant changes in the CPK, LDH, CRP, troponin-I, myoglobin, NSE, or aldolase blood levels.
Boline et al. (1995)	RCT with 2 groups	150 patients between 18 and 70 years old with tension-type headaches (for at least 3 months, frequency 1 headache per week)	Weekly 20 minute treatment of SM for 6 weeks with a focus on upper 3 cervical segments	6 weeks treatment with amitriptyline: 10 mg/day in week 1, 20 mg/day in week 2, 30 mg/day in subsequent weeks	Patient reported daily headache intensity, weekly headache frequency, over-the-counter medication usage & functional health status (SF-36) at 4 weeks after treatment cessation compared to baseline	**Experimental group: all changes significant** • 32% reduction in headache intensity • 42% reduction in headache frequency • 30% reduction in use of over-counter medication • 16% improvement in functional health status **Control group: no changes significant** • No improvement or slight worsening compared to baseline
Boyle et al. (2010)	Secondary analysis of a randomized clinical trial (RCT)	47 patients in the treatment arm of a larger RCT, with a primary complaint of mechanical neck pain	CSM as part of multimodal treatment program of manual physical therapy and exercise (6 clinic sessions, twice weekly for 3 weeks, and a home exercise program)	Cervical nonthrust mobilizations (sham CSM) as part of multimodal treatment program of manual physical therapy and exercise (6 clinic sessions, twice weekly for 3 weeks, and a home exercise program)	Neck Disability Index (NDI), 2 visual analog scales for cervical and upper extremity pain, and a 15-point global rating of change scale	• Both subgroups in this secondary analysis demonstrated improvement in short- and long-term pain and disability scores. • Low statistical power ($\beta \leq .28$) and the resultant small effect size indices (–0.21 to 0.17) preclude the identification of any between-group differences. • No serious adverse reactions were reported by patients in either subgroup.

Goertz et al. (2016)	Pilot sham-controlled clinical trial with 2 groups	51 participants with prehypertension or stage 1 hypertension (systolic blood pressure ranging from 135 to 159 mmHg or diastolic blood pressure ranging from 85 to 99 mmHg)	Toggle recoil SM (involves a non-rotary, high-velocity thrust to the C1/C2 vertebrae)	Sham SM treatment	Changes in systolic and diastolic blood pressure	• Adjusted mean change from baseline to week 6 was greater in the sham group (systolic, −4.2 mm Hg; diastolic, −1.6mmHg) than in the SM group (systolic, 0.6mmHg; diastolic, 0.7mmHg), but the difference was not statistically significant. • No serious and few adverse events were noted.
Haas et al. (2010)	2 X 2 balanced factorial design	80 patients with cervicogenic headache	SM (once or twice per week for 8 weeks) (chiropractor)	Gentle massage	Pain and disability	Small dose effects of adjusted mean difference $\leq$5.6
Hurwitz et al. (2005)	Balanced 2 X 2 X 2 factorial design	280 patients with neck pain presenting to 4 southern California health care clinics	SM with or without heat, and with or without electrical muscle stimulation	Mobilization with or without heat and with or without electrical muscle stimulation	Adverse events	• (30.4%) had 212 adverse symptoms as a result of chiropractic care. • Increased neck pain or stiffness was the most common symptom, reported by 25% of the participants. Less common were headache and radiating pain. • Patients randomized to manipulation were more likely than those randomized to mobilization to have an adverse symptom occurring within 24 hours of treatment (adjusted odds ratio [OR] = 1.44, 95% confidence interval [CI] = 0.83, 2.49). • Heat and EMS were only weakly associated with adverse symptoms (heat: OR = 0.94, 95% CI = 0.54, 1.62; EMS: OR 1.09, 95% CI = 0.63, 1.89). • Moderate-to-severe neck disability at baseline was strongly associated with adverse neurologic symptoms (OR = 5.70, 95% CI = 1.49, 21.80).

Jull et al. (2002)	RCT with 4 groups	200 patients with chronic neck disorder with headache	(i) CSM; (ii) EX; (iii) CSM + EX (minimum 8 and a maximum of 12 treatments over 6 weeks, each session no longer than 30 minutes) (physiotherapist)	No intervention	Change in headache frequency from baseline to immediately after treatment and at month 12	At the 12-month follow-up, both SM and EX had significantly reduced headache frequency in comparison to control (P < .05)
Rivett et al. (1999)	Two-group experimental study	20 participants: 16 patients treated with physiotherapy & 4 volunteers	Participants with signs or symptoms indicative of neurovascular ischemia on pre-manipulative testing	Participants with no signs or symptoms indicative of neurovascular ischemia on pre-manipulative testing	Reliability of pre-manipulative testing protocol (verified using duplex Doppler ultrasonography with colorflow imaging)	• The reliability of pre-manipulative testing was supported. • Significant changes in flow velocity of the vertebral artery (and to a lesser extent of the internal carotid artery) were shown in end-range positions involving rotation and extension. • No meaningful significant differences were found between the two groups.
Vernon et al. (2009)	Randomized, placebo-controlled clinical trial with 4 groups	19 healthy adults between the ages of 18 and 50 years and who met the diagnostic criteria of tension type headache	Real cervical manipulation + real amitriptyline; Real cervical manipulation + placebo amitriptyline; Sham cervical manipulation + real amitriptyline	Sham cervical manipulation + placebo amitriptyline	Headache frequency obtained from a headache diary in the last 28 days of the treatment period	• A statistically significant main effect of chiropractic treatment was obtained (−2.2 [−10.2 to 5.8], P = .03) which was just below the 3-day reduction set for clinical importance. • A clinically significant effect of the combined therapies was obtained (−9 [20.8 to 2.9], P =.13), but this did not achieve statistical significance. • Adjusted analysis revealed neither the main effects of chiropractic nor amitriptyline were statistically significant or clinically important; however, the effect of the combined treatments was −8.4 (−15.8 to −1.1) which was statistically significant (P = .03) and reached criterion for clinical importance

RCT, randomized controlled trial; **CSM**, cervical spine manipulation; **SM**, spinal manipulation; **EX**, exercise; **EMS,** electrical muscle stimulation;

Appendix D: Retrospective

Author	Methodology	Population	Measured Events
Dziewas et al. (2003)	Retrospective study via standardised interview of patients with cervical artery dissection to assess preceding traumata, vascular risk factors, presenting local and ischemic symptoms, and patient outcome.	126 patients consecutively admitted to a hospital during the period from 1992 to 2001 with cervical artery dissections.	• Patients with ICAD presented more often with a partial Horner's syndrome and had a higher prevalence of fibromuscular dysplasia than patients with VAD ($p<.01$). • Patients with VAD complained more often of neck pain, more frequently reported a preceding chiropractic manipulation and had a higher incidence of bilateral dissections than patients with ICAD ($p<.01$). • Bilateral VAD was significantly related to a preceding chiropractic manipulation. ($p<.01$) • Multivariate analysis showed that the variables stroke and arterial occlusion were the only independent factors associated with a poor outcome.
Haldeman et al. (2002)	Retrospective review of 64 medical legal cases of stroke temporally associated with cervical spine manipulation.	64 cases where a cerebrovascular ischemic event had occurred following CSM between 1978 and 1994. Cases involved claims of malpractice on the part of the practitioner of manipulation.	• 92% of cases presented with a history of head and/or neck pain and 25% of cases presented with sudden onset of new and unusual headache and neck pain often associated with other neurological symptoms that may represent a dissection in progress. • Strokes occurred at any point during the course of treatment; certain patients reporting onset of symptoms immediately after first treatment while in others the dissection occurred after multiple manipulations. • No apparent dose-response relationship to these complications. • These strokes were noted following any form of standard cervical manipulation technique including rotation, extension, lateral flexion and non-force and neutral position manipulations.
ICAD, internal carotid artery dissection and **VAD**, vertebral artery dissection.			

Appendix E: Prospective

Author	Methodology	Population	Measured Events
Albuquerque et al. (2011)	Prospectively maintained endovascular database was reviewed. Factors assessed: time to symptomatic presentation, location of the injured arterial segment, neurological symptoms, endovascular treatment, surgical treatment, clinical outcome, and radiographic follow-up.	Patients presenting with craniocervical arterial dissections after chiropractic manipulation.	• Thirteen patients (8 women and 5 men, mean age 44 years, range 30–73 years) presented with neurological deficits, head and neck pain, or both, typically within hours or days of chiropractic manipulation. • Three patients had vertebral artery dissections that continued rostrally to involve the basilar artery. • Two patients had ICAD): 1 involved the cervical ICA and 1 involved the petrocavernous ICA. • Clinical follow-up was obtained in all patients (mean 19 months): – Three patients had permanent neurological deficits, and 1 died of a massive cerebellar stroke. – The remaining 9 patients recovered completely.
Licht et al. (2000)	A prospective study at a university hospital vascular laboratory on vertebral artery blood flow in patients with a positive pre-manipulative test for contraindication to spinal manipulative therapy	20 consecutive patients with a positive pre-manipulative referred by chiropractors in private practice from 3 Danish counties.	• No significant difference in peak flow velocity or time averaged mean flow velocity with different head positions was found. • Nineteen of 21 chiropractors would treat a patient with a positive pre-manipulative test if the vascular examination was normal. • Eight of the patients with a positive pre-manipulative test were treated without complications. • Six are now symptom-free, and 2 have improved symptoms. • The remaining 8 patients refused manipulation and continue to have the same symptoms.
CSM, cervical spine manipulation; and **ICAD**, internal carotid artery dissection			

Appendix F: Surveys

Author	Methodology	Population	Key Findings
Adams & Sim (1998)	Self-administered postal questionnaire on practice of and attitudes towards manipulation and its complications.	300 UK manipulative therapists who were members of two professional associations representing differing approaches to manual therapy: the Society of Orthopaedic Medicine (SOM) and the Manipulation Association of Chartered Physiotherapists (MACP)	• Anxiety about possible complications was a prominent reason adduced by 'non-users' and 'partial users' for their avoidance of manipulative procedures. • 19% of users had encountered complications from manipulation, which were most common in the cervical region and were predominantly non-serious. • 12% of therapists had stopped manipulating the cervical spine, or did so only very occasionally; the main reason given was because of the risk of stroke or death and the fear of subsequent litigation. • Of the 21 patients who had experienced complications following manipulation of the cervical spine, 13 (62%) were reported to have undergone pre-manipulative testing. • The majority of SOM members and a minority of MACP members used generalized cervical rotary manipulations — thought by some to be potentially dangerous. • Attitudes to manipulation were generally positive, although overall respondents were uncertain as to whether its benefits outweighed its risks. • Members of the SOM emerged as more frequent users of manipulation and as less conservative in their attitudes to certain aspects of manipulation.
Haldeman et al. (2002)	Self-administered postal questionnaire on clinical perceptions of the risk of vertebral artery dissection after cervical manipulation.	455 licensed chiropractors chosen from the membership database of the Canadian Chiropractic Protective Association (CCPA). The systematic sample was obtained by choosing every eighth chiropractor from the 3,534 members in the CCPA database	• 73.5% of all chiropractic office visits to the respondent chiropractors resulted in some form of cervical adjustment or manipulation • 134,466,765 chiropractic contacts resulted in cervical manipulations during the 10-year study period (1988 to 1997) • An average of 4.3 reports per year with 2.3 cases per year confirmed to have been strokes after a cervical manipulation that resulted in residual symptoms • The likelihood that a chiropractor could anticipate being made aware of a stroke after treatment is approximately 1:8,063,974 office visits or 1:5,846,381 cervical manipulations
Hurley et al. (2002)	82-item, self-administered postal questionnaire on the socio-demographics, practices, opinions of risk, and attitudes towards	150 randomly selected Ontario physiotherapists who perform spinal manipulation.	• Of the 118 respondents who performed spinal manipulation, 41 performed CSM. • Respondents strongly agreed with three out of six indications listed in the survey for applying CSM: segmental fixation, stiff but stable joint, internal derangement (over 70%). • Respondents also strongly agreed (over 88%) that all screening tests listed in the survey should be performed prior to applying CSM: tests for irritability, stability, vascular and

	Clinical Practice Guideline on CSM.		neurological systems. • Respondents rated patient education, other manual therapy, and exercise as the most common adjuncts to CSM (over 88%). • Respondents reported seeing mild complications or side effects only rarely following the application of CSM. Fourteen percent of respondents reported having a written CSM policy or CPG on CSM in their work setting.
Lee et al. (1995)	Self-administered postal survey questionnaire.	Four hundred eighty-six neurologists (all members of the American Academy of Neurology in California) were surveyed, 177 responded.	• 29% (n=51) of respondents reported a total of 102 neurologic complications: 55 strokes, 16 myelopathies, and 30 radiculopathies were reported. • Patients were between the ages of 21 and 60, and the majority experienced complications following cervical manipulation. **Stroke:** • Thirty-seven neurologists (21% of those responding) reported 56 cases of stroke. • Fifty-three strokes (95% of all strokes reported) were in the vertebral artery distribution, compared with only three in the carotid distribution (p less than 0.001, two-tailed binomial test). • Angiographically proven dissection accounted for 25 strokes (45%). For the remainder of the strokes, either the mechanism was unknown or angiography was not performed. • Forty-eight stroke patients (86%) were left with at least mild deficits 3 months after the onset of their strokes. Of those with persistent disability, 46% had marked or severe deficits. **Myelopathy:** • Sixteen cases of myelopathy were reported by 13 neurologists. • Thirteen cases (81%) occurred in the cervical region, one in the thoracic region, and two in the lumbosacral region. • Fourteen of the myelopathy patients (88%) were left with at least mild deficits. Of these, eight (57%) had marked or severe deficits. **Radiculopathy:** • Thirty cases of radiculopathy were reported by 11 neurologists. • Twenty-two cases (73%) occurred in the cervical region. The remainder occurred in the lumbosacral region. • Twenty-nine radiculopathy patients (97%) were left with at least mild deficits. Of these, 16 (55%) had marked or severe deficits.

Stevinson et al. (2001)	Self-administered postal form on the number of cases of serious neurological complications developing within 24 hours of CSM referred to them within a 12 month period (2 August 1998 to 31 July 1999)	323 members of the Association of British Neurologists	• 24 respondents reported at least one case each, contributing to a total of about 35 cases. These included 7 cases of stroke on brainstem territory (4 with confirmation of vertebral artery dissection), 2 cases of stroke in carotid territory and 1 case of acute subdural hematoma. There were 3 cases of myelopathy and 3 of cervical radiculopathy.
Thiel et al. (2007)	Prospective national survey to estimate the risk of serious and relatively minor adverse events following chiropractic CSM.	377 U.K. chiropractors	• Data were obtained from 28,807 treatment consultations and 50,276 cervical spine manipulations. • There were no reports of serious adverse events which translates to an estimated risk of a serious adverse event of: – ~ 1 per 10,000 treatment consultations immediately after cervical spine manipulation – ~ 2 per 10,000 treatment consultations up to 7 days after treatment – ~ 6 per 100,000 cervical spine manipulations. • Minor side effects with a possible neurologic involvement were more common: – The highest risk immediately after treatment: fainting/dizziness/light-headedness at ~ 16 per 1000 treatment consultations. – Up to 7 days after treatment: ▪ headache at ~ 4 per 100 ▪ numbness/tingling in upper limbs at ~ 15 per 1000 ▪ fainting/dizziness/light-headedness at ~ 13 per 1000 treatment consultations
CSM, cervical spine manipulation			

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