Systematic review

Adverse events and manual therapy: A systematic review

Dawn Carnes, Thomas S. Mars, Brenda Mullinger, Robert Froud, Martin Underwood

A B S T R A C T

Objective: To explore the incidence and risk of adverse events with manual therapies.

Method: The main health electronic databases, plus those specific to allied medicine and manual therapy, were searched. Our inclusion criteria were: manual therapies only; administered by regulated therapists; a clearly described intervention; adverse events reported. We performed a meta-analysis using incident estimates of proportions and random effects models.

Results: Eight prospective cohort studies and 31 manual therapy RCTs were accepted. The incidence estimate of proportions for minor or moderate transient adverse events after manual therapy was ~41% (CI 95% 17–68%) in the cohort studies and 22% (CI 95% 11.1–36.2%) in the RCTs; for major adverse events ~0.13%. The pooled relative risk (RR) for experiencing adverse events with exercise, or with sham/passive/controls interventions compared to manual therapy was similar, but for drug therapies greater (RR 0.05, CI 95% 0.01–0.20) and less with usual care (RR 1.91, CI 95% 1.39–2.64).

Conclusions: The risk of major adverse events with manual therapy is low, but around half manual therapy patients may experience minor to moderate adverse events after treatment. The relative risk of adverse events appears greater with drug therapy but less with usual care.

1. Method

1.1. Definitions

We defined manual therapy as: any techniques administered manually, using touch, by a trained practitioner for therapeutic purposes. Throughout our research, depending on the author descriptions, we used the following classification terms for adverse events (Carnes et al., 2010).

- 'Major': medium to long term; moderate or severe intensity
- 'Moderate': medium to long term; moderate intensity
- 'Minor': short term and mild intensity

1.2. Searches and selection

We searched Medline (using OVID), Science Direct, Web of Science, PEDro (Physiotherapy Evidence Database) Index of Chiropractic literature, Cambridge Journals, AMED (Allied and Alternative Medicine Database) and JAMA (Journals American Medical Association) from inception to March 2008 using the following terms and derivatives of them customised for each search engine: (chiropractic, osteopathy, orthopaedic, physiotherapy, manual...
therapist, manipulation, cavitation, mobilisation, articulation, adjustment) AND (adverse event, effect, reaction, outcome, complication, response, side effects, spine, vertebra, muscle, disc, body, vascular, neurological). In addition we tracked citations from articles.

Our inclusion criteria were: randomised controlled trials (RCTs) and prospective cohort studies that contained original data about adverse events from manual therapy delivered by statutory registered professional(s) or a regulated professional(s) in a manual therapy; the intervention or therapy involved physical and/or manual contact with an individual with therapeutic intent, administered without the use of mechanical, automated, electronic, computer or pharmacological aids/products; patients were conscious during the intervention. We excluded mixed and multidisciplinary interventions where the manual therapy effects would be unclear/undeterminable, and self-administered interventions, including exercise programmes.

Two reviewers (DC and TM) searched the databases and selected relevant articles independently. A third party (MU) acted as an arbitrator in cases of uncertainty. The inclusion and exclusion criteria were applied at each stage of the review selection process. At the abstract selection stage we separated the database into RCT and non-RCT manual therapy and adverse event articles. Due to poor reporting of adverse events, especially in the older manual therapy efficacy trials, we decided to review and extract data from RCTs published after the publication of the CONSORT statement (Altman, 1996). The CONSORT group recommended minimum standards for RCT reporting (http://www.consort-statement.org), this included publishing data on adverse events in trials.

1.3. Quality assessment

We used a modified CASP quality appraisal template for the cohort studies (http://www.prru.nhs.uk/Pages/PHD/resources.htm (accessed 4.4.09)). This comprised of 15 different methodological questions, the criteria assessed ranged from generic, for example, was the aim clearly stated?, to specific, for example, was temporality/causation considered? We used a modified musculoskeletal appraisal template for the RCTs (Koes et al., 1995). This is a weighted appraisal system using 17 quality criteria. Each criterion is allocated points depending on importance. Criteria assessed are: the study population, the intervention, the effect and data presentation and analysis. Scores are appointed accordingly and a composite score out of 100 given. The quality assessment enabled us to grade studies from high to low; studies in the upper quartile range of quality scores were classiﬁed as high those in the mid-upper range were classiﬁed as medium; studies in the two lower quartiles (i.e. below half of the appropriate quality criteria were not satisﬁed) were low quality. A sample of papers (10%), were jointly reviewed to check the quality appraisal process: only minor disagreements occurred with some of the weighted scores, and these were not sufﬁcient to unduly affect the ﬁnal classiﬁcation categories.

1.4. Statistical analysis

1.4.1. Prospective cohort studies

We extracted data from the cohort studies on subjects with minor, moderate, or major adverse events. Using a random effects model, we meta-analysed data estimating the incidence of minor/ moderate or major adverse events.

1.4.2. Randomised controlled trials

Firstly, we used all data from the manual therapy arms of selected RCTs to estimate the incidence of minor, moderate or major adverse events using a random effects model in a similar manner to that used for the cohort studies. Secondly, we fitted random effects models to determine the relative risk (RR) of adverse events from manual therapy compared with: exercise, drug therapy, usual general practitioner or medical care, sham, passive or control interventions. Where no adverse events were observed, we estimated the upper half of 95% conﬁdence interval (CI) using the Exact method (Clopper and Pearson, 1934).

2. Results

There were 230 RCT articles selected for full paper review. Our searches identiﬁed 60 non-RCT articles and 36 articles on RCTs that fulﬁlled our inclusion criteria (Fig. 1). To maximise the quality of evidence reviewed we focused our analyses on prospective cohort studies and RCTs only. We report here data from eight prospective cohort studies (nine articles, Table 1) and 31 RCTs (ﬁve articles presented data from the same trials, Table 2). The remaining articles consisted of reviews of literature, questionnaire surveys, quasi-experimental and before and after studies. No deaths, cerebrovascular accidents or stroke were reported in any of the prospective cohort studies or RCTs.

2.1. Prospective cohort studies

Eight prospective cohort studies were speciﬁcally designed to investigate adverse events with manual therapy. These studies represented at least 36,949 manual therapy treatments that included manipulation in 22,898 patients (Table 1).

2.1.1. Major adverse events

Of the eight studies, one (Thiel et al., 2007) reported 14 cases of ‘unbearably severe side effects’ in 4712 treatments (0.13%). Thiel et al. (2007) reported an upper risk rate for ‘serious adverse events’ using Hanley’s ‘rule of three’ (Hanley and Lippman-Hand, 1983) of approximately 0.01% (3/28,109 consultations). Combining all the data from the cohort studies (Table 1) we estimated, an upper 95% CI incidence risk rate of major adverse events (as per our deﬁnition) of 0.007% (0/42,451) after treatment or 0.01% (0/22,833) per patient.

2.1.2. Minor and moderate adverse events

The pooled proportion estimate of incidence of minor or moderate adverse events in patients or after treatment consultations (some patients may have had more than one treatment) was ~41% (95% CI 17–68%). The majority of minor or moderate adverse events reported by patients occurred within 24 h of treatment (53% (Barrett and Breen, 2000), 58% (Leboeuf-Yde et al., 1997), 87% (Senstad et al., 1996b)) and most resolved within 48 h (64% (Cagnie et al., 2004), 74% (Leboeuf-Yde et al., 1997), 94% (Senstad et al., 1996b)). Rubinstein et al. (2007) reported that 72% of adverse events occurred after the first treatment.

2.2. Randomised controlled trials

We identiﬁed 36 papers detailing adverse event data from 31 RCTs, which together represented 5060 participants (Table 2). One hundred and eleven trial papers did not explicitly report any adverse event data; these were excluded from our analyses (Fig. 1).

2.2.1. Major adverse events

There were no reports of any major adverse events in any trial. The 31 RCTs included 2281 participants who received manual therapy and 2779 who received other therapies. Fifteen trials reported that no adverse events occurred regardless of the intervention administered. We estimated an upper incidence rate of
major adverse events of ~0.13% (0/2301) after manual therapy treatment.

2.2.2. Mild and moderate adverse events

The pooled estimate of incidence of recorded minor or moderate adverse events in the manual therapy arms of the RCTs was 22% (95% CI 11.1–36.2%). Meta-analyses of data comparing manual therapy with other interventions are shown in Figs. 2 and 3 (Plots A–D, Plot A exercise vs manual therapy, Plot B medication vs manual therapy, Plot C general practitioner/usual care vs manual therapy and Plot D sham/passive and control interventions vs manual therapy). Manual therapy interventions, which predominately included manipulation, produced more adverse events than general practitioner care (RR 1.91, CI 95% 1.39–2.64); about the same number as exercise (RR 1.04, CI 95% 0.83–1.31), and fewer than drug therapy (RR 0.05 CI 95% 0.0–0.20). There was a non-significant trend for manual therapy to produce more adverse events than sham, passive or control interventions (RR 1.84 CI 95% 0.93–3.62, Fig. 3).

An $I^2$ value of 0% indicates absence of heterogeneity between pooled studies, larger values indicate increasing heterogeneity (Higgins et al., 2003). The $I^2$ statistic in plots A–D shows low statistical heterogeneity, additionally, clinical homogeneity was good and therefore pooling of data was appropriate (Higgins et al., 2003). All studies included manual therapy which included, or could include, manipulation. The exercise interventions arms were similar. The medication arm comparisons were NSAIDs and amitriptyline (Nelson et al., 1998). In a sensitivity analysis, excluding Nelson et al. the pooled data indicated the risk of taking medication was still greater than manual therapy. In the two studies comparing GP and usual care, the ‘interventions’ were matched with usual care plus best practice advice. The sham and passive controls whilst varied did not include manipulation.

3. Discussion

This systematic review of published RCTs and cohort studies confirms that, in line with the reports of others (Senstad et al., 1996a,b; Leboeuf-Yde et al., 1997; Barrett and Breen, 2000; Cagnie et al., 2004; Rubinstein et al., 2007), around half of people treated with manual therapy can expect minor to moderate adverse events after treatment, especially after the first treatment (Rubinstein...
et al., 2007). However, the incidence of major adverse effects is
small; there were no reports of a catastrophic adverse event such as
death or stroke. Importantly, our study provides the first pooling of
data from randomised controlled trials of manual therapy on the
incidence of adverse events. Our analysis shows that the relative
risk of minor or moderate adverse events was similar for manual
therapy and exercise treatments, and for sham/passive/control
interventions. Also, in comparison with manual therapy, the risk of
having an adverse event was greater with drug therapy but less
with general practitioner/usual care.

3.1. Methodological issues

We found an approximate two-fold difference in the rates of
reported mild or moderate adverse events between the prospective
cohort studies and the manual therapy arms of randomised
controlled trials (41% vs 22% respectively). As the cohort studies
were specifically designed to identify adverse events, they might be
expected to give a more accurate assessment, so this finding
suggests under-reporting of adverse events in RCTs. Typically, the
RCTs provided poor descriptions and definitions of adverse events
as they were not the primary outcome measure. Additionally, strict
trial recruitment protocols generally dictate participants have few
risk factors, thereby contributing to a lower reported incidence of
adverse events. However, as long as there was no systematic
reporting bias between the arms within each trial, we have a
reasonable estimate of the relative risk from manual therapy.

Manual therapy has not been subjected to the same scrutiny and
surveillance as pharmacological interventions and there is no
equivalent to post-marketing surveillance as used in the pharma-
aceutical industry. There are methodological difficulties when
collecting and reporting manual therapy adverse event data (Ernst,
2001; Stevinson et al., 2001; Kerry et al., 2008). Unclear definitions,
the variety of manual therapies, different time periods over which
data are collected, whether the patient or the practitioner reports
the adverse event, and varying data collection methods (free
response or tick list choice) all affect analysis and outcome. Addi-
tionally, issues of confidentiality, patient satisfaction, and loss of
patients at follow-up can all influence true incidence figures in
observational studies (Thiel and Bolton, 2006; Thiel et al., 2007).
Reporting bias by both patients and practitioners, patient selection
bias, and patients who may be treated concurrently by other health
professionals and may well self-medicate further affect findings,
and strict adherence to protocols can be difficult (Thiel et al., 2007).

We detected similar risks of adverse events occurring for
manual therapy and for exercise. Although our data showed
manual therapy produced more adverse events than sham, passive
and control interventions this was not statistically significant. This
finding needs to be set against the evidence of effectiveness for
manual therapies in the treatment of low back pain (NICE Guide-
lines, 2009), a condition for which medication is often prescribed.
Four RCTs compared manual therapy with either NSAIDs (any)
(Giles et al., 1999, 2003), diclofenac (Hancock et al., 2007), or
amitriptyline (Nelson et al., 1998). Our meta-analysis showed that
the relative risk of having minor or moderate adverse event with
manual therapy (high velocity thrust) was significantly less than
the risk of taking the medication. Others have estimated the risk of
death from using NSAIDs for osteoarthritis to be 100–400 times the
risk of death from cervical manipulation (Dabbs and Lauretti, 1995).
It has been estimated that lumbar manipulation is 37,000–148,000
times safer than NSAIDs and 55,500–444,000 times safer than
surgery for the treatment of lumbar disc herniation (Oliphant,
2004). Cauda equina syndrome has been calculated to be
7400–37,000 times more likely to occur as a complication of
surgery than from spinal manipulation (Oliphant, 2004).

We estimated the upper 95% confidence interval for risk of a
major adverse event as $0.003\%$, using the Exact method
(according to binomial theory); other studies have used Hanley's
rule of three (Hanley and Lippman-Hand, 1983). Hanley explained
that where no adverse event had been observed one cannot assume
there is no risk simply because none occurred. He suggested that if
no patients ($n$) show an adverse event, then the upper 95%
confident limit for the risk may be estimated as 3/n. Using this method, Thie et al. (2007) estimated the upper 95% confidence limit of risk for serious adverse events following chiropractic care as ~0.01%. Both methods produced data that indicated the risk of major adverse events is low.

Despite our initial search identifying many published articles, editorials, letters and case studies (n = 498) reporting the risk of strokes or cervical artery dissections specifically from cervical manipulation, none were reported in any of the studies we reviewed. However, cohort studies and randomised controlled trials are not the best research method for estimating the frequency of very rare events.

To give a perspective of risk, regardless of care, ~208 adults per 100,000 in the general population may suffer a stroke (Cashley et al., 2008). The background incidence of stroke, based on patient

<table>
<thead>
<tr>
<th>Author</th>
<th>Quality rating</th>
<th>Interventions</th>
<th>MT</th>
<th>n</th>
<th>Exercise n</th>
<th>Drug n</th>
<th>GP/usual care n</th>
<th>Sham passive control n</th>
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<tr>
<td>Bove et al. (1998)</td>
<td>Low</td>
<td>Soft tissue and SM (37) vs soft tissue and placebo manipulation (38)</td>
<td>0</td>
<td>37</td>
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<td>Bronfort et al. (2001)</td>
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<td>SM and low technology exercise (63) vs MedX exercise (60) vs spinal manipulation (64)</td>
<td>16</td>
<td>127</td>
<td>9</td>
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<td>Burton et al. (2000)</td>
<td>Med.</td>
<td>SM (20) vs chemonucleolysis (20) (single injection of chymopapain)</td>
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<td>20</td>
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<td>Cherkin et al. (2001)</td>
<td>Med.</td>
<td>Acupuncture (94) vs massage (78) vs self care education (90)</td>
<td>10</td>
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<td>Chiropractic care (10) vs medical care (9) vs self care education (9)</td>
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<td>5</td>
<td>9</td>
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<td>General exercise (80) vs motor control exercise (80) vs SM (80)</td>
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<td>Giles et al. (1999)</td>
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<td>Needle acupuncture (20) vs NSAI medication (21) vs chiropractic spinal manipulation (36)</td>
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<td>36</td>
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<td>3</td>
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<td>Giles et al. (2003)</td>
<td>Med.</td>
<td>Needle acupuncture (34) vs NSAI medication (40) vs chiropractic SM (35)</td>
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<td>35</td>
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<td>7</td>
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<td>Haas et al. (2004)</td>
<td>Med.</td>
<td>3 visits (8) vs 9 visits (8) vs 12 visits (8)</td>
<td>0</td>
<td>24</td>
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<td>Hancock et al. (2007)</td>
<td>Med.</td>
<td>SM + diclofenac (60) vs placebo SM diclofenac (60) vs SM and placebo diclofenac (59) vs placebo SM and placebo diclofenac (60)</td>
<td>0</td>
<td>120</td>
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<td>119</td>
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<td>Hawk et al. (2005)</td>
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<td>Chiropractic SM and trigger point therapy (54) vs sham SM and efferage (57)</td>
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<td>Med.</td>
<td>Brief pain management programme (201) vs manual physiotherapy (201)</td>
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<td>Med.</td>
<td>Manual therapy (56) vs exercise therapy (53)</td>
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<td>Med.</td>
<td>SM therapy (69) vs low force mimic manoeuvre (69)</td>
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<td>69</td>
<td></td>
<td>3</td>
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<td>Hoving et al. (2002, 2006)</td>
<td>High</td>
<td>Manual therapy (60) vs exercise therapy (59) vs GP care (64)</td>
<td>42</td>
<td>60</td>
<td>39</td>
<td>59</td>
<td>22</td>
<td>64</td>
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<td>Hsieh et al. (2002)</td>
<td>Med.</td>
<td>Backschool programme (48) vs myofascial therapy programme (51) vs joint manipulation (49) vs combined joint manipulation and myofascial therapy (52)</td>
<td>13</td>
<td>101</td>
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<td>6</td>
<td>48</td>
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<td>Hurwitz et al. (2002, 2006)</td>
<td>Med.</td>
<td>Medical care (170) vs medical care + physical therapy (170) vs chiropractic care (169) vs chiropractic care and physical modalities (172)</td>
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<td>Hurwitz et al. (2004, 2005)</td>
<td>Med.</td>
<td>SM with and without heat and with and without EMS (171) vs mobilisation with and without heat and with and without EMS (165)</td>
<td>48</td>
<td>171</td>
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<td>Jull et al. (2002)</td>
<td>Med.</td>
<td>SM (51) vs SM plus exercise (49) vs therapeutic exercise (52) vs control (48)</td>
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<td>100</td>
<td>0</td>
<td>52</td>
<td>0</td>
<td>48</td>
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<td>Nelson et al. (1998)</td>
<td>High</td>
<td>SM (77) vs amitriptyline (70) vs combined (71) vs chiropractic adjustment (9) vs brief massage (8) vs control (6)</td>
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<td>77</td>
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<td>141</td>
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<td>Med.</td>
<td>SM with and without heat and with and without EMS (171) vs mobilisation with and without heat and with and without EMS (165)</td>
<td>48</td>
<td>171</td>
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<td>Santilli et al. (2006)</td>
<td>Med.</td>
<td>SM (53) vs simulated SM (49)</td>
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<td>20</td>
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<td>Med.</td>
<td>Chiropractic (179) vs physiotherapeutic care (144)</td>
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<td>Strunk and Hondras (2008)</td>
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<td>Cervical SM (3) vs combined SM and muscle energy technique (3)</td>
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<td>Low</td>
<td>Cervical SM therapy (83) vs control (detuned interferential) (40)</td>
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<td>83</td>
<td></td>
<td>0</td>
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<td>UK BEAM team (2004)</td>
<td>High</td>
<td>General practice (338) vs exercise (310) vs SM (353) vs SM and exercise (333)</td>
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<td>353</td>
<td>0</td>
<td>310</td>
<td>0</td>
<td>338</td>
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<td>Vicenzino et al. (2001)</td>
<td>Low</td>
<td>Lateral glide mobilisation (8) vs placebo (8) vs control (8)</td>
<td>0</td>
<td>8</td>
<td></td>
<td>0</td>
<td>16</td>
<td></td>
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<tr>
<td>Williams et al. (2003)</td>
<td>Med.</td>
<td>Usual GP care (109) vs GP care and additional 3 sessions of Osteopathic SM (92)</td>
<td>0</td>
<td>92</td>
<td></td>
<td>0</td>
<td>109</td>
<td></td>
</tr>
</tbody>
</table>

**Totals** | 107 | 2301 | 50 | 781 | 57 | 321 | 27 | 372 | 12 | 656 |

characteristics, in those seeking chiropractic care was estimated as ~308 people per 100,000 people per year regardless of treatment (Cashley et al., 2008). Cassidy et al. (2008) found that those under 45 years who had a vertebrobasilar artery stroke were three times more likely than controls to have visited a chiropractor or primary care physician beforehand. Both studies illustrate that those at risk of having a stroke or cervical artery dissection are those who are likely to visit either their general practitioner or manual therapist due to the nature of their symptoms, namely sudden onset severe unusual headache and/or neck pain and stiffness (Cashley et al., 2008; Cassidy et al., 2008).

3.2. Limitations and future research

Our review was comprehensive; we applied our previously developed definition of types of adverse events (Carnes et al., 2010) to allow comparison of data for the different treatment modalities. However, classifying manual therapies was difficult because they are often complex multiple interventions and to truly ascribe causality was impossible in this study.

Time frames for collecting data remain an issue. Some latency may be observed with arterial pathologies, between a few hours and months. Predisposing events may act as triggers, or be a cause. Where there is latency between the observed event and the stroke, the exact aetiology becomes even less clear (Rubinstein, 2008). The multi-factorial nature of cervical artery dissection (Rubinstein et al., 2005) means the exact cause of the pathology is even harder to determine. Many studies in this field are based on retrospective cases, cadavers and Doppler flow measures, all of which have methodological limitations, making research in this field complex.

Further analysis of the nature and type of adverse events also needs to be considered. The rigorous reporting of adverse events in manual therapy efficacy trials is essential to allow for future pooling of data for meta-analysis.
4. Conclusion

Nearly half of patients after manual therapy experience adverse events that are short-lived and minor; most will occur within 24 h and resolve within 72 h. The risk of major adverse events is very low, lower than that from taking medication. We suggest that risk is inherent in all health interventions and should be weighed against patient-perceived benefit and alternative available treatments.

Competing interests

Dawn Carnes, Thomas Mars and Robert Froud are trained Osteopaths, there are no other competing interests

Contributors

Dawn Carnes was the Principle Investigator and managed the review and guarantees the scientific rigour and accuracy of the content of the paper. Tom Mars did the searches, selection of papers, data extraction and analysis with Dawn Carnes. Brenda Mullinger contributed advice and editing assistance, Martin Underwood provided expertise, advice and comments on each successive draft. Robert Froud gave statistical advice and produced the forest plots.

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Ethics

No ethics approvals were required for this research.

References


