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Original article

Adverse events among seniors receiving spinal manipulation and exercise in a randomized clinical trial

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ABSTRACT

Spinal manipulative therapy (SMT) and exercise have demonstrated effectiveness for neck pain (NP). Adverse events (AE) reporting in trials, particularly among elderly participants, is inconsistent and challenges informed clinical decision making.

This paper provides a detailed report of AE experienced by elderly participants in a randomized comparative effectiveness trial of SMT and exercise for chronic NP.

AE data, consistent with CONSORT recommendations, were collected on elderly participants who received 12 weeks of SMT with home exercise, supervised plus home exercise, or home exercise alone. Standardized questions were asked at each treatment; participants were additionally encouraged to report AE as they occurred. Qualitative interviews documented participants' experiences with AE. Descriptive statistics and content analysis were used to categorize and report these data.

Compliance was high among the 241 randomized participants. Non-serious AE were reported by 130/194 participants. AE were reported by three times as many participants in supervised plus home exercise, and nearly twice as many as in SMT with home exercise, as in home exercise alone. The majority of AE were musculoskeletal in nature; several participants associated AE with specific exercises. One incapacitating AE occurred when a participant fell during supervised exercise session and fractured their arm. One serious adverse event of unknown relationship occurred to an individual who died from an aneurysm while at home. Eight serious, non-related AE also occurred.

Musculoskeletal AE were common among elderly participants receiving SMT and exercise interventions for NP. As such, they should be expected and discussed when developing care plans.

1. Background

Neck pain is common and a growing public health concern among seniors (Vaupel et al., 1998; Hartvigsen et al., 2003, 2004). Spinal manipulative therapy (SMT) and exercise are two non-pharmacological therapies with demonstrated effectiveness for neck pain in the general population (Hurwitz et al., 2008; Miller et al., 2010; Kay et al., 2012) including the elderly (Maiers et al., 2013). When considering the clinical utility of any intervention, it is essential to weigh the balance of benefit versus harm (Ioannidis et al., 2004). This may be of greater consequence for an elderly population, where risk of harm is heightened due to general decline in health, competing co-morbid conditions, poorer balance, and slower recovery times. Further, there has been a call for increased research of non-pharmacological treatments in the elderly to minimize the risks associated with pain medication, including complications associated with drug interactions (Fitzcharles et al., 2010; Abdulla et al., 2013).

There are few clinical trials reporting AE associated with SMT and exercise (Gross et al., 2010; Kay et al., 2012) and fewer still that include the elderly (Dougherty et al., 2012). While generally underreported in the literature, studies report AE in 31–56% of adults receiving SMT. These are typically described as non-serious, transient, and musculoskeletal in nature (Cagnie et al., 2004; Hurwitz et al., 2004; Thiel et al., 2007; Rubinstein et al., 2008; Eriksen et al., 2011; Bronfort et al., 2012; Walker et al., 2013). A recent randomized clinical trial (RCT) investigated the occurrence of AE associated with usual chiropractic care (primarily manipulation, soft tissue therapy, range of motion exercises, and mobilization) compared to sham treatment. Among adults aged 20–85 with spine pain, the authors found no difference in relative risk. Further, the authors concluded that AE after chiropractic treatment

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may likely be the result of natural history variation and nonspecific effects (Walker et al., 2013). While the exercise literature has more studies of AE among older adults, it too suffers from under-reporting. One systematic review examined trials investigating progressive strength training in adults over 60 years of age (Liu and Latham, 2010). Among 121 studies identified, 68 assessed AE, 43 of which reported that AE occurred. The majority of AE were musculoskeletal in nature, including muscle strain and joint pain. Serious AE were more rare, and were most commonly falls and cardiovascular events.

AE were systematically collected on a sub-sample of individuals participating in an RCT performed by our group, comparing the effectiveness of spinal manipulative therapy and exercise interventions among seniors with chronic neck pain (Maiers et al., 2013). The purpose of this paper is to report on the AE that were recorded, including occurrence, categorization by seriousness, and type of adverse event by intervention group. Additionally, patients' qualitative experiences with AE are described.

2. Methods

An RCT was conducted to determine the relative short- and long-term effectiveness of spinal manipulative therapy with home exercise (SMT with home exercise), supervised rehabilitative exercise and home exercise (supervised plus home exercise), and home exercise alone for seniors with neck pain (Maiers et al., 2007). Participants needed to have a primary complaint of weekly, mechanical neck pain with an average rating of $\geq$3 (0–10) over the previous two weeks. Additional inclusion criteria consisted of age 65 years or older, independent ambulation and community dwelling, stable pain medication, and a score of $\geq$20 on the Folstein Mini-Mental State Examination (Folstein et al., 1975).

Approval for the trial was granted by the institutional review boards of all participating institutions. Informed consent was obtained from all participants. Risks described in the consent form included pain and muscle soreness with any of the treatments. In addition, it was noted that, while rare, cervical spinal manipulation had been associated with vertebrobasilar stroke (Cassidy et al., 2008).

2.1. Home exercise

Home exercise consisted of four, 45–60 min sessions provided by 9 practitioners (exercise therapists or chiropractors) certified by study investigators to give instruction on standardized exercises and patient education (Maiers et al., 2007). Sessions included basic pain management and postural information and practical demonstrations of body mechanics for common activities of daily living. Simple neck and back exercises to improve flexibility, balance, and coordination were demonstrated and prescribed to do daily at home (American Geriatrics Society Panel on Exercise and Osteoarthritis, 2001). These exercises were individualized based on patient ability and included graded progressions once 20 repetitions of an exercise could be done with proper form.

2.2. Spinal manipulative therapy

Spinal manipulative therapy (SMT) was delivered by 11 chiropractors with a minimum 5 years of clinical practice (Maiers et al., 2007). Areas of the cervical spine treated were identified by pain provocation (Seffinger et al., 2004) and static/motion palpation (Haldeman, 1983) findings. Treatment consisted primarily of manual SMT to induce joint motion, using a diversified, thrust technique. Mobilization, a low velocity type of joint oscillation, was less frequently employed (Peterson & Bergmann, 2011). The patient position, provider contact, and level of force applied were modified to accommodate the age and physical condition of the study participants. Adjunct therapies included limited use of light soft tissue massage, assisted stretching, and hot and cold packs applied to the cervical and upper thoracic area. The number and frequency of treatments was determined by the individual chiropractor, with a maximum of 20 visits.

2.3. Supervised rehabilitative exercise

Supervised rehabilitative exercise consisted of 20, 1-h exercise sessions supervised by one of 9 exercise therapists certified to deliver the intervention by study investigators (Maiers et al., 2007). Exercises were individualized according to patients' abilities in terms of load and repetitions. Supervised exercise sessions expanded on the home exercise program with additional strengthening exercises for the neck and upper torso and progressions to participant tolerance. Exercise therapists supervised each session to monitor form, modify exercises, and provide encouragement to complete repetitions.

2.4. Adverse events data collection

Consistent with CONSORT recommendations (Ioannidis et al., 2004), AE are defined in this paper as “side effects that are harmful.”

Several methods were used to collect AE data on study participants, including standardized solicitation by providers, unsolicited reporting by patients as AE occurred, and qualitative interviews. Standardized questions were employed with the entire sample of individuals in the SMT with home exercise group. Due to a delay in protocol implementation, AE questions were collected in a consecutive convenience sub-sample of those in the supervised plus home exercise ($n = 59$) and home exercise alone ($n = 57$) groups. Questions were asked by providers prior to each treatment visit. Inquiry began with, “Did you experience any side effects or problems after the last treatment?” A simple “yes” or “no” response from the patient was elicited. If “yes,” the patient was asked to describe their experience, which was recorded in a narrative format in the treatment notes. Interventions were modified if necessary, as per the study provider with consultation from the investigative team. Study participants were also encouraged to report AE as they occurred outside their treatment appointments by contacting study staff. In these instances, study clinicians made contact with the participant to document clinical details.

An AE was classified as “severe” if it resulted in incapacitation for more than 24 h, resulting in loss of work, bed rest, or decreased social activities. An adverse event was defined as “serious” if it resulted in permanent or severe disability, hospitalization, or death (http://www.grants.nih.gov/ClinicalTrials_fdaaa/definitions.htm). Severe and serious AE triggered extensive evaluation to determine possible causal relationship, adjudicated by the principal investigator and co-investigative team, who were not blinded to treatment allocation. All serious AE were reported to the IRB.

Qualitative interviews, conducted with all participants at the end of the 12-week intervention phase, created an additional, incidental opportunity to collect information about AE (Maiers et al., 2007). Assured confidentiality, those who consented to be recorded were asked semi-structured questions about satisfaction with care, perceived change, whether study care was worthwhile, and what was liked most and least about study treatment.

2.5. Analysis

Descriptive statistics were used to analyze baseline and clinical characteristics of study participants, as well as AE data collected

during treatment encounters and compliance with study intervention. Categories of AE were defined a priori, reflecting those most commonly reported in the literature (Rubinstein et al., 2008; Liu and Latham, 2010; Eriksen et al., 2011) and added to or revised using an iterative process based on those reported by this sample. Content analysis was used to analyze transcripts of qualitative interview data. Themes that emerged from analysis were organized in NVivo® v9.2 (QSR International Pty Ltd, Victoria, Australia) to quantify their occurrence and explore relationships among them (Miles and Huberman, 1994). Interviews in which AE were indicated in response to any question were identified and used to inform this paper. Other themes that emerged from the qualitative analysis will be reported in a subsequent publication.

3. Results

A total of 241 individuals were enrolled in the study, with comparable baseline demographic and clinical characteristics across groups (Table 1). Results showed statistically significant between-group differences in favor of SMT with home exercise after 12 weeks of treatment, compared to both supervised plus home exercise, and home exercise alone. Compliance, defined as attending 80% of the recommended sessions, was generally high in all three intervention groups. The average number of SMT visits was 15.1 (range 5–19); the average number of supervised exercise sessions was 16.6 (range 0–19). Compliance with exercises done at home was not measured in any of the groups. AE data collection rates are reported in Fig. 1.

3.1. Non-serious adverse events

AE were reported by 130/194 participants on whom complete AE data was collected, with 73% of those reporting 1–2 different types of AE (see Fig. 2). Table 2 describes the different types of AE and their definitions, in addition to their incidence in each randomly assigned group. Compared to the home exercise alone group ($n = 40$), participants randomized to the supervised plus home exercise group reported three times as many AE ($n = 140$), and participants randomized to the SMT with home exercise group reported almost twice as many AE ($n = 74$). The overwhelming majority of AE were musculoskeletal in nature, with over one-third reported as an aggravation of neck pain symptoms. Importantly, no participants withdrew from study participation due to non-serious AE.

One severe, related adverse event occurred during a supervised exercise session when a participant lost his balance and fell to the floor. Imaging confirmed a fracture of the radial head; the participant used a soft sling to immobilize his arm for one week.

Table 1
Baseline demographic and clinical characteristics.

Characteristic	SMT with home exercise	Supervised plus home exercise	Home exercise	Total
N	80	82	79	241
Age (yrs)	71.7 ± 5.2	72.6 ± 5.6	72.7 ± 5.3	72.3 ± 5.4
Gender (% F)	45.0	51.2	44.3	46.9
Duration (median, IQR yrs)	6.5 (2.0–19.0)	7.5 (1.8–20.0)	5.0 (2.0–15.0)	6.0 (2.0–18.0)
Patient-rated neck pain (0–10)	5.3 ± 1.5	4.9 ± 1.3	4.9 ± 1.3	5.1 ± 1.4
Neck disability index (%)	22.8 ± 9.4	22.9 ± 9.2	24.2 ± 9.9	23.3 ± 9.5

SMT = spinal manipulative therapy.

3.2. Serious adverse events

One serious adverse event of unknown relationship occurred to an individual during the intervention phase. This individual died at home of an abdominal aortic aneurysm approximately one week following his fourth treatment session in the supervised plus home exercise group. It is unknown when he had last performed home exercises.

Additionally, eight serious AE occurred during the study and were judged likely to be non-related by study investigators due to their nature and lack of temporal relationship. They include bradycardia and arrhythmia ($n = 2$) and myocardial infarction ($n = 1$) in the chiropractic with home exercise group; pneumonia ($n = 1$), stroke ($n = 1$), and tachycardia ($n = 1$) in the supervised plus home exercise group; and bladder cancer ($n = 1$) and stroke ($n = 1$) in the home exercise group.

Two participants withdrew from the intervention phase due to serious, non-related AE experienced during the intervention phase: one post-stroke; a second due to pneumonia.

3.3. Qualitative interview results

During the post-treatment phase interviews, AE were noted by 38/222 participants, ten of whom raised the issue of their experiences with AE across multiple questions. Aggravation of NP was most commonly cited ($n = 15$), followed by an increase in pain: in general ($n = 9$), in the lower extremity ($n = 6$), and in the upper extremity ($n = 3$). Thirty-four participants inferred an association between their AE and a specific exercise. Descriptions commonly included language that minimized concern over the AE, even accepting AE as a part of treatment: "*I did get a sore neck from the head [retraction against resistance], but they said could happen…I could feel I had really worked the muscles and they felt kind of sore.*" (home exercise patient #8200) Three individuals qualified their negative experience by noting that their provider made modifications to treatment to address AE.

Notably, two participants shared their experience with AE that had a more dramatic impact on activities and quality of life:

"*[Home exercise] made my legs and back and arms and everything else more sore. When I have a lot of pain…you get so tired. It takes your energy away.*"

SMT with home exercise patient #9654.

"*I did exactly what I was supposed to, increased [exercises] gradually, and then all of a sudden my neck got so bad…it took me a couple of weeks with a lot of ibuprofen. I felt like I was a zombie with all that I was taking.*"

Home exercise patient #8107.

Four mentioned co-morbidities that they felt impacted their treatment and were the cause of AE.

"*I have no cartilage in my knee joint and the knee would get uncomfortable about two-thirds of the way through the exercises.*"

Supervised plus home exercise patient #11418.

4. Discussion

The AE identified in this study were primarily musculoskeletal or pain related and non-serious. This is consistent with other literature on SMT and exercise (Thiel et al., 2007; Rubinstein et al., 2008; Liu and Latham, 2010; Eriksen et al., 2011; Evans et al., 2012;

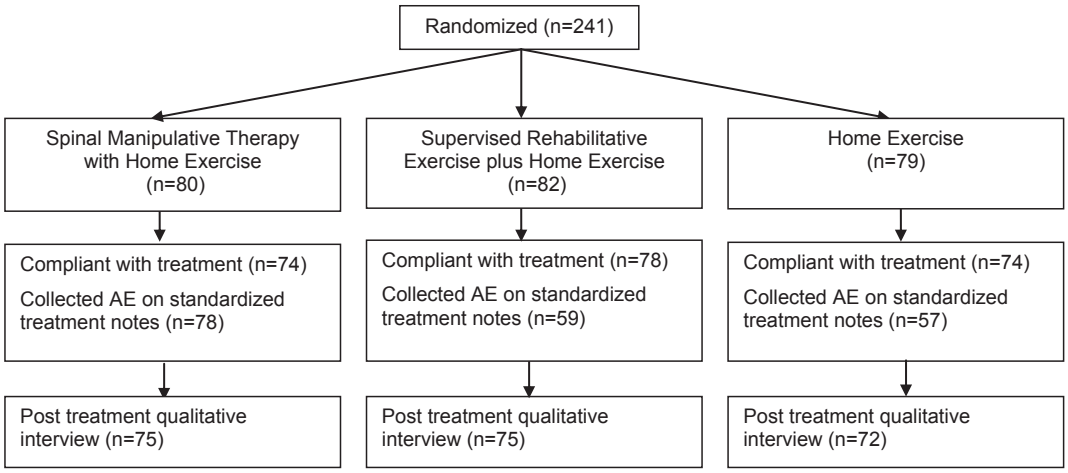

Fig. 1. AE data collection flowchart AE = adverse events.

Walker et al., 2013). Moreover, musculoskeletal AE were so common among study participants that these may be considered normal reactions to SMT and exercise therapies in this population and should be expected. The multimodal intervention groups in this study (supervised plus home exercise and SMT with home exercise) reported more AE; whether that is attributable to an increase in the incidence of AE or increased reporting is uncertain. Aggravated neck pain and muscle soreness were frequently cited, most notably among those in the supervised plus home exercise group. It appears that supervision did not mitigate the provocation of AE among the participants who were randomized to the more intensive exercise program. While further research would be needed to determine thresholds of AE risk relative to exercise intensity in seniors, patients should be made aware of this potential and informed of self care strategies to cope with transient AE. Of note, extremity joint aggravation was a commonly reported AE in this study. Although recommended exercises may focus on the spine, the possibility of extremity joint pain and soreness should be discussed with patients, particularly those who have known arthritic co-morbidities (Neogi and Zhang, 2013).

A patient fall during an exercise session constituted the only severe, related adverse event. While study providers and staff were mindful of taking measures to minimize the risk of falls in our facility, this event underscores the need for close supervision and modification of supervised exercise programs to accommodate functional limitations of some seniors. This is an important clinical consideration for providers implementing exercise interventions with this population.

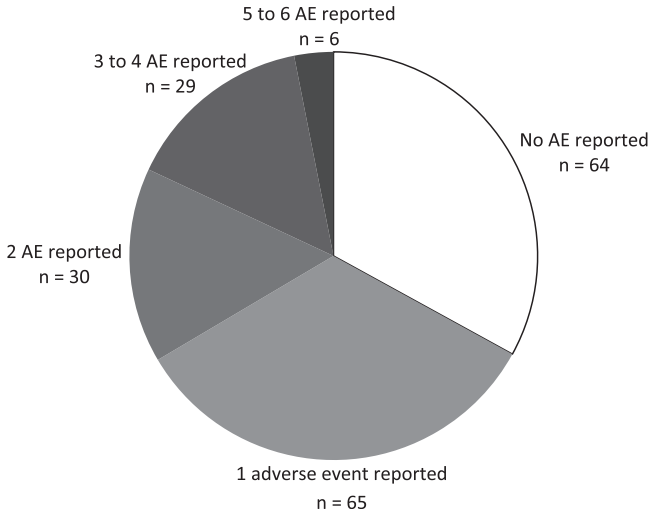

Fig. 2. Number of unique non-serious AE reported per participant. AE = adverse events.

Patients' perceptions are critical to understanding the experience of AE and the extent to which individuals perceive their impact. People tend to underestimate what they consider to be "common" risk (Moore et al., 2008). There may be a misconception among some that non-invasive therapies, like SMT and exercise, are without risk of harm (Carlesso et al., 2011). One qualitative study of expectations for managing pain induced by exercise and mobilization found a range of views, from ambivalence and acceptance of AE as part of the "healing process," to having a negative impact on health-related quality of life (Alami et al., 2011). This study echoed the range of rationales offered by participants to explain or minimize AE. Participants often normalized their AE as part of the therapeutic process or identified co-morbidities like arthritis as underlying culprits. While many participants associated AE with specific exercises, providers were noted for supporting care with modifications to treatment as necessary, to patients' satisfaction.

Another qualitative study of manual therapy patients found greater tolerance for harm when the likelihood of benefit was perceived to be favorable (Carlesso et al., 2011). Prior to study treatment, patients in this RCT reported greater expectations for improvement with the multi-modal groups compared to home exercise alone. Primary results found a clinically important decrease in pain in favor of SMT with home exercise compared with supervised plus home exercise, or home exercise alone, in the short-term (Maiers et al., 2013). Those receiving SMT with home exercise reported fewer AE than those in the supervised plus home exercise group, although less than the home exercise alone group. Providers should discuss possible risk of harm alongside potential benefit from SMT and exercise therapies to better inform shared decision-making by patients (Herxheimer, 2005; Naik et al., 2012). This conversation can provide patients with important alternatives to commonly used pharmacological interventions for neck pain, which may have relatively greater risk of harm (Abdulla et al., 2013).

Stroke is a significant public health concern (US Department of Health and Human Services, 2003); the risk of stroke occurring as an adverse event with exercise and SMT has also been raised as an area of concern (Ernst, 2001, 2002; Mostofsky et al., 2011; Wand

Table 2
Non-serious AE noted by study participants.

Type of adverse event	Definition	SMT with home exercise $n = 78$	Supervised plus home exercise $n = 59$	Home exercise $n = 57$	Total $n = 194$
Aggravated NP	Includes region of occiput to the 3rd thoracic vertebra	29 38% (28–49%)	40 68% (56–79%)	22 39% (27–52%)	91 47% (40–54%)
Muscle soreness	In any region, includes words like “sore” or “aching”	10 13% (8–22%)	26 44% (33–57%)	5 9% (4–19%)	41 22% (16–28%)
LE joint pain	Includes hip, knee, ankle, and toe joints	5 7% (3–15%)	22 38% (27–50%)	5 9% (4–19%)	32 17% (12–23%)
Back pain	Includes thoracic, lumbar, and sacral regions	6 8% (4–16%)	16 28% (18–40%)	3 6% (2–15%)	25 13% (9–19%)
UE joint pain	Includes shoulder, elbow, wrist, and finger joints	7 9% (5–18%)	13 22% (14–35%)	0	20 11% (7–16%)
Stiffness	Any area described with words like “tight” or “stiff”	6 8% (4–16%)	12 21% (12–33%)	1 2% (0–10%)	19 10% (7–15%)
Headache	Includes all types of headache	8 11% (6–19%)	6 11% (5–21%)	2 4% (1–12%)	16 9% (6–13%)
Dizziness	Dizziness or vertigo	1 2% (0–7%)	3 5% (2–14%)	1 2% (0–10%)	5 3% (2–6%)
Radiating symptoms	Pain in UE or LE; not associated with the joints	0	1 2% (1–9%)	1 2% (0–10%)	2 1% (1–4%)
Paresthesia	Numbness or tingling in UE or LE	2 3% (1–9%)	0	0	2 1% (1–4%)
Fatigue	Fatigue, tired or sleepiness	0	1 2% (1–9%)	0	1 1% (1–3%)

Key: LE = Lower extremity; UE = Upper extremity; data presented as *n*, percentage (95% confidence interval).

et al., 2012; Boyne et al., 2013; Biller et al., 2014). Seniors have a 2–6-fold increase in the risk of stroke during the hours immediately following moderate or vigorous physical activity (Anderson et al., 2003; Koton et al., 2004; Krarup et al., 2007; Mostofsky et al., 2011). Regular exercise appears to be protective for stroke overall (Mostofsky et al., 2011), and current recommendations encourage seniors to engage in regular exercise at a level sufficient to challenge their cardiovascular capacity and functional ability (American College of Sports Medicine; Centers for Disease Control and Prevention, 2014). Two participants who suffered a stroke while enrolled in this trial received exercise interventions designed to be mild to moderate in intensity. Both stroke events were determined to be temporally independent from physical exertion or exercise activity, and subsequently deemed non-related.

The incidence of a stroke event associated with SMT is very rare (Haldeman et al., 2001; Cassidy et al., 2008). Further, case–control studies demonstrate this association primarily in adults under the age of 45 (Haynes et al., 2012), suggesting it is a less relevant risk concern for the elderly. A recent analysis of Medicare data in 1.1 million beneficiaries 65–99 years of age compared the incidence of stroke with visits for chiropractic cervical spine manipulation compared to medical primary care. There was no difference in the incidence of any type of stroke between the two groups, and the incidence of vertebrobasilar stroke was negligible (Whedon et al., 2013).

Serious AE occurred in similar numbers across the treatment groups in this study. Although serious AE are infrequent, providers of SMT and exercise therapy should use clinical indicators with caution to identify seniors at increased risk. While the most commonly used screening tests used to identify poor candidates for SMT lack validity (Hutting et al., 2013; Scholten-Peeters et al., 2014), a clinical reasoning framework has been proposed in attempt to guide clinicians through a clinical reasoning process to minimize risk. Recommendations include taking a thorough patient history and considering any physical examination findings that may suggest possible contraindications to care in the context of the full patient presentation and the individual's preferences (Rushton et al., 2014). The lack of clear evidence in this area underscores the need for open communication between providers and patients about what is and is not known about risk, in addition to clinical experience and the patients' expectations for care.

4.1. Strengths

This study is important in that it reports on AE occurring during an RCT. We utilized a detailed protocol to systematically collect AE information, with clear pathways in place to engage study clinicians, participants, investigators, project managers, and the IRB. The design of an RCT may lend itself to better evidence of harms than from epidemiological research (Ioannidis and Lau, 2002). A comparison of harms reported in randomized versus non-randomized studies across several topics demonstrated that non-randomized studies tended to generate more conservative estimates of harm (Papanikolaou et al., 2006). This may be a disadvantage to clinicians when advising their patients of risk. Unfortunately, harm associated with interventions in clinical trials is commonly underreported (Pitrou et al., 2009; Turner et al., 2011) and is further complicated by the use of inconsistent terminology and the absence of reporting standards. Recommendations have been made by the CONSORT group to improve the reporting of harms in clinical trials. These include differentiation between side effects, which do not necessarily imply harm, and AE, defined as side effects that are harmful (Ioannidis et al., 2004). This paper complies with CONSORT recommendations for reporting AE.

4.2. Limitations

This study is limited in the strength of generalizations that can be drawn about AE associated with the therapies used in this study. While the trial was adequately powered to investigate the comparative effectiveness of these treatments on pain, the sample size was too small to detect uncommon AE. A large trial or meta-analysis of several RCTs would be needed provide adequate power to address absolute and relative risks of AE among the elderly with these interventions (Papanikolaou et al., 2006). Further, while a three-month course of treatment may be typical for these therapies, this time frame may be too short to detect all possible AE.

Underreporting could be expected in light of our data collection methods. AE questions were asked by the provider and at the time of treatment; it is possible that the therapeutic relationship between provider and participant may have influenced AE reporting. A standardized process for collecting AE data was late in being implemented with the supervised and home exercise interventions, omitting approximately one quarter of those visits. AE were not asked about specifically during qualitative interviews, nor were interview comments about AE member-checked after analysis or triangulated with clinical records. An attempt to attribute AE to individual trial therapies was not made, primarily because several therapies were combined in the context of study intervention (e.g., SMT with home exercise and supervised plus home exercise).

5. Conclusions

Non-serious musculoskeletal AE were common among elderly study participants receiving SMT and exercise interventions for chronic neck pain. In light of their high occurrence, these AE may be regarded as normal reactions to SMT and exercise and should be anticipated and discussed by care providers with their patients.

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