Neuromusculoskeletal Medicine (OMT) Review Article

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Dropout associated with osteopathic manual treatment for chronic noncancerous pain in randomized controlled trials

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Abstract

Context: Reviews exploring harm outcomes such as adverse effects (AE), all cause dropouts (ACD), dropouts due to inefficacy, and dropouts due to AE associated with osteopathic manipulative treatment (OMT) or osteopathic manual therapy (OMTh) are scant.
Objectives: To explore the overall AE, ACD, dropouts due to inefficacy, and AE in chronic noncancerous pain (CNCP) patients receiving OMTh through a systematic review of previous literature.
Methods: For this systematic review and meta-analysis, the authors searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Physiotherapy Evidence Database (PEDro), EMCare, and Allied and Complementary Medicine Database (AMED), and Ostmed.Dr, as well as the bibliographical references of previous systematic reviews evaluating OMTh for pain severity, disability, quality of life, and return to work outcomes. Randomized controlled trials with CNCP patients 18 years or older with OMTh as an active or combination intervention and the presence of a control or combination group were eligible for inclusion. In this sub-study of a previous, larger systematic review, 11 studies (n=1,015) reported data that allowed the authors to perform meta-analyses on ACD and dropouts due to AE. The risk of bias (ROB) was assessed with the Cochrane ROB tool and the quality of evidence was determined with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.
Results: The pooled analysis showed that ACD was not significantly different for visceral OMTh (vOMTh) vs. OMTh control (odds ratio [OR]=2.66 [95% confidence interval [[CI]], 0.28, 24.93]) or for OMTh vs. standard care (OR=1.26 [95% CI, 0.84, 1.89]; I^2=0%). Single study analysis showed that OMTh results were nonsignificant in comparison with chemonucleolysis, gabapentin, and exercise. OMTh in combination with gabapentin (vs. gabapentin alone) and OMTh in combination with exercise (vs. exercise alone) showed nonsignificant ACD. Dropouts due to AE were not significantly different, but the results could not be pooled due to an insufficient number of studies.
Conclusions: Most articles did not explicitly report AEs, ACD rates, or dropouts due to AEs and inefficacy. The limited data available on dropouts showed that OMTh was well tolerated compared with control interventions, and that the ACD and dropouts due to AEs were not significantly different than comparators. Future trials should focus on explicit reporting of dropouts along with beneficial outcomes to provide a better understanding of OMTh efficacy.

Keywords: adverse events; chronic noncancerous pain (CNCP); dropouts; osteopathic manipulative therapy (OMTh); osteopathic manipulative treatment (OMT); tolerability.

Chronic noncancerous pain (CNCP) is among the most common reasons for patients to consult general practitioners and specialist pain clinics, with back pain being the most common reason for osteopathic consultations [1–4].

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Management of CNCP is multidisciplinary and, depending on the underlying cause, treatments for CNCP range from pharmacological interventions and psychotherapy to physical treatments such as physiotherapy, chiropractic treatments, massage therapy, and osteopathic manipulative treatment (OMT) or osteopathic manual therapy (OMTh) [5, 6]. Although the same principles are followed in either manual treatment approach, OMT is performed by physicians, whereas OMTh is performed by nonphysicians [7]. Since OMT and OMTh are defined differently based on the specific licensure of the practitioner, we will be referring to both as OMTh throughout the rest of the article. OMTh is reportedly a safe and effective treatment approach and is employed as a primary or adjunctive treatment to manage CNCP [6–9]. OMTh requires a comprehensive understanding of anatomy and physiology based on osteopathic principles, and practitioners use that knowledge to mobilize and influence the patient's body. The risk of complications and adverse effects with OMTh is lesser than with other manipulation techniques [10]; the scope and acceptance of OMTh continues to broaden as considerable advances continue to be made by the osteopathic profession in both research and the politics of healthcare [11–14]. Considering both the benefits and potential risks of any treatment is vital for both patients and healthcare providers to establish realistic expectations and to make informed decisions [15, 16].

Most systematic reviews focus on beneficial outcomes for intervention; however, less than 10% of systematic reviews and meta-analyses explore harm outcomes such as tolerability and adverse effects (AE) [17, 18]. One potential reason that authors of review articles do not focus on harm outcomes is inconsistent reporting of harm outcomes and lack of standardized reporting methods [19]. A meta-analysis as part of a systematic review aims to provide a thorough, comprehensive, and unbiased statistical summary of data from the literature [20, 21]. We recently published another systematic review and meta-analysis exploring the effectiveness of OMTh in CNCP patients [22]. During that review, it became apparent that there is a need to report transparent and critically appraised results from existing literature about the harm effects of OMTh in the management of CNCP.

The existing studies supporting OMTh safety and efficacy suffer from limitations that may contribute to OMTh being misunderstood and underutilized [23–25]. Previous studies [26] have explored the tolerability of OMTh by CNCP in cross-sectional surveys or prospective observational studies; however, since OMTh is a therapeutic hands-on intervention, randomized controlled trials (RCT) are considered a more suitable study design to assess dropout rates and AE. The goal of this review was to explore the tolerability, all cause dropout (ACD), and dropouts due to AE from OMTh.

Methods

To describe harm outcomes such as ACD rates and dropouts due to AE, we reviewed the data from individual studies that were previously reported in a separate systematic review that explored the effectiveness of OMTh in CNCP [22]. The original study was registered with Prospero (#CRD42019125659).

We developed keywords using the MeSH word analyzer (http://MeSH.med.yale.edu/) and developed a broad search strategy that was implemented from database inception to July 2019. We utilized Ovid to search MEDLINE, Embase, EMCare, Allied and Complementary Medicine (AMED), Physiotherapy Evidence Database (PEDRO), and Cochrane Central Register of Controlled Trials (CENTRAL) databases, as well as Ostmed.Dr, for eligible studies. The bibliographical references of previous systematic reviews were also searched for eligible trials. As our goal was to report the AE and dropouts associated with OMTh in relation to studies included in our previous review [22], we did not update our search strategy. The search strategy is provided in the Supplemental Material, which was also published with our previous review [22].

Our eligibility criteria included RCT enrolling patients 18 years or older with CNCP that employed OMTh as an active or combination intervention and involved comparison with any other intervention or control. Eligible trials explored the effectiveness of OMTh on pain severity, disability, QOL, or RTW in CNCP. The methodology, inclusion criteria, and exclusion criteria are reported in the previously published study [22] and we conducted our meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27]. For this review, we included the studies among those reviewed that reported tolerability outcomes such as AE, as well as ACD due to AE and inefficacy.

We excluded RCT that enrolled fewer than 10 participants per arm at baseline or if the author(s) reported composite score. Studies with a focus on cancerous pain, pain developed during pregnancy, headaches, pain due to gynecological abnormalities, irritable bowel syndrome (IBS), or other visceral pain such as prostatitis were also excluded. We excluded crossover trials, as there is a possibility of carry-over effect and methodological challenges limits their applicability [20, 28]. Given that OMTh is governed by a set of principles and uses a combination of methods to treat the body [29], we excluded studies that specifically investigated a single technique without employing additional use of general OMTh.

Data collection and analysis plan

Title, abstract, full text screening, data abstraction, and risk of bias (ROB) were compiled in duplicates and independently by a team of reviewers (H.F., J.B., A.B., A.A.). Included studies and results were compared between independent reviewers and teams, and any discrepancies were reviewed with adjudication with third reviewer (Y.R.). We extracted information about the number of events associated with ACD and dropouts due to AE according to the definition previously reported [30–32]. In previous reviews, all comparators in varying osteopathic studies would be pooled together resulting in high heterogeneity and, therefore, less reliable results. We employed the same

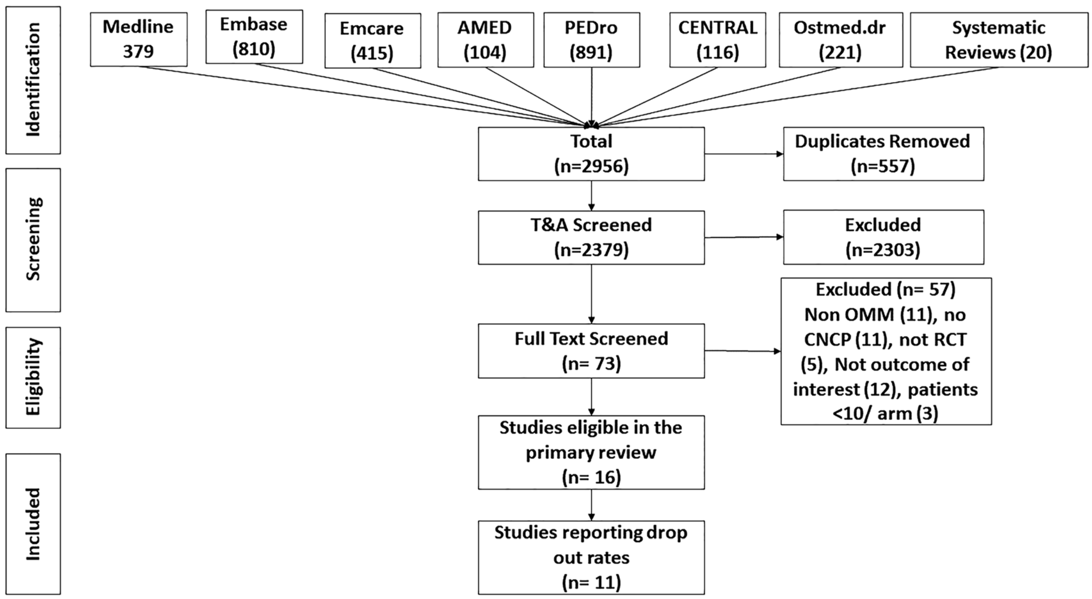

Figure 1: PRISMA flowchart of the included studies.

strategy from the primary study [22] to pool according to the homogeneity between OMTh and the comparator type(s). A previous systematic review with meta-analysis [33] reported no significant difference between exercise and physiotherapy; therefore, in our meta-analysis, we merged physiotherapy and group exercise comparators. Albers et al. [34] and Licciardone et al. [35] were three-arm studies and, based on the similarities between the OMTh applied and comparators, respectively, we merged those two arms.

Quality of evidence

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool [36–39]. GRADE consists of five components: ROB, inconsistency, imprecision, publication bias, and indirectness.

Risk of bias: ROB was analyzed using modified Cochrane ROB tools on the following components: random sequence generation, allocation concealment, blinding of participants, health care providers, outcome assessors, and dropout rates [40].

Heterogeneity (Inconsistency): The heterogeneity of the pooled studies was determined by visual inspection of forest plots and using the I^2 statistic [20]. For heterogeneity, we used a cutoff of 60% or inconsistency in the effect estimates of individual studies on visual inspection of the forest plot [35].

Imprecision: Imprecision was determined with 95% confidence interval (CI).

Publication bias: We did not have 10 or more studies in the pooled analysis and therefore could not assess publication bias.

Indirectness, inconsistency: The clinical characteristics of the participants and width of the 95% CI, respectively, were assessed for indirectness and inconsistency.

Analysis: When possible, we performed meta-analysis in random effect model (REM) and reported results with odds ratio (OR) with 95% CI. The statistical analysis was performed with Review Manager 5.3 (Review Manager RevMan; computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014).

Results

Our search from all databases collectively yielded 2,956 studies by title and abstract screening (Figure 1) [22]. Of the 2,956 titles and abstracts, we included 16 studies in our initial review [22], but only 11 studies [34, 35, 41–49] reported AE and dropout rates in patients (n=1,015). Descriptions of the study characteristics and reported dropouts are given in Table 1 and Table 2.

There was variety in the type of pain between the included studies: five included patients with low back pain [35, 41, 43, 44, 46], while one study was specific to those with sciatica related to lumbar disc herniation (LDH) [41]. Two studies included patients with fibromyalgia [34, 45], one included patients with osteoarthritis [42], one with unspecified musculoskeletal pain [47], one study included patients with chronic shoulder pain [44], and one study with chronic neck pain [48]. The follow up duration ranged from 42 to 365 days. Only three studies explicitly reported [35, 42, 44] that cointerventions were allowed during the trial period.

Table 1: Characteristics of the included studies.

Study	Mean age, years (SD)	Female patients, %	Pain region	Were patients with comorbid psychological and medical conditions included?	Was disability/litigation considered part of exclusion criteria?	Were other medications allowed?	Duration of trial or follow up period, days	Number of participants in intervention group	Number of participants in control or comparison groups
Albers 2017 [34]	54.9 (13.1)	3.3	Fibromyalgia	No	NR	NR	84	34	14
Altinbilek 2018 [42]	54.8 (8.4)	89.4	Knee OA	Yes	NR	No; except for paracetamol	151	44	41
Burton 2000 [41]	41.9 (10.6)	52.5	LBP/LDH	Yes	Yes	NR	365	15	15
Chown 2008 [43]	43.6	58.5	Chronic LBP	Yes	NR	Steroids were not allowed	365	39	59
Knebl 2002 [49]	65-85*	62.1	Chronic shoulder pain	Yes	NR	NR	105		29+
Licciardone 2003 [35]	49.9 (8.0)	64.6	Chronic nonspecific LBP	Yes	Yes	Yes	84	32	34
Licciardone 2013 [44]	40.5 (16.3)	62.5	Chronic nonspecific LBP	Yes	Yes	Yes	56	230	225
Marske 2018 [45]	51.2	93.2	Fibromyalgia	No	NR	NR	42	21	8
Marti Salvador 2018 [46]	18-60*	NR	Chronic nonspecific LBP	No	NR	No	56	33	33
Papa 2012 [47]	77 (6.7)	70.5	Chronic nonspecific body pain	Yes	NR	NR	42	37	35
Schwerla 2008 [48]	35.4–54.2*	75.6	Chronic nonspecific neck pain	No	Yes	NR	84	21	16

OA, Osteoarthritis; LBP, low back pain; LDH, lumbar disc herniation; NR, not reported. *Studies did not report a mean age, only provided a range with no SD. +Knebl [49] only reported the total number of patients involved but did not distinguish between intervention or control groups.

Table 2: Summary of the OMTh and the comparator interventions.

Study	Treatment groups	Osteopathic manipulation	Comparator	Per protocol or clinician-directed	Cointerventions use allowed
					Description
Albers 2017 [34]	OMTh	Direct and indirect techniques (muscle energy, MFR, HVLA, functional techniques, and balanced ligamentous tension) and cranial/sacral techniques	SC	Clinician directed	Pharmaceutical use NR but patients were excluded if they underwent manual therapy treatment or alternative treatment procedures during the study period
Altinbilek 2018 [42]	OMTh + Exercise	Standardized mobilization and compression for bilateral patellofemoral and tibiofemoral joints followed by a lower extremity pumping technique. These techniques are taught to the patient to apply at home as well	Exercise consisted of quadriceps muscle strengthening exercise, leg lifting, and muscle stretching such as iliotibial band, hamstring stretching, strengthening abductor and adductor muscles of the hip	Per protocol	No – Prevented from taking non-steroidal antiinflammatory drugs 1 week before and during the study. Paracetamol up to 3 g/daily was allowed and drugs for systemic conditions continued
Burton 2000 [41]	OMTh	Soft tissue stretching in combination with low amplitude passive articulatory maneuvers and high velocity thrust to the lumbar spine and buttock musculature	Chemonucleolysis under general anesthesia, a single dose of chymopapain	Clinician directed	No – patients with previous manipulations on the same area were excluded
Chown 2008 [43]	OMTh	Soft tissue massage, inhibition, muscle stretching, muscle energy, high velocity thrust (varying), articulation, mobilization, exercise advice, discussion of psychosocial issues, education, nutritional/dietary advice	– Group exercise: Problem identification, anatomy education, home stretching exercise programme, basic postural setting use of transverses, multifidus – Manipulative physiotherapy: Education/advice, joint mobilization, soft tissue mobilization, global exercise for mobility, electrotherapy, postural correction	Clinician directed	No – patients with manipulations such as physiotherapy, acupuncture in the previous 3 months were excluded as well as users of steroids and anticoagulants
Knebl 2002 [49]	OMTh	Treatment was defined as administration of the seven-step Spencer technique which is an articular treatment involving compression, traction, and muscle energy in various planes and axes	The positions of the Spencer technique without administration of the actual corrective forces (isometric muscle contraction)	Per protocol	NR
Licciardone 2003 [35]	OMTh	Combination of MFR, strain–counter strain, muscle energy, soft tissue, high-velocity–low-amplitude thrusts, and cranial–sacral	ROM activities, light touch, and simulated OMTh techniques	Clinician directed	Yes – Usual or other low back care allowed in both arms except OMTh or chiropractic manipulation

Table 2: (continued)

Study	Treatment groups	Osteopathic manipulation	Comparator	Per protocol or clinician-directed	Cointerventions use allowed
					Description
Licciardone 2013 [44]	OMTh	The lumbosacral, iliac, and pubic regions were targeted using high-velocity, low-amplitude thrusts; moderate velocity, moderate-amplitude thrusts; soft tissue stretching, kneading, and pressure; MFR; positional treatment of myofascial tender points; and isometric muscle activation	Sham OMTh involved hand contact, active and passive range of motion, and techniques that simulated OMTh but used such maneuvers as light touch, improper patient positioning, purposefully misdirected movements, and diminished physician force	Clinician directed	Yes – patients could self-initiate LB cotreatments including prescription and non-prescription drugs, exercise programs, lumbar supports, complementary, alternative medicine, and physical therapies
Marske 2018 [45]	OMTh & OMTh + Gabapentin	Treatment modalities included MFR, muscle energy, counter strain, facilitated positional release, articular ligamentous, high velocity/low amplitude, and cranial sacral OMTh. Indirect moving to direct as tolerated by the patient	Gabapentin with variable dose (300 –900 mg/day)	Clinician directed	Concurrent medications were continued
Marti Salvador 2018 [46]	Diaphragm OMTh	Lumbar MFR, normalization of the ilio-lumbar ligament, pumping, traction to the lumbar and sacral regions, techniques directed to the diaphragm included pumping, inhibition, muscle stretching, and a global abdominal hemodynamic maneuver	Manual contact was applied but with no therapeutic intention	Per protocol	Yes – Cointerventions were not analyzed, a noted limitation of the study
Papa 2012 [47]	OMTh	Different techniques were used based on the results of the exam, objective techniques were performed on any body part that the osteopath found to be correlated with the disorder and the patient's functional limitation with considerations to myofascial, visceral, articulating and head structures	Postural examination and palpation of non-specific different parts of the body in different positions supine	Clinician directed	Yes – patients were subjected to the usual therapy established as a result of medical specialist visits but were not reported
Schwerla 2008 [48]	OMTh	Osteopathic techniques included direct techniques (high velocity, muscle energy, MFR), indirect techniques (functional techniques, balanced ligamentous tension), visceral and/or cranial techniques	Inert therapeutic ultrasound	Clinician directed	Yes – Excluded patients with concomitant physical therapy, corticosteroid use, anticoagulants. Patients kept a diary of analgesic and muscle relaxant use

MT, manual therapy; MFR, myofascial release; HVLA, high velocity low amplitude; OMTh, osteopathic manual therapy; CCT, conventional conservative therapy; ROM, range of motion; SC, standard care; vOMTh, visceral osteopathic manual treatment; SE, specific exercise; NR, not reported.

Table 3: Risk of bias in the included studies.

Study	Random sequence generation	Allocation concealment	Blinding of the participants	Blinding of the health care provider	Blinding of the outcome assessors	Drop out >20%`
Albers 2017 [34]	Low risk	Low risk	High risk	High risk	High risk	Low risk
Altinbilek 2018 [42]	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Burton 2000 [41]	Low risk	Low risk	High risk	High risk	High risk	High risk
Chown 2008 [43]	Low risk	Low risk	High risk	High risk	Low risk	High risk
Knebl 2002 [49]	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Licciardone 2003 [35]	Low risk	Low risk	High risk	High risk	Low risk	High risk
Licciardone 2013 [44]	Low risk	Low risk	High risk	High risk	Low risk	High risk
Marske 2018 [45]	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Marti Salvador 2018 [46]	Low risk	Low risk	High risk	High risk	Low risk	High risk
Papa 2012 [47]	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Schwerla 2008 [48]	Low risk	Low risk	High risk	High risk	High risk	Low risk

Descriptions of the OMTh approach for each study are given in Table 2. Overall, methods of osteopathic treatment used were directed to superficial, intermediate, and deep structures with a combination of direct or indirect methods using a type of activating force (compression or traction) with the patient active or passive (respiration, isometric contraction). Comparators varied and included exercise [42, 43], pharmacological [45], standard care [35, 44], and general OMTh [46].

Risk of bias

A summary of the ROB is given in Table 3. None of the included studies met all criteria of the ROB. All studies were high risk for blinding of participants, health care providers, and high dropout rates. Except for three studies [34, 41, 48], all studies performed independent outcome assessments.

Adverse events and drop out due to adverse events

A summary of adverse events outcomes is reported in Table 4. Only one study [44] explicitly reported an AE associated with OMTh that led to dropout. In Licciardone et al. [44], one patient reported recurring increase in back spasticity after treatments, which was attributed to OMTh. Overall in Licciardone et al. [44], 27 (6%) patients experienced AE; 16 (6.95%) from OMTh and 11 (4.88%) from the control group. Six patients from OMTh and three patients from the control group were considered to have serious AE; however, no events were explicitly related to the study intervention and there were no significant differences between the main effects' group in the frequency of AEs.

In Marske et al. [45], one patient from each arm – OMTh and OMTh combined with gabapentin – reported an AE; however, the authors did not specify what the AE were. The AE were mild-to-moderate in severity and none required intervention [45]. The number of reported AE decreased with time in all groups but there was a significant difference in OMTh only (mean difference, −5.7; p<0.01) and combination groups (mean difference, −3.7; p=0.03) [43].

Two patients (5.5%) from the control group in Schwerla et al. [48] dropped out due to aggravation in pain.

All cause dropout rate

Two hundred and 87 out of total 1,015 participants (28.28%) had ACD. The overall ACD rate in OMTh vs. controls was 22.67 vs. 30.07%, respectively (n=107 and n=156, respectively). Some reported reasons for dropouts included patients who were unable to meet the study demands [34], patients who chose to cease treatment [42], patients had flare up in previously diagnosed conditions [38], or patients who became pregnant [46]. Unfortunately, in most studies, the reasons for ACD were not specified [35, 41, 43, 48, 49]. In Papa et al. [47] and Knebl et al. [49], the patients' reasons for dropping out were not reported nor did the authors report ACD rates for each arm; therefore, we did not include Papa et al. [47] and Knebl et al. [49] in the pooled analysis. One study [38] reported high ACD in both arms, OMTh vs. exercise at 50.64 and 63.12% respectively. The authors noted major problems with recruitment and retention of patients, finding that patients were more likely to show up to one-on-one sessions. They cited dual pressures of scheduling with both the patients and the practitioners and a lack of administrative time, which impacted retrieval of follow up statistics [38].

ACDs: pooled analysis

OMTh vs. standard care

Three studies [35, 44, 48] (n=587) reported ACD in comparison with 20.78% ACDs (122 of 587 participants; 22.59 vs.

Table 4: Outcomes of the unpooled studies.

Study	Interventions	ACD, n(%)	Dropout due to AE, n(%)	Dropout due to inefficacy	Comments
Albers 2017 [34]	vOMTh (n=36)	1 (2.77)	0	NR	n=1 dropped out due to not able to meet with study demand
	Control (n=14)	0	0	NR	NA
*Altinbilek 2018 [42]	OMTh + Exercise (n=50)	6 (12%)	NR	NR	Patients in both arms dropped out on their own will
	Exercise (n=50)	9 (6%)	NR	NR	ES=0.62 [0.20, 1.90]
*Burton 2000 [41]	OMTh (n=15)	5 (33.33%)	NR	NR	No explanation about the dropout rate was given
	Chemonucleolysis (n=15)	5 (33.33%)	NR	NR	ES=0.62 [0.20, 1.90]
*Chown 2008 [43]	OMTh (n=79)	40 (50.63%)	NR	NR	Difficulties with scheduling and administrative time to conduct follow-ups was reported. One on one OMT sessions were more likely to be attended compared to group sessions
	Exercise (n=160)	101 (63.12%)	NR	NR	ES=0.60 [0.35, 1.03]
Knebl 2002 [49]	OMTh group + control group (n=31)	2 (6.4%)	NR	NR	One patient died and one patient refused. Not clearly stated which arm patients were in
Licciardone 2003 [35]	OMTh (n=48)	16 (33.33%)	NR	NR	ACD was 24.17%. Further detail for dropout rates was not given
	Control (n=43)	9 (20.93%)	NR	NR	
Licciardone 2013 [44]	OMTh (n=230)	33 (14.345)	1 (0.43%)	NR	n=1 developed back spasticity due to OMT
	Control (n=225)	26 (11.55%)	0	NR	No further detail given
*Marske 2018 [45]	OMTh (n=13)	2 (15.38)	1 (7.69%)	NR	Total two patients dropped from OMTh group, n=1 developed AE due to OMTh, transportation problems for 2nd loss *ES (OMT vs. Gabapentin) =0.36 [0.05, 2.50]
	Gabapentin (n=12)	4 (33.33%)	1 (8.33%)	NR	Notes treatment reaction, transportation and pregnancy but did not note how many in each category
	OMTh + Gabapentin (n=10)	0	0	NR	NA *ES (OMTh + Gabapentin vs. Gabapentin) =0.08 [0.00, 1.74]
Martí-Salvador 2018 [46]	vOMTh (n=33)	2 (6.06%)	0	NR	Two patients in OMTh group got pregnant due to which patients had to discontinue OMTh
	Control (n=33)	0	0	NR	NA
Papa 2012 [47]	OMTh (n=37)	24	NR	NR	n=24 dropped out from the study. Author did not specified number of dropouts for each arm; n=4 dropped out due to underlying medical conditions, n=6 dropped out due to transportation problems
	Control (n=35)		NR	NR	
Schwerla 2008 [48]	OMTh (n=23)	2 (8.69%)	0	NR	1 dropped out for reason not given; 1 had incomplete data
	Control (n=18)	2 (11.11%)	2 (5.55%)	NR	2 dropped due to aggravation in pain in control group

ACD, all cause dropouts; AE, adverse events; ES, effect size; OMTh, osteopathic treatment; SC, standard care; vOMTh, visceral osteopathic treatments; gOMTh, general osteopathic treatment. *Studies were not poolable/outcome was reported by single study. ES (odd ratio) with 95% confidence interval was calculated to determine the significance level between OMT and control group.

18.88% for OMTh vs. control groups, respectively; Figure 2). There is moderate quality evidence that ACD rates between OMTh and standard care were not significant (OR=1.26 [CI, 0.84, 1.89]; I^2=0%].

Visceral OMTh vs. OMTh control

Two studies [34, 46] (n=116) reported ACD in this comparison with 2.5% ACDs (three of 116 participants; 4.34 vs. 0%

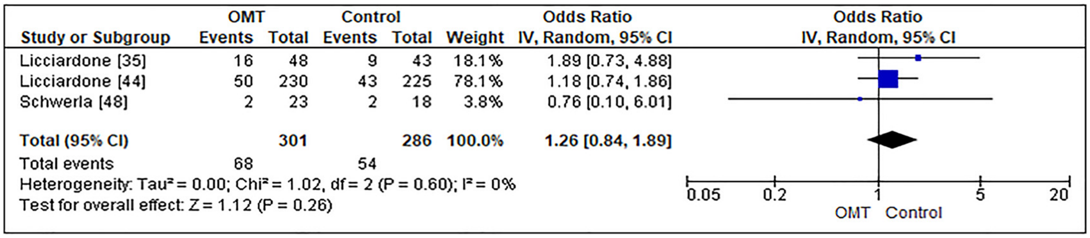

Figure 2: All cause dropouts (comparison: osteopathic manipulative therapy vs. control).

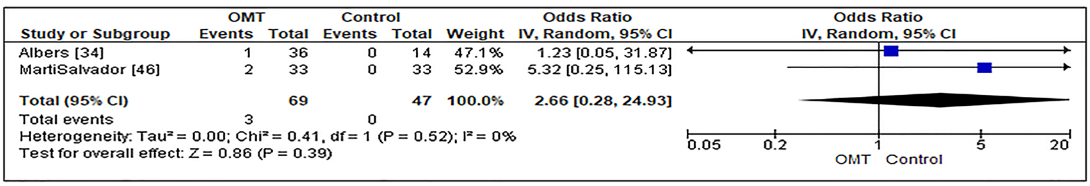

Figure 3: All cause dropouts (comparison: general osteopathic treatments vs viscerall osteopathic treatment).

Table 5: GRADE quality of evidence.

Outcome	Number of studies	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Quality of evidence
All cause dropouts							
OMTh vs. SC	3 (n=587)	High	Low	Low	Not detected	Not detected	Moderate
vOMhT vs. gOMTh	2 (n=116)	High	Low	Low	Not detected	Not detected	Moderate

GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; OMTh, osteopathic treatment; SC, standard care; vOMTh, visceral osteopathic treatments; gOMTh, general osteopathic treatment.

for OMTh and control group, respectively; Figure 3). Moderate quality evidence showed no statistically significant difference in ACD between visceral OMTh (vOMTh) and control OMTh (OR=2.66 [CI, 0.28, 24.93]; I^2=0%].

The GRADE assessment for the ACD and dropouts due to AE is reported in Table 5. The quality of evidence for pooled analyses was moderate due to a high ROB result.

Dropout rates due to inefficacy

No study reported dropouts due to inefficacy.

Discussion

In this review, we critically appraised tolerability outcomes reported as AE, ACD, dropouts due to AE, and inefficacy within RCTs, exploring the effectiveness of OMTh in CNCP after we noticed a degree of oversight in the currently-available literature and were unable to address this fully in our previous systematic review and meta-analysis [22]. To the best of our knowledge, this is the first review that has attempted to specifically explore the risks and reasons for dropouts from OMTh in comparison to other interventions in CNCP RCT studies. Our results indicated that although ACD were higher in OMTh groups compared with control groups, there was no significant difference noted. Aggravation of pain was specified within the OMTh group in two studies [44, 48] and one study [48] within the control group. One study [45] noted a treatment reaction to the control medication. Differences between OMTh and control group dropouts due to AE were not significant. Unfortunately, only five studies [34, 44–46, 48] out of 11 reported specific data on AE. From our main review, we found that with important patient outcomes such as pain, disability, QOL, and RTW, OMTh was well tolerated and was not statistically different from the comparators. From our initial review [22] including 16 studies, there were only 11 studies that included any data on ACD or AEs which could be included in this review. Few of those studies included details on why patients dropped out or provided insights on how to improve the problem in the future, and fewer reported complete data on AE (Table 4). Overall, the current literature reporting AE of OMTh is lacking and our hope is that this review will encourage improved reporting in future studies to build the strength and confidence in OMTh research.

Strengths and limitations

A key strength of our review was that we focused on specific outcomes, which are often underreported and overlooked: tolerability outcomes of ACD, dropout rates due to AE, and inefficacy. Our search strategy was broad, and our review was methodologically rigorous because we reported our results clearly and transparently, allowing for more precise interpretation of our results.

Our review also had several limitations. First, we inherited limitations from the primary studies having high ROB, which we downrated for major bias components such as random sequence generation and blinding. Although none of the included studies met all criteria of ROB, this is a common limitation to all procedure-based clinical trials since it is nearly impossible to blind both patients and practitioner(s). Second, the eligible studies were not sufficiently powered and the dropout rate in the eligible studies was very high. Third, due to the nature and reporting of current evidence, we were unable to pool the dropout rates for many important comparisons.

In the context of existing literature exploring the tolerability outcomes of OMTh in CNCP, our review is unique in its study design. In a survey of 884 patients by Degenhardt et al. [26], the incidence of AE due to OMTh was 2.5% (95% CI, 1.3–4.7%). Women (n=44; 97.8%) reportedly experienced more AE than men (n=1; 2.23) (OR, 13.9; 95% CI, 1.7–115.6; p=0.01), with pain/discomfort the most commonly identified type of AE at 0.9% (95% CI, 0.5–1.6%). Vogel et al. [50] reported AE from OMTh in 2039 patients, of which 4% (n=82) patients reported mild disability and 10% (n=130) sought attention from other health care providers during treatment [50]. However, Degenhardt et al. [26] and Vogel et al. [50] explored dropout rates in observational studies and did not compare the dropout rates to other interventions. Our review is unique in that we explored the ACD and AE of OMTh compared with controls in CNCP reported in previously published RCT. RCTs are a more suitable study design to explore the effectiveness and tolerability of a treatment compared with observational studies due to an increase in control as well as being able to more critically assess variables and bias, and it is important to compare the AE of OMTh to other recommended treatment modalities. Therefore, our review provides better evidence for the safety of OMTh compared with previous studies.

Clinical implications and future directions

There was moderate quality evidence that OMTh in managing CNCP is associated with low ACD and dropouts due to AE. For this review, we extracted tolerability outcomes from studies that were included in our previous systematic review [22]. Making multiple publications using the same data set can be acceptable, provided the goals are explained explicitly and the research question and rationale are adding significant contribution to the scientific community [51, 52]. As mentioned, most systematic reviews and metaanalyses focus on beneficial outcomes of an intervention with little to no emphasis on tolerability outcomes [17–19]. For any intervention and especially within osteopathic practice, treatment philosophy is based on safety, equitability, effectiveness, and orientation to patients [53–55]. As OMTh is increasingly utilized and is considered a safe and effective method of treatment, it is imperative to fully understand both the benefits and potential harms. Understanding the risks of treatment is important for both the healthcare provider and patients, as having an understanding of OMTh-associated ACD and dropouts due to AE will allow clinicians to create a safe practice and patients to establish realistic expectations, give adequate consent, and make an informed choice among all available interventions. Our goal was to emphasize the importance of exploring the tolerability of OMTh in the management of CNCP patients in osteopathic research. We hope that future studies reporting on the effectiveness of OMTh will also report reasons for dropouts, ACD rates, and any AE experienced during the study.

Conclusions

In this systematic review with meta-analysis, we critically appraised the existing literature to explore OMTh in CNCP patients with a focus on tolerability and drop out effects. The current evidence is based on studies with high risk of bias and small sample sizes. Like any other intervention and manipulation therapy, OMTh is not exempt from AE and dropouts, and was not significantly different than comparators such as physiotherapy and standard care (e.g., drug intervention). Moderate quality evidence showed that ACD from OMTh were not significantly different than the control interventions; however, data on reporting AE and dropout rates with osteopathic treatment in RCTs were sparse and not explicitly reported in the included trials. Information about tolerability and AE is important for patients to make informed decisions and establish realistic expectations of treatment. Therefore, more pragmatic RCTs comparing the effectiveness of OMTh with other treatment modalities such as pharmacological agents and physical therapies are required to determine the overall effectiveness of OMTh in the management of CNCP while trying to keep data transparent so that it can be compared with other studies. It is also imperative that future research should focus on OMTh in the management of specific CNCP conditions and include general and visceral treatments to determine the relative effectiveness of various OMTh approaches.

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References

1. Reid KJ, Harker J, Bala MM, Truyers C, Kellen E, Bekkering GE, et al. Epidemiology of chronic non-cancer pain in Europe: narrative review of prevalence, pain treatments and pain impact. Curr Med Res Opin 2011;27:449–62.
2. Blyth FM, Briggs AM, Schneider CH, Hoy DG, March LM. The global burden of musculoskeletal pain-where to from here? Am J Publ Health 2019;109:35–40.
3. Schopflocher D, Taenzer P, Jovey R. The prevalence of chronic pain in Canada. Pain Res Manag 2011;16:445–50.
4. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, Debar L, et al. Prevalence of chronic pain and high-impact chronic pain among adults – United States, 2016. MMWR Morb Mortal Wkly Rep 2018; 67:1001–6.
5. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. Lancet 2011;377:2226–35.
6. Bogduk N. Management of chronic low back pain. Med J Aust 2004; 180:79–83.
7. Giusti R. Glossary of osteopathy terminology. 3rd ed. USA: AACOM; 2017.
8. Fawkes CA, Leach CMJ, Mathias S, Moore AP. A profile of osteopathic care in private practices in the United Kingdom: a national pilot using standardised data collection. Man Ther 2014; 19:125–30.
9. Burke SR, Myers R, Zhang AL. A profile of osteopathic practice in Australia 2010-2011: a cross sectional survey. BMC Muscoskel Disord 2013;14:227.
10. Carnes D, Mars TS, Mullinger B, Froud R, Underwood M. Adverse events and manual therapy: a systematic review. Man Ther 2010; 15:355–63.
11. Licciardone JC, Schultz MJ, Amen B. Osteopathic manipulation in the management of chronic pain: current perspectives. J Pain Res 2020;13:1839–47.
12. Saracutu M, Rance J, Davies H, Edwards DJ. The effects of osteopathic treatment on psychosocial factors in people with persistent pain: a systematic review. Int J Osteopath Med 2018; 27:23–33.
13. Busse JW, Craigie S, Juurlink DN, Buckley Norman, Wang Li, Couban Rachel, et al. Guideline for opioid therapy and chronic noncancer pain. Can Med Assoc J 2017;189:E659–66.
14. Steel A, Peng W, Sibbritt D, Adams J. Introducing national osteopathy practice-based research networks in Australia and New Zealand: an overview to inform future osteopathic research. Sci Rep 2020;10:846.
15. Carnes D, Mullinger B, Underwood M. Defining adverse events in manual therapies: a modified Delphi consensus study. Man Ther 2010;15:2–6.
16. Carlesso LC, Cairney J, Dolovich L, Hoogenes J. Defining adverse events in manual therapy: an exploratory qualitative analysis of the patient perspective. Man Ther 2011;16:440–6.
17. McIntosh HM, Woolacott NF, Bagnall AM. Assessing harmful effects in systematic reviews. BMC Med Res Methodol 2004;4:19.
18. Ernst E, Pittler MH. Assessment of therapeutic safety in systematic reviews: literature review. BMJ 2001;323:546.
19. Zorzela L, Golder S, Liu Y, Pilkington K, Hartling L, Joffe A, et al. Quality of reporting in systematic reviews of adverse events: systematic review. BMJ (Clin Res Ed) 2014;348:f7668.
20. Julian PTH, Sally G. Cochrane handbook for systematic reviews of interventions. Chichester, West Sussex, Hoboken NJ: John Wiley & Sons; 2008.
21. Schmucker CM, Blümle A, Schell LK, Schwarzer G, Oeller P, Cabrera L, et al. Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research. PloS One 2017;12:e0176210.
22. Rehman Y, Ferguson H, Blair J, Bozek A, Allison A, Johnston R. The effectiveness of osteopathic manual treatment in the reduction of pain severity, functional improvement and return to work in chronic non-cancer pain patients: meta-analysis and systematic review. J Am Osteopath Assoc 2020;120:888–906.
23. Licciardone JC, Herron KM. Characteristics, satisfaction, and perceptions of patients receiving ambulatory healthcare from osteopathic physicians: a comparative national survey. J Am Osteopath Assoc 2001;101:374–85.
24. Adams J, Sibbritt D, Steel A, Peng W. A workforce survey of Australian osteopathy: analysis of a nationally-representative sample of osteopaths from the Osteopathy Research and Innovation Network (ORION) project. BMC Health Serv Res 2018;18:352–52.
25. Alvarez Bustins G, López Plaza P-V, Carvajal SR. Profile of osteopathic practice in Spain: results from a standardized data collection study. BMC Compl Alternative Med 2018;18:129.
26. Degenhardt BF, Johnson JC, Brooks WJ, Norman L. Characterizing adverse events reported immediately after osteopathic manipulative treatment. J Am Osteopath Assoc 2018;118: 141–9.

27. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche P, Ioannidis J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339: b2700.
28. Moore RA, Derry, S, Wiffen, PJ. Challenges in design and interpretation of chronic pain trials. Br J Anaesth 2013;111: 38–45.
29. Licciardone JC, Brimhall AK, King LN. Osteopathic manipulative treatment for low back pain: a systematic review and meta-analysis of randomized controlled trials. BMC Muscoskel Disord 2005;6:43.
30. Roose SP. Tolerability and patient compliance. J Clin Psychiatr 1999;60(17 Suppl):14–7; discussion 46–8.
31. Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-reported outcomes in cancer clinical trials: measuring symptomatic adverse events with the national cancer institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). Am Soc Clin Oncol Educ Book 2016;35:67–73.
32. Atkinson TM, Ryan SJ, Bennett AV, Stover A, Saracino R, Rogak L, et al. The association between clinician-based common terminology criteria for adverse events (CTCAE) and patient-reported outcomes (PRO): a systematic review. Support Care Canc 2016;24:3669–76.
33. Gutiérrez-Espinoza H, Araya-Quintanilla F, Cereceda-Muriel C, Álvarez-Bueno C, Martínez-Vizcaíno V, Cavero-Redondo I. Effect of supervised physiotherapy versus home exercise program in patients with subacromial impingement syndrome: a systematic review and meta-analysis. Phys Ther Sport 2020;41: 34–42.
34. Albers J, Jakel A, Wellmann K, von Hehn U, Schmidt T. Effectiveness of 2 osteopathic treatment approaches on pain, pressure-pain threshold, and disease severity in patients with fibromyalgia: a randomized controlled trial. Complement Med Res 2018;25:122–8.
35. Licciardone JC, Stoll ST, Fulda KG, Russo D, Winn W, Swift J. Osteopathic manipulative treatment for chronic low back pain: a randomized controlled trial. Spine 2003;28:1355–62.
36. Atkins D, Best D, Briss PA, Eccles M, Dalck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ (Clinical Res Ed) 2004;328:1490.
37. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401–6.
38. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336:995.
39. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924.
40. Higgins JPT, Altman DG, JAC S. Cochrane handbook for systematic reviews of interventions; [Chapter 8]: assessing risk of bias in included studies. The Cochrane Collaboration; 2011.
41. Burton AK, Tillotson K, Cleary J. Single-blind randomised controlled trial of chemonucleolysis and manipulation in the treatment of symptomatic lumbar disc herniation. Eur Spine J: Off Publ Eur Spine Soc Eur Spinal Deformity Soc Eur Section Cervical Spine Res Soc 2000;9:202–7.
42. Altinbilek T, Murat S, Yumusakhuylu Y, Icagasioglu A. Osteopathic manipulative treatment improves function and relieves pain in knee osteoarthritis: a single-blind, randomized-controlled trial. Turk J Phys Med Rehabil 2018;64:114–20.
43. Chown M, Whittamore L, Rush M, Allan S, Stott D, Archer M. A prospective study of patients with chronic back pain randomised to group exercise, physiotherapy or osteopathy. Physiotherapy 2008;94:21–8.
44. Licciardone JC, Minotti DE, Gatchel RJ, Kearns CM, Singh KP. Osteopathic manual treatment and ultrasound therapy for chronic low back pain: a randomized controlled trial. Ann Fam Med 2013;11:122–9.
45. Marske C, Bernard N, Palacios A, Wheeler C, Preiss B, Brown M, et al. Fibromyalgia with gabapentin and osteopathic manipulative medicine: a pilot study. J Alternative Compl Med 2018;24:395–402.
46. Marti-Salvador M, Hidalgo-Moreno L, Domenech-Fernandez J, Lison JF, Arguisuelas MD. Osteopathic manipulative treatment including specific diaphragm techniques improves pain and disability in chronic nonspecific low back pain: a randomized trial. Arch Phys Med Rehabil 2018;99:1720–9.
47. Papa L, Mandara A, Bottali M, Gulisano V, Orfei S. A randomised control trial on the effectiveness of osteopathic manipulative treatment in reducing pain and improving the quality of life in elderly patients affected by osteoporosis. Clin Cases Miner Bone Metabol: Off J Ital Soc Osteoporos Miner Metabol Skeletal Dis 2012;9:179–83.
48. Schwerla F, Bischoff A, Nurnberger A, Genter P, Guillaume JP, Resch KL. Osteopathic treatment of patients with chronic non-specific neck pain: a randomised controlled trial of efficacy. Forsch Komplementmed 2008;15:138–45.
49. Knebl J, Shores J, Gamber R, Gray W, Herron K. Improving functional ability in the elderly via the Spencer technique, an osteopathic manipulative treatment: a randomized, controlled trial. J Am Osteopath Assoc 2002;102:387–96.
50. Vogel T, Keeping S, Barton T, Marlin N, Froud R, Eldridge S, et al. Clinical risk osteopathy and management scientific report. London: The CROaM Study; 2013.
51. Kirkman BL, Chen G. Maximizing your data or data slicing? Recommendations for managing multiple submissions from the same dataset. Manag Organ Rev 2011;7:433–46.
52. Fine MA, Kurdek LA. Publishing multiple journal articles from a single data set: issues and recommendations. J Fam Psychol 1994;8:371–9.
53. Mitchell PH. Chapter 1, defining patient safety and quality care. In: Hughes RG, editor. Patient safety and quality: an evidence-based handbook for nurses. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008.
54. Steel A, Blaich R, Sundberg T, Adams J. The role of osteopathy in clinical care: broadening the evidence-base. Int J Osteopath Med 2017;24:32–6.
55. Carnes D. What can osteopaths learn from concerns and complaints raised against them? A review of insurance and regulator reports. Int J Osteopath Med 2016;22:3–10.

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