Osteopathic Manual Treatment for Pain Severity, Functional Improvement, and Return to Work in Patients With Chronic Pain

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Context: Chronic non-cancer pain (CNCP) is associated with disability, poor quality of life (QOL), and failure to return to work (RTW). Osteopathic manipulative treatment (OMT) or osteopathic manual therapy (OMTh) are increasingly offered to patients with CNCP; however, the existing systematic reviews and meta-analyses in the literature that explore the effectiveness of OMTh have major limitations.

Objective: To systematically evaluate the quality of evidence documenting the effectiveness of OMTh for patients with CNCP using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, and to evaluate the efficacy of OMTh in patients with CNCP through a meta-analysis of pooled data from previous studies.

Methods: We searched online the databases Ovid, MEDLINE, Embase, OSTMED.DR, EMCare, Allied and Complementary Medicine Database (AMED), Physiotherapy Evidence Database (PEDro), and Cochrane Central Register of Controlled Trials (CENTRAL), as well as the bibliographic references of previous systematic review articles evaluating OMTh for pain severity, disability, QOL, or RTW outcomes. Eligibility included randomized controlled trials methodology, CNCP patients 18 years or older, use of previously validated assessment tools, use of OMTh as an active or combination intervention, and presence of a control or comparison group. We pooled studies based on the homogeneity between OMT comparator treatment and outcomes. Risk of bias was assessed with the Cochrane risk of bias tool and the quality of evidence was determined with GRADE.

Results: Sixteen randomized controlled trials (n=1158 patients) were eligible for data extraction. Moderate quality evidence showed that OMTh vs. standard care was significantly associated with a reduction in pain [standardized mean difference (95% CI)=[−.37 (−.58, −.17)] and disability [−.28 (−.46, −.10)], as well as improved QOL [.67 (.29, 1.05)]. Moderate quality evidence showed that OMTh plus exercise vs. exercise only was significantly associated with reduction in pain severity [−1.25 (−1.67, −.83)] and disability [−1.15 (−1.57, −.74)]. Moderate quality evidence showed that using visceral OMTh vs. general OMTh was significantly associated with reduction in pain severity [−.74 (−1.09, −.39)] and disability [−.52 (−.91, −.13)]. In comparison to physiotherapy, gabapentin, and OMTh plus gabapentin, OMTh did not show any significant effect for any of the outcomes. OMTh vs. standard care did not show significant improvement in RTW at 12 weeks, although the effect was significant at 8 weeks after OMTh.

Conclusion: Moderate quality evidence suggests that OMTh is effective for CNCP patients. There was a significant association between visceral OMTh and reduced pain severity and disability. More robust, high-quality randomized controlled trials with larger sample sizes are required to further explore the effectiveness of the OMTh in the management of CNCP.

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Chronic noncancer pain (CNCP) affects approximately 19% of the general population¹⁻³ and includes a range of conditions that involve mechanical (eg, low back pain, osteoarthritis) and neuropathic (eg, fibromyalgia) disorders. CNCP interferes with activities of daily living, contributes to psychologic distress, and is associated with disability and work loss,²⁻⁵ causing substantial socioeconomic impact.⁶⁻⁸ CNCP is also among the most common reasons for patients to consult general practitioners and specialist pain clinics.^{5,6} Management of CNCP is multi-disciplinary: combination treatments are reported to provide better pain relief and functional outcomes.^{9,10} Depending on the underlying cause, treatments for CNCP include pharmacologic intervention, psychotherapy, and physical treatments such as physiotherapy, chiropractic treatments, massage therapy, and osteopathic manipulative treatment (OMT) or osteopathic manual therapy (OMTh).¹⁰⁻¹² Although the same principles are followed in the manual treatment approach, OMT is performed by physicians, whereas OMTh is performed by nonphysicians.

OMTh is increasingly employed to manage CNCP^{13,14} and, like other manual therapies, is known to alter biomechanical, neurophysiologic, and various other patient-related factors through anatomic and physiologic connections to the autonomic nervous system.¹⁵⁻¹⁸ OMTh requires a comprehensive understanding of anatomy and physiology and, based on osteopathic principles, uses that knowledge to mobilize and influence the patient's body. The 4 main principles of osteopathy¹⁹⁻²¹ are that the body is a unit and the person is a unit of body, mind, and spirit; the body is capable of self-regulation, self-healing, and health maintenance; structure and function are reciprocally interrelated; and rational treatment is based on an understanding of the basic principles of body unity, self-regulation, and the interrelationship of structure and function.

Although OMTh is increasingly offered to patients to help manage CNCP, it is still widely underused, and research into its benefits remains in its infancy.²²⁻²⁴ Previous systematic reviews and meta-analyses exploring

the effectiveness of OMTh have had a variety of limitations such as language restriction,²⁵ narrow search strategies,²⁵ inclusion criteria not being restricted to randomized controlled trials (RCTs)²⁶ or to OMTh topics,^{26,27} inclusion of studies with both acute and chronic pain,²⁸⁻³⁰ or inclusion of duplicate studies (such as substudies of larger trials).²⁶ Given these limitations, interpreting the results of reviews and meta-analyses in the current literature and drawing conclusions about the effectiveness of OMTh can be challenging. Therefore, larger, high-quality data exploring the effectiveness of OMTh in the management of CNCP is sorely needed. Our goal was to conduct a systematic review and meta-analysis to explore the effectiveness of OMTh in CNCP and its effect on pain reduction, functional impairment, quality of life (QOL), and return to work (RTW). We also evaluated the quality of evidence in a thorough and consistent manner using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.^{31,32}

Methods

We conducted our meta-analysis according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.³³ The study protocol was registered with Prospero (Registration #CRD42019125659).

The keywords for our searches were developed using the MeSH word analyzer (<http://MeSH.med.yale.edu/>). Searches were conducted starting in July 2018 and were updated in July 2019. We developed a broad search strategy using Ovid to search MEDLINE, Embase, OSTMED.DR, EMCare, Allied and Complementary Medicine Database (AMED), Physiotherapy Evidence Database (PEDro), and Cochrane Central Register of Controlled Trials (CENTRAL) databases. The bibliographic references of previous systematic reviews²³⁻²⁹ were also searched for eligible trials. The Ovid MEDLINE literature search strategy is provided in the [eAppendix](#). Our eligibility criteria included randomized controlled trials

(RCTs) that had enrolled CNCP patients 18 years of age or older, employed OMTh as an active or combination intervention, and compared OMTh to any other intervention or control. Eligible trials explored the effectiveness of OMTh on pain severity, disability, QOL, or RTW outcomes and were reported with previously validated tools. We excluded RCTs that enrolled <10 participants per arm at baseline or if the authors reported a composite score. Studies with a focus on cancerous pain, pain developed during pregnancy, headaches, pain due to gynecologic abnormalities, purely irritable bowel syndrome (IBS), or other visceral pain such as prostatitis were also excluded. We excluded crossover trials because of the possibility of carry-over effect and because methodologic challenges limit their applicability.^{34,35} Because OMTh is governed by a set of principles and uses a combination of methods to treat the body,³⁰ we excluded studies that were specifically investigating a single technique without employing additional use of general OMTh. An amendment in our original Prospero protocol was made because we initially excluded pilot trials but found we did not have enough eligible studies and therefore broadened our inclusion criteria to include pilot trials.

Data Collection and Analysis Plan

Title and abstract, full text screening, data abstraction, and risk of bias (ROB) were compiled in duplicate and independently by a team of reviewers (Y.R., H.F., J.B., A.B., A.A.). We extracted information related to the trial design, patient demographics, interventions, outcomes, and ROB. When possible, we pooled studies according to the type of OMTh and comparator for each outcome. OMTh is applied according to an individual's condition and at the discretion of the examiner with variations; therefore, for pooling purposes we considered relative similarities between OMTh, treatment comparators, and outcomes across studies.^{35,36} We reported results with standardized mean difference (SMD) with a 95% confidence interval (CI) interval. Albers et al³⁷ and Licciardone et al³⁸ were 3-arm studies and, based on the similarities between the

OMTh applied and comparators, respectively, we merged the 2 arms. If we had 2 studies in the pooled analysis, we reported results with fixed effect model (FEM); if we had more than 2 studies in the pooled analysis, we reported results with random effect model (REM). For FEM, we also checked with REM for change in variability. We analyzed data with change scores, but in cases where change scores were not reported, we pooled with the final score according to Cochrane's criteria.³⁵ If quantitative pooling was not possible, we reported outcomes descriptively.

Quality of Evidence

The quality of evidence was assessed using GRADE,^{31,32} which consists of 5 components: ROB, inconsistency, imprecision, publication bias, and indirectness.

Risk of bias: ROB was analyzed using a modified Cochrane ROB tool on the following components: random sequence generation, allocation concealment, blinding of participants, healthcare provider, outcome assessors, and dropout rates.³⁵

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

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

Indirectness and inconsistency: The clinical characteristics of the participants and width of the confidence interval, respectively, were assessed for indirectness and inconsistency.

Sensitivity and Subgroup Analysis

We did not have enough studies to perform subgroup analysis according to the *a priori* specified in our Prospero protocol. We pooled studies comparing the effectiveness of OMTh against sham and OMTh against standard care (SC). Our rationale was based on

the fact that studies with sham comparison allowed patients to continue usual treatment; therefore, we explored subgroup analysis to assess whether our rationale to pool studies with sham treatment and SC was justifiable. We also performed a sensitivity analysis to compare to previous systematic reviews by pooling studies according to low back pain (LBP) only, while ignoring the differences in control treatments/comparators.

The statistical analysis was performed with Review Manager 5.3 (Review Manager [RevMan] version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Results

Our searches from all databases yielded 2956 studies for screening (Figure 1), out of which 16 studies were eligible for data extraction. A summary of the included studies is given in Table 1.

The collective sample size from all eligible studies was 1158. The median age of the eligible population was 43.3 years, with a range of 23 to 78 years. Chronic LBP was the most prevalent pain type among the included studies.³⁹⁻⁴⁵ Three studies explored the effectiveness of OMTh in the treatment of neck pain,^{39,40,46} and other studies explored the effectiveness of OMTh in knee arthritis,⁴¹ shoulder pain,⁴² temporomandibular

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Table 1.
Baseline Characteristics of the Included Studies

Author/ Year	Age, mean (SD)	Gender-female (%)	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 2018 ³⁷	54.9 (13.1)	3.3	Fibromyalgia	No	NR	NR	84	34	14
Altinbilek 2018	54.8 (8.4)	89.4	Knee OA	Yes	NR	No; except for paracetamol	151	44	41
Burton 2000 ⁴⁹	41.9 (10.6)	52.5	LBP/ LDH	Yes	Yes	NR	365	15	15
Chown 2008 ⁵²	43.6	58.5	Chronic LBP	Yes	NR	Steroids were not allowed	365	39	59
Cuccia 2010 ⁴³	39.5 (13.1)	58.7	TMD	No	NR	NR	168	25	25
Knebl 2002 ⁴²	65-85	62.1	Chronic shoulder pain	Yes	NR	NR	105	NR	NR
Licciardone 2003 ³⁸	49.9 (8.0)	64.6	Chronic nonspecific LBP	Yes	Yes	Yes	84	32	34
Licciardone 2013 ⁵⁰	40.5 (16.3)	62.5	Chronic nonspecific LBP	Yes	Yes	Yes	56	230	225
Marske 2018 ⁴⁴	51.2	93.2	Fibromyalgia	No	NR	NR	42	11/10	8
Marti-Salvador 2018 ⁴⁸	18-60	NR	Chronic nonspecific LBP	No	NR	No	56	33	33
Papa 2012 ⁴⁵	77 (6.7)	70.5	Chronic nonspecific body pain	Yes	NR	NR	42	37	35
Schwerla 2008 ⁴⁰	35.4-54.2	75.6	Chronic nonspecific neck pain	No	Yes	NR	84	21	16
Silva 2018 ⁴⁶	25.4 (8.29)	NR	Non-specific neck pain	No	No	No	7	14	14
Stepnik 2018 ³⁹	23-53	83.9	Chronic Neck Pain	No	No	NR	NR	16	15
Tamer 2017 ⁴⁷	39.9 (5.1)	53.9	Chronic nonspecific LBP	No	Yes	No	42	20	19
Vismara 2012 ⁵¹	43.7 (9.8)	100	Chronic LBP	No	Yes	NR	NR	10	11

Abbreviations: LBP, low back pain; LDH, lumbar disc herniation; NR, not reported; OA, osteoarthritis; TMP, temporomandibular disorder.

Table 2.
Summary of OMTh Treatments and Comparator Interventions

Author/ Year	Treatment groups	Osteopathic manipulation	Comparator	Per protocol or clinician directed therapy	Cointervention use allowed description
Albers 2018 ³⁷	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 ⁴¹	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 anti-inflammatory drugs 1 week before and during the study. Paracetamol up to 3g/ daily was allowed and drugs for systemic conditions continued.
Burton 2000 ⁴⁹	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 ⁵²	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.
Cuccia 2010 ⁴³	OMTh	MFR, joint articulation, membranous tension, muscle energy, high-velocity, low-amplitude thrust and cranial-sacral therapy.	Use of an oral appliance, physical therapy, therapies such as hot or cold packs (or both), transcutaneous electrical nerve stimulation.	Clinician directed	Yes - Non-steroidal medications, anti-inflammatory, analgesics and/or muscle relaxants were allowed when prescribed by their medical practitioner

(continued)

Table 2 (continued).
Summary of OMTh Treatments and Comparator Interventions

Author/ Year	Treatment groups	Osteopathic manipulation	Comparator	Per protocol or clinician directed therapy	Cointervention use allowed description
Knebl 2002 ⁴²	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 7 positions of the Spencer technique without administration of the actual corrective forces (isometric muscle contraction).	Per protocol	NR
Licciardone 2003 ³⁸	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.
Licciardone 2013 ⁵⁰	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 ⁴⁴	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 (300mg to 900mg/day).	Clinician directed	Concurrent medications were continued.
Marti-Salvador 2018 ⁴⁸	Diaphragm OMTh	Lumbar MFR, normalization of the iliolumbar 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.

(continued)

Table 2 (continued).
Summary of OMTh Treatments and Comparator Interventions

Author/ Year	Treatment groups	Osteopathic manipulation	Comparator	Per protocol or clinician directed therapy	Cointervention use allowed description
Papa 2012 ⁴⁵	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 ⁴⁰	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.
Silva 2018 ⁴⁶	OMTh	Osteopathic manipulation technique to the stomach followed by the liver.	Placebo manipulation technique	Per protocol	No - Patients using analgesics, muscle relaxants and anti-inflammatory drugs in the 5 days prior to the intervention were excluded.
Stepnik 2018 ³⁹	OMTh	Osteopathic techniques employed 5 specific techniques to the anterior neck region. These included superficial fascia stretch, pretracheal fascia stretch, carotid sheath stretches, deep cervical fascia stretches, and suspensory ligament of pleural cupula stretch	Laser therapy using Polaris 2 laser (turned off)	Per protocol	NR
Tamer 2017 ⁴⁷	vOMTh	Soft tissue mobilization, muscle-energy techniques, manipulation and mobilization for lumbar and thorax regions, lymphatic and liver pumping techniques, pelvic floor, diaphragm relaxation techniques, arterial, venous and neural techniques, fascial mobilization for visceral organs.	Soft-tissue mobilizations, muscle-energy techniques, manipulation and mobilization for lumbar and thorax regions.	Clinician directed	Yes - Physiotherapy used in conjunction with both treatment arms aimed at spinal stabilization strengthening and stretching.

(continued)

Table 2 (continued).
Summary of OMTh Treatments and Comparator Interventions

Author/ Year	Treatment groups	Osteopathic manipulation	Comparator	Per protocol or clinician directed therapy	Cointervention use allowed description
Vismara 2012 ⁵¹	OMTh + SE	High-velocity, low-amplitude thrust in thoracic spine, cranial techniques, and MFR at the practitioner's discretion.	Active exercises, and education: reinforcing and stretching of the back muscles; self-mobilizing the spine and pelvis; posture and breathing techniques; providing patients with correct ergonomic knowledge for the safe use of the spine and information on the changes in spinal physiology, pain, and posture as related to obesity and other risk factors.	Clinician directed	NR

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

joint (TMJ) pain,⁴³ fibromyalgia,^{37,44} or nonspecific musculoskeletal pain.⁴⁵ Except for 7 studies,^{39,40,43,44,46-48} all others excluded patients with other medical or psychologic conditions. Six studies^{38,40,47,49-51} excluded patients with disability claims or with ongoing litigation. Six studies specifically stated excluding patients with cancer.^{37,38,40,41,48,50} Only 2 authors^{48,50} accounted for missing data in their RTCs.

Description of OMTh and treatments are given in [Table 2](#). Overall, methods of osteopathic treatments used were per protocol or were clinician directed. Most studies were specific in stating that treatment methods were up to the discretion of the practitioner, whereas a few studies^{42,47,48} attempted to employ a specific treatment protocol. Comparators vary from SC or sham,^{37-40,43,45,50} pharmacologic,⁴⁴ exercise or physiotherapy,^{41,51,52} other OMTh,⁴⁶⁻⁴⁸ and chemonucleolysis.⁴⁹

Risk of Bias

A summary of the ROB is given in [Table 3](#). None of the included studies met all criteria for ROB. Except

for 2 studies,^{39,43} all other studies were low risk for allocation concealment and random sequence generation. Except for 7 studies,^{37,39,40,43,47,49,51} outcomes were assessed by an independent evaluator, whereas in 2 studies patients were blinded to manipulation.^{42,46}

Pooled Analysis

Pain severity: Among the 16 studies, poolable data were available from 13 studies.^{37-41,43,45-48,50-52} The collective sample size from all poolable studies for pain outcomes was 996. In total, we had 3 pooled analyses based on OMTh and comparators for pain severity ([Figure 2](#)). The GRADE is reported in [Table 4](#).

OMTh vs. SC: Six studies^{37,38,40,43,45,50} with 710 patients were included in this analysis. Moderate quality evidence showed that as compared to SC, OMTh was significantly associated with pain reduction [SMD (95%CI) = -.37 (-.58, -.17)].

Visceral OMTh vs. general OMTh: Three studies⁴⁶⁻⁴⁸ with 133 patients were included in this analysis. Moderate quality evidence showed that, as

Table 3.
Risk of Bias in the Included Studies

Authors	Random sequence generation	Allocation concealment	Blinding of the participants	Blinding of the healthcare provider	Blinding of the outcome assessors	Drop out > 20%
Albers 2018 ³⁷	Low risk	Low risk	High risk	High risk	High risk	Low risk
Altinbilek 2018 ⁴¹	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Burton 2000 ⁴⁹	Low risk	Low risk	High risk	High risk	High risk	High risk
Chown 2008 ⁵²	Low risk	Low risk	High risk	High risk	Low risk	High risk
Cuccia 2010 ⁴³	High risk	High risk	High risk	High risk	High risk	High risk
Knebl 2002 ⁴²	Low risk	Low risk	Low risk	High risk	Low risk	High risk
Licciardone 2003 ³⁸	Low risk	Low risk	High risk	High risk	Low risk	High risk
Licciardone 2013 ⁵⁰	Low risk	Low risk	High risk	High risk	Low risk	High risk
Marske 2018 ⁴⁴	Low risk	Low risk	High risk	High risk	Low risk	High risk
Marti-Salvador 2018 ⁴⁸	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Papa 2012 ⁴⁵	Low risk	Low risk	High risk	High risk	Low risk	Low risk
Schwerla 2008 ⁴⁰	Low risk	Low risk	High risk	High risk	High risk	Low risk
Silva 2018 ⁴⁶	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Stepnik 2018 ³⁹	High risk	High risk	High risk	High risk	High risk	Low risk
Tamer 2017 ⁴⁷	Low risk	Low risk	High risk	High risk	High risk	Low risk
Vismara 2012 ⁵¹	Low risk	Low risk	High risk	High risk	High risk	Low risk

compared to general OMTh [gOMTh], visceral OMTh [vOMTh] was significantly associated with pain reduction [SMD (95%CI) = -0.74 (-1.09 , -0.39)].

OMTh plus exercise vs. exercise only: Two studies^{41,51} with 106 patients were included in this analysis. Moderate quality evidence showed that OMTh in combination with exercise was significantly associated with pain reduction [SMD (95% CI) = -1.25 (-1.67 , -0.83)].

Disability

Of the eligible 16 studies, poolable data concerning disability was available from 8 studies.^{39,41,47-52} The collective sample size from all poolable studies for disability outcomes was 742. There were 3 pooled analyses based on OMTh and the various comparators in total (Figure 3A-C).

OMTh vs. SC: Two studies^{40,50} with 486 patients were included in this analysis. Moderate quality evi-

dence showed that, as compared with SC, OMTh was significantly associated with reduction in disability and/or function [SMD (95%CI) = -1.04 (-1.23 , -0.85)].

vOMTh vs. gOMTh: Two studies^{47,48} with 105 patients were included in this analysis. Moderate quality evidence showed that vOMTh as compared to gOMTh was significantly associated with improvement in disability (SMD (95%CI) = -0.52 (-0.91 , -0.13)).

OMTh plus exercise vs. exercise only: Two studies^{41,51} with 106 patients were included in this analysis. Moderate quality evidence showed that OMTh combined with exercise as compared to exercise alone was significantly associated with improvement in disability [SMD (95% CI) = -1.15 (-1.57 , -0.74)].

Quality of life: Of the eligible 16 studies, poolable data were available from 2 studies.^{37,45} The collective sample size from all poolable studies for QOL outcomes was 120. Due to the small number of studies,

Figure 2.

Pain outcome. (A) OMT vs. standard care, (B) vOMTh vs. gOMTh, (C) OMT + exercise vs. exercise.

Abbreviations: OMT, osteopathic manipulative treatment; gOMTh, general osteopathic manipulative therapy; OMTh, osteopathic manipulative therapy; vOMTh, visceral osteopathic manipulative therapy.

we had single pooled analysis (Figure 3D). Moderate quality evidence showed that OMTh was significantly associated with improved QOL as compared to SC [SMD (95% CI) = .67 (.29, 1.05)].

For any of the pooling with FEM, the effect size did not change when reanalyzed with REM. The summary of the non-poolable studies and RTW are given in Table 5. Three studies^{38,49,50} showed that the effects of OMTh on pain, disability, and RTW were short term, with the effect declining by final follow up.

Return to work: Two studies^{38,50} explored the effectiveness of OMTh on RTW. Licciardone et al⁵⁰ reported improvements in the number of days of work missed within 4 weeks. Patients in the OMTh group had significant RTW at 4 weeks, but not at 12-week follow up.

Subgroup and sensitivity analysis: We performed a sensitivity analysis that was based on LBP but ignored differences in OMTh intervention and comparators and found high heterogeneity ($I^2 = 59\%$; $P = .0006$;

Figure 4A), which supports the rationale to pool according to OMTh types and comparators. Similarly, the subgroup analysis between sham and SC comparators did not show any significant differences between the two subgroups. The test of interaction ($I^2 = 61.4\%$; $P = .11$) between both groups was not significant, thus justifying our reason to pool sham and SC comparators together (Figure 4B).

Discussion

Overall, our results indicate OMTh can be employed as an effective treatment approach for CNCP patients. Moderate quality evidence showed that vOMTh was significantly associated with reduction in pain severity and disability. OMTh in combination with exercise (vs. exercise only) was significantly associated with reduction in pain severity and disability. Although OMTh was not significantly associated with RTW

Table 4.
GRADE Table (Quality of Evidence)

Intervention	Number of studies and (n=)	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Quality of evidence
Pain severity							
OMTh + Exercise vs. Exercise (Moderate)	2 (n=106)	High	Low risk	Precise	Not detected	Not detected	0+++
OMTh vs. SC (Moderate)	6 (n=710)	High	Low risk	Precise	Not detected	Not detected	0+++
vOMTh vs. gOMTh (Moderate)	3 (n=133)	High	Low risk	Precise	Not detected	Not detected	0+++
Disability							
vOMTh vs. gOMTh (Moderate)	2 (n=79)	High	Low risk	Precise	Not detected	Not detected	0+++
OMTh vs. SC (Moderate)	2 (n=486)	High	Low risk	Precise	Not detected	Not detected	0+++
OMTh + Exercise vs. Exercise (Moderate)	2 (n=106)	High	Low risk	Precise	Not detected	Not detected	0+++
Quality of life							
OMTh vs. SC (Moderate)	2 (n=120)	High	Low	Precise	Not detected	Not detected	0+++
Risk of bias among all the included studies was high, which lowers the quality of evidence.							

Abbreviations: gOMTh, general OMTh; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; OMTh, osteopathic manual therapy; SC, standard care; vOMTh, visceral OMTh.

compared to SC, it showed significant effects in reducing pain, disability, and improving QOL. When compared with other interventions such as chemonucleolysis, physiotherapy, and pharmacologic agents, OMTh did not show significant improvements in pain severity, disability, or QOL; however, the evidence regarding OMTh in comparison with chemonucleolysis, physiotherapy, and gabapentin is based on single studies.

Strengths and Limitations

The key strengths of our review were that, first, we focused on broader patient important outcomes such as reduction in pain severity, functional limitations, improvement in QOL, and RTW. Second, our search strategy was broad and up to date, and methodologic-

ally our review was very rigorous, because we reported our results clearly and transparently, allowing for more precise interpretation. Third, this is, to the best of our knowledge, the first systematic review and meta-analysis that pooled studies based on the similarity between the interventions and comparators, which acted to reduce the heterogeneity in our pooled analyses. We performed a sensitivity analysis based on LBP, ignoring the differences in OMTh and comparators as in previous reviews, and found that heterogeneity was 59% ($p=.02$), thus supporting our rationale to pool studies based on homogeneity of comparator.

Our review also had several limitations. First, we inherited limitations from the primary studies, such as high ROB, for which we downrated quality of evidence for major bias components such as random sequence

Figure 3.

Disability outcomes (A) OMTh vs. standard care, (B) vOMTh vs. gOMTh, (C) OMTh + exercise vs. exercise, and (D) quality of life outcome measure, standard care vs OMTh.

Abbreviations: OMT, osteopathic manipulative treatment; gOMTh, general osteopathic manipulative therapy; OMTh, osteopathic manipulative therapy; vOMTh, visceral osteopathic manipulative therapy.

generation and lack of blinding. Although none of the included studies in our review met all criteria of ROB, this is a common limitation to all procedure-based clinical trials, because it is nearly impossible to blind both patients and practitioner(s). Second, the eligible studies were not powered enough and dropout rate in the eligible studies was very high; except for 2 studies,^{48,50} no others accounted for missing data. Small sample sizes and high dropout rates increase the risk of error in interpreting the results because of over- or underestimating the effect.^{53,54} This was obvious in the study⁵⁰ that used a large sample size and intention to treat; the results were more precise than any other study with a small sample size in pooled analyses. Third, we did not have enough studies to do subgroup analyses based on our *a priori* evidence as reported in the protocol, including ROB, duration of chronic pain, and frequency of OMTh; comorbid psychologic and/or

medical conditions; and the use of cointerventions. Fourth, because of the nature of current evidence, we were unable to explore the effectiveness of OMTh in comparison to medical interventions in a pooled analysis⁴⁴ and, because of incomplete reporting of data, many studies were unpoolable,^{42,49,52} particularly for RTW.^{38,50}

Most of our findings align with previous systematic reviews²⁸⁻³⁰; however, our pooled results showed lower heterogeneity. High heterogeneity in a pooled analysis can confound the interpretation of the results⁵⁵⁻⁵⁷ and often indicates that studies are either clinically or methodologically different and should be reported descriptively.³⁵ As with previous reviews,²⁸⁻³⁰ the quality of evidence (GRADE assessment) in our review was moderate. Previous reviews downrated the GRADE assessment for high heterogeneity but not for high ROB. With respect to ROB, random sequence generation and

Table 5.
Outcomes of Unpoolable Studies

Author	Number of participants analyzed		Outcome measuring scale	Conclusion ES=SMD (95% CI)
	OMTh	Comparator		
Pain				
Burton 2000 ⁴⁹	15	15	VAS	At the beginning of the treatments, OMTh showed significant improvement in pain severity but at 12 months follow up the effect was not significant. <i>ES</i> =-.07 [-.79, .64]
Knebl 2002 ⁴²	NR	NR	Pain rating scale (0-10)	A total of 29 subjects were randomly assigned to either a treatment (OMTh) group or a control group for 14 weeks had significantly decreased perceived pain (<i>P</i> <.01).
Marske 2018 ⁴⁴	10	8	WBF	OMTh + Gabapentin vs. Gabapentin: Within group difference showed that Patients receiving combination of OMTh and Gabapentin had significant improvement in the pain reduction [-2.9 (-5.6, -.3) vs. -.6 (-3.2, 2)] respectively. Between group difference showed no significant improvement between combination of OMTh and gabapentin vs. gabapentin alone. <i>ES</i> =-.65 [-1.61, .31]
	11	8		OMTh vs. Gabapentin: within group difference showed that patients receiving OMTh had significant improvement in the pain reduction as compared to the gabapentin alone [-2.4 (-4.0, -.80 vs. -.6 (-3.2, 2)] respectively. Between group difference showed no significant difference between OMTh vs. gabapentin. <i>ES</i> =-.64 [-1.57, 0.30]
Disability outcomes				
Burton 2000 ⁴⁹	15	15	RDQ	At the beginning of the treatments, OMTh showed significant improvement in disability but at 12 months follow up the effect was not significant. <i>ES</i> =-.22 [-.93, 0.5]
Chown 2008 ⁵²	39	Group Exercise=35 Physiotherapy=24	ODI	OMTh vs. Exercise= Within group difference showed reduction in disability for OMTh, physiotherapy and group exercises [-5.0 (-1.6 to -8.4)], [-4.1 (-1.4 to -6.9)] and [-4.5 (-.9 to -8)] respectively. Between group difference for OMTh vs. Physiotherapy and OMTh vs. group exercises were non-significant [-.09 (-.55, .37)]; [-.05 [-.56, .46)], respectively.
Licciardone 2003 ³⁸	32	Sham=19 No intervention=15	RMDQ	There was improvement initially, but it declined with time. However, there were no significant changes over time among the treatment groups in the RMDQ.
Quality of Life outcome				
Chown 2008 ⁵²	28	Group Exercise=35 Physiotherapy= 4	Euro-QOL	Patients in the physiotherapy group and OMTh group had a significant improvement in the QOL at 6 months [0.10 (.01 to .18)] and [.11 (.02 to .19)] respectively but not in group exercise [.08 (-.02 to .18)]. Between group difference showed no significant improvement in OMTh vs. physiotherapy and OMTh vs. group exercise [.04 (-.41, .50)] and [.13 (-.40, .66)] respectively.

(continued)

Table 5 (continued).
Outcomes of Unpoolable Studies

Author	Number of participants analyzed		Outcome measuring scale	Conclusion ES=SMD (95% CI)
	OMTh	Comparator		
Licciardone 2003 ³⁸	32	34	SF-36- Physical component summary	OMTh was not significantly associated with improvement in physical component summary score. <i>ES=.08 [-.40, .57]</i>
Licciardone 2013 ⁵⁰	230	225	SF-36 - General health	OMTh was not significantly associated with improvement in overall general health. <i>ES=0 [-.18, .18]</i>
Schwerla 2008 ⁴⁰	22	18	QOL, SF-36 - Bodily pain	The values of the osteopathic group showed better results for all aspects and a significant reduction for 'bodily pain' (<i>P=.019</i>).
Return to Work				
Licciardone 2003 ³⁸	32	Sham=19 No intervention=15	Number of lost workdays in the past 4 weeks	There were no substantial changes among the treatment for lost work or school days over time.
Licciardone 2013 ⁵⁰	180	180	Number of lost workdays in the past 4 weeks	The OMTh participants were less likely than the sham OMTh participants to report work disability due to LBP at the week 4 and 8 mark, respectively. Neither of the groups showed significant improvements at week 12.

Abbreviations: ES, standard mean deviation (95% confidence interval); LBP, low back pain; NR, not reported; ODI, Oswestry Disability Index; OMTh, osteopathic manual therapy; QOL, quality of life; RDQ, Reflex Disease Questionnaire; RMDQ, Roland Morris Disability Questionnaire; SF-36, Short Form Health Survey; SMD, standardized mean difference; VAS, visual analog scale; WBF, Wong-Baker FACES Pain Rating Scale.

blinding are considered major influencers^{56,57} and will lower the confidence. We downrated the quality of evidence for high ROB, but heterogeneity in our pooled analyses was low, which makes the interpretation more transparent. A few studies in our review identified the effect of OMTh as short term^{30,38,43,49,50}; similar findings were also reported in previous studies²⁶ and are a common occurrence with other manipulation techniques.^{58,59} As compared to previous reviews, our search strategy was broader, more up to date, and included studies with CNCP²⁸⁻³⁰ and RCTs^{27,60} only. We were also cautious about not including duplicate or substudies of the main trials, which was a limitation of a previous review.²⁶

Clinical Implications

There was moderate quality evidence that OMTh is effective in reducing pain severity and disability and

improving QOL. An interesting finding in our review was that pain symptoms improved with OMTh, although OMTh provided significant RTW at 4 weeks but not at 12-week follow up. It is important to consider that reduction in pain may not necessarily be the only contributor, because RTW also depends on the psychologic and physical demands of the individual's workplace.⁶¹ As we focused on patient-important outcomes, there is a potential that improvements in pain, disability, and QOL with OMTh will improve patient's psychosocial well-being and self-esteem, which may enhance the likelihood of RTW. This might also be considered as evidence that, because of chronicity and deconditioning associated with CNCP, more frequent and longer courses of OMTh will be helpful with the multiple aspects of involvement, because the pathophysiology becomes more complex and maintains achieved levels of musculoskeletal function.⁶²⁻⁶⁴

Figure 4.

Sensitivity and subgroup analysis. (A) Based on low back pain while ignoring the OMTh type and comparator type. (B) Based to compare the sham OMTh vs. standard care (pain severity). *Abbreviations:* OMTh, osteopathic manipulative therapy.

Another important finding in our review is that when vOMTh techniques were included in treatment, there was improved effectiveness as compared to gOMTh techniques in pain reduction and disability. Possible explanations for this might be a greater consideration for the anatomic and fascial connections relative to viscerosomatic reflexes potentially involved in LBP, which constitutes key osteopathic philosophy.⁶⁴⁻⁶⁶

Conclusion

This is the most comprehensive review to date, to our knowledge, done with methodologic rigor that considers the effectiveness of OMTh in CNCP. Our findings provide evidence that OMTh alone or in combination with exercise is effective in pain, disability and increasing QOL. vOMTh techniques are proven more effective

than gOMTh, which does not consider visceral involvement. Due to the more complex pathophysiology involved, more frequent regular OMTh might provide better results.⁶²⁻⁶⁴ Our results should, however, be interpreted cautiously because of small sample sizes, high ROB, and high dropout rates. In the future, there is a need for high quality RCTs with larger sample sizes to better demonstrate the effectiveness of OMTh in the management of CNCP.

Author Contributions

Drs Rehman, Ferguson, Blair, Bozek, Alison, and Johnston provided substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; Drs Rehman, Ferguson, Blair, Bozek, Johnston drafted the article or revised it critically, provided expert advice for important intellectual content; all authors gave final approval of the version of the article to be published; and all authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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