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REVIEW

Management of Acute Pain From Non–Low Back Musculoskeletal Injuries

A Systematic Review and Network Meta-analysis of Randomized Trials

Jason W. Busse, DC, PhD; Behnam Sadeghirad, PharmD, MPH, PhD; Yvgeniy Oparin, MD; Eric Chen, HBSc; Anna Goshua, BHSc; Curtis May, BKin; Patrick J. Hong, MD; Arnav Agarwal, MD; Yaping Chang, PhD; Stephanie A. Ross, PhD; Peter Emary, DC, MSc; Ivan D. Florez, MD, MSc; Salmi T. Noor, MSc; William Yao, BHSc; Annie Lok, MHE; Syed Hussain Ali, MD; Samantha Craigie, MSc; Rachel Couban, MA, MISt; Rebecca L. Morgan, MPH, PhD; Kayli Culig, BHSc; Sonia Brar, MD; Khashayar Akbari-Kelachayeh, BHSc; Alex Pozdnyakov, MD; Yaad Shergill, DC; Laxsanaa Sivananthan, HBSc; Bahareh Zihayat, PharmD; Aninditee Das, MD; and Gordon H. Guyatt, MD, MSc

Background: Patients and clinicians can choose from several treatment options to address acute pain from non–low back musculoskeletal injuries.

Purpose: To assess the comparative effectiveness of outpatient treatments for acute pain from non–low back musculoskeletal injuries by performing a network meta-analysis of randomized clinical trials (RCTs).

Data Sources: MEDLINE, EMBASE, CINAHL, PEDro (Physiotherapy Evidence Database), and Cochrane Central Register of Controlled Trials to 2 January 2020.

Study Selection: Pairs of reviewers independently identified interventional RCTs that enrolled patients presenting with pain of up to 4 weeks' duration from non–low back musculoskeletal injuries.

Data Extraction: Pairs of reviewers independently extracted data. Certainty of evidence was evaluated by using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Data Synthesis: The 207 eligible studies included 32 959 participants and evaluated 45 therapies. Ninety-nine trials (48%) enrolled populations with diverse musculoskeletal injuries, 59 (29%) included patients with sprains, 13 (6%) with whiplash, and 11 (5%) with muscle strains; the remaining trials included various injuries ranging from nonsurgical fractures to contusions. Topical nonsteroidal anti-inflammatory agents (NSAIDs) proved to have the greatest net benefit, followed by oral NSAIDs and acetaminophen with or without diclofenac. Effects of these agents on pain were modest (around 1 cm on a 10-cm visual analogue scale, approximating the minimal important difference). Regarding opioids, compared with placebo, acetaminophen plus an opioid improved intermediate pain (1 to 7 days) but not immediate pain (≤2 hours), tramadol was ineffective, and opioids increased the risk for gastrointestinal and neurologic harms (all moderate-certainty evidence).

Limitations: Only English-language studies were included. The number of head-to-head comparisons was limited.

Conclusion: Topical NSAIDs, followed by oral NSAIDs and acetaminophen with or without diclofenac, showed the most convincing and attractive benefit–harm ratio for patients with acute pain from non–low back musculoskeletal injuries. No opioid achieved benefit greater than that of NSAIDs, and opioids caused the most harms.

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Acute pain from non–low back musculoskeletal injuries includes strains and sprains lasting 4 weeks or less. Musculoskeletal injuries are common, most often affect working-age men, and resulted in more than 65 million health care visits in the United States in 2010. Musculoskeletal injuries accounted for 4% of all health care visits to U.S. physician offices and outpatient clinics, as well as 15% of all emergency department visits (1).

Although patients and clinicians can choose among many treatment options for acute musculoskeletal pain (2–6), patient outcomes are often poor. In a North American survey of 842 patients with acute pain, 40% reported unchanged or increased pain after visiting the emergency department and 74% were discharged while having moderate to severe pain (7).

The most recent systematic review of treatment for acute musculoskeletal injuries had limitations, including failure to generate pooled effect estimates, appraise the overall certainty of evidence, and assess the comparative effectiveness of interventions (8). We addressed these limitations in a systematic review and network meta-analysis (NMA) of randomized clinical trials (RCTs) addressing treatment for acute pain from non–low back musculoskeletal injuries.

METHODS

We adhered to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) extension statement for reporting of systematic reviews incorporating NMAs (9), registered our review with PROSPERO (CRD42018094412), and published our protocol (10). This review informed a clinical practice

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Data Sources and Searches

An academic librarian developed search strategies (10) for MEDLINE, EMBASE, CINAHL, PEDro (Physiotherapy Evidence Database), and Cochrane Central Register of Controlled Trials from inception to 2 January 2020. To identify additional eligible studies, we reviewed reference lists from eligible trials and relevant reviews and guidelines.

Study Selection

Eligible studies were parallel-design trials that enrolled adult patients (aged ≥18 years) with acute pain from non–low back–related musculoskeletal injuries (pain duration ≤4 weeks or defined by authors as "acute"); randomly assigned at least 10 patients per study group; and compared currently available pain relief interventions, provided in an outpatient setting, with one another or versus a placebo or sham. Ten pairs of reviewers independently screened titles, abstracts, and full-text articles of potentially eligible studies and resolved disagreement through discussion. We used online systematic review software (DistillerSR [Evidence Partners]) for literature screening.

Data Extraction and Quality Assessment

Seven pairs of reviewers independently extracted data from eligible studies and assessed risk of bias by using a modified Cochrane Risk of Bias Tool (11, 12). Abstracted data included participant and trial characteristics, details of interventions and comparators, and patient-important outcomes (namely pain, physical function, health-related quality of life, patient satisfaction, return to work, proportion of patients with relief, reinjury, and adverse events). For trials with different follow-up lengths, we abstracted data from the longest follow-up for all outcomes except pain, which we abstracted at the 3 most common posttreatment time points reported among eligible trials: 15 minutes to 2 hours, 1 to 7 days, and 3 weeks to 6 months. We contacted study authors for missing or unclear information.

Data Synthesis and Analysis

Pooling different instruments that report on a common domain typically is done by converting each instrument to SD units and combining effects across studies as the standardized mean difference; however, this approach has limitations, including difficulties in interpretation and vulnerability to baseline heterogeneity of enrolled patients (13, 14). Therefore, by using linear transformation and assuming that instruments reporting on shared domains have similar measurement properties, we converted all measures of pain intensity and physical functioning to 10-cm visual analogue scales (VASs) (15). We pooled each direct paired comparison of pain or physical function reported by more than 1 study as the weighted mean difference (WMD) and associated 95% CI by using change scores from baseline to the end of follow-up to address interpatient variability. If authors did not report change scores, we estimated them by using the baseline and end-of-study scores and the associated SDs and the median correlation coefficient reported by the trials at lowest risk of bias. To optimize interpretability of our findings for continuous outcomes, we used the network estimate of treatment effects to model the risk difference (RD) for achieving the minimally important difference (MID) (15), the smallest change in a patient-reported outcome that patients perceive as important (16). We used an MID of 1 cm for both the 10-cm VAS for pain (17) and the 10-cm VAS for physical function (18). In our presentation of the results, RDs refer to the modeled estimates in relation to the MID (that is, the proportion of patients who achieve an MID gain in the intervention vs. the control group).

For dichotomous outcomes, we calculated the pooled odds ratio (OR) and modeled RD with corresponding 95% CIs. Initially, we performed a conventional pairwise meta-analysis by using a DerSimonian–Laird random-effects model and then performed a frequentist NMA using the methodology of multivariate meta-analysis assuming a common heterogeneity parameter (19, 20), using the *mvmeta* command and network suite in Stata (StataCorp) (21, 22). For direct comparisons with 3 or more studies, we performed a sensitivity analysis using a Hartung–Knapp random-effects model for conventional pairwise meta-analysis.

We assessed heterogeneity between RCTs for each direct comparison with visual inspection of forest plots and the I^2 statistic (23). Heterogeneity of 0% to 40% was considered as "might not be important," 30% to 60% as "moderate heterogeneity," 50% to 90% as "substantial heterogeneity," and 75% to 100% as "considerable heterogeneity." The Cochrane Collaboration has proposed overlapping categories to convey that there are no strict cutoffs for interpreting heterogeneity, and categorization depends on the magnitude and direction of effects, as well as the strength of evidence for heterogeneity. When possible, we explored the following a priori hypotheses, determined before analysis through discussions between our study team and a technical expert panel, to explain heterogeneity between trials: First, different clinical conditions will show different treatment effects. Second, more severe injuries will show smaller treatment effects than less severe injuries. Third, older patients will show smaller treatment effects than younger patients. Fourth, longer follow-up will show smaller treatment effects than shorter follow-up. Fifth, higher-dose or higher-intensity treatment will show larger treatment effects. For all direct comparisons, if at least 10 RCTs contributed to a meta-analysis, we assessed small-study effects by using the Harbord test for binary outcomes and Egger test for continuous outcomes (24).

We used the "design-by-treatment" model (global test) to assess the coherence assumption for each network (25). We used the node-splitting method to evaluate local (loop-specific) incoherence (26, 27) in each closed loop of the network separately as the difference between direct and indirect evidence.

After reviewing the literature (28) and consulting with our technical expert panel, we elected to combine

all acute musculoskeletal conditions in our analyses. Upon consultation with a clinical pharmacologist, a pharmacist, and the technical expert panel, we included pharmacologic treatments with similar properties and clinical effects in single nodes, which was our primary network of interventions. We explored the appropriateness of these groupings by deriving the statistical consistency of each network and local loops of evidence for each outcome, neither of which showed evidence of incoherence. We conducted a sensitivity analysis considering all interventions as separate nodes, as a secondary network of interventions.

We did not perform NMA if 10 or fewer studies reported an outcome, but we did report a conventional pairwise meta-analysis if 2 or more studies were available. We estimated the ranking probabilities by using the surface under the cumulative ranking curve, mean ranks, and rankograms. We used Stata 15.1 for all analyses.

Certainty of Evidence

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for rating the certainty of evidence for each network estimate (29–31). Network estimate certainty was based on the source of evidence, direct or indirect, that most contributed to the network estimate. We rated down the certainty for incoherence between the indirect and direct estimates (31, 32), or we used the direct or indirect estimate of effect instead of the network estimate if supported by higher certainty of evidence. We did not rate down the certainty rating of the network estimate twice if both intransitivity and incoherence were present. We evaluated imprecision by using the network estimate; if the 95% CI excluded the null effect, we did not rate down for imprecision unless the comparison was informed by fewer than 300 observations for continuous outcomes or 300 events for binary outcomes.

Categorization of Interventions

We categorized interventions from most to least effective on the basis of the treatment effect estimates for benefits and harms obtained from the NMA, as well as their associated certainty of evidence. For each effectiveness outcome, we created groups of interventions as follows: the reference intervention (placebo) and interventions no different from placebo, which we refer to as "among the least effective"; interventions superior to placebo but not superior to other interventions, which we describe as "inferior to the most effective but superior to the least effective" (category 2 interventions); and interventions that proved superior to at least 1 category 2 intervention (which we defined as "among the most effective"). We used the same approach for harm outcomes but designated groups as follows: no more harmful than placebo, less harmful than some alternatives but more harmful than placebo, and among the most harmful. We then categorized interventions as those with moderate- or high-certainty evidence and those with low- or very-low-certainty evidence relative to placebo (33).

Role of the Funding Source

The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

RESULTS

Of 26 224 citations, 207 trials including 32 959 patients proved eligible (**Supplement Figure 1** and **Supplementary Appendix 1**; all supplemental content is available at Annals.org). Of the 9 authors contacted for additional data, 2 responded. The median of the mean age among patients in the eligible trials was 34 years (interquartile range, 28 to 39 years). Among 154 trials that provided this information, the median average pain score at baseline was 6.5 cm (interquartile range, 5.3 to 7.3 cm) on a 10-cm VAS. Among the 207 trials, 63 (30%) reported receiving no funding or nonindustry funding, 59 (29%) reported industry funding, 8 (4%) reported receiving donated drugs from industry, and 77 (37%) had no funding statement. Fourteen of the 207 studies (7%) included in our review reported whether patients were involved in litigation or seeking or receiving disability benefits: 10 trials used these features as exclusion criteria (34–43), 3 trials enrolled 68 patients who had engaged a lawyer and 430 patients who had filed a compensation claim (44–46), and 1 trial enrolled 13 patients receiving sickness benefits (47).

Among eligible trials, 99 (48%) enrolled populations with diverse musculoskeletal injuries; 59 (29%) included patients with sprains, 13 (6%) with whiplash, and 11 (5%) with muscle strains. The remaining trials included various injuries, ranging from nonsurgical fractures to contusions. Sixty trials (29%) enrolled persons with isolated ankle injuries, 54 (26%) with various injuries, 23 (11%) with neck injuries, 19 (9%) with injuries of the upper and lower limbs, and 14 (7%) with isolated upper limb injuries; 14 trials (7%) did not specify an injury location. The remaining 23 trials enrolled patients with isolated injuries to the hamstring muscle, knee, lower limb, hip, elbow, chest, or ribs (**Supplement Tables 1** to **3**)

Of the eligible studies, 15 did not contribute outcome data and 22 became observational studies after interventions were collapsed into common nodes. Interventions in 16 RCTs unconnected to the rest of the network for any outcome were excluded from the NMA (**Supplement Tables 3** and **4**). Of the remaining 154 trials, after oral nonsteroidal anti-inflammatory drug (NSAID), topical NSAID, and acetaminophen–opioid treatment groups were merged, an additional 32 studies were excluded from our primary NMA (**Supplement Tables 2**, **5**, and **6**). Among studies evaluating joint manipulation, osteopathic physicians, chiropractors, and physical therapists provided treatment directed at the ankle and the cervical and thoracic spine (**Supplement Table 7**). Details on exercise therapy are provided in **Supplement Table 8**.

Risk of Bias

Most trials (76% [158 of 207]) were at high risk of bias for at least 1 domain; 115 (56%) adequately generated their randomization sequence, 150 (73%) concealed allocation, 121 (59%) blinded patients, 116 (56%) blinded health care providers, 128 (62%) blinded data collectors, and 129 (62%) blinded outcome assessors. Forty-three trials (21%) reported 20% or more of the outcome data as missing (Supplement Tables 9 to 11).

Pain Relief at 2 Hours or Less

Twenty-eight RCTs involving 4464 patients reported pain relief at 2 hours or less (Supplement Figure 2). In 10 of the 25 direct comparisons, 2 or more studies were available for conventional pairwise meta-analysis, in which heterogeneity was substantial ($I^2 \geq 54\%$) in 7 comparisons (Supplement Table 12). We found no evidence of global or loop-specific incoherence (Supplement Figure 3).

Compared with placebo, moderate-certainty evidence showed that topical NSAIDs reduced pain within 2 hours of treatment, with a mean effect approximating the MID (WMD, −1.02 cm [95% CI, −1.64 to −0.39 cm] on a 10-cm VAS for pain; MID of 1 cm; RD for achieving the MID, 23%), as did topical NSAIDs plus menthol gel (WMD, −1.68 cm [CI, −3.09 to −0.27 cm]; RD, 36%), oral NSAIDs (WMD, −0.93 cm [CI, −1.49 to −0.37 cm]; RD, 21%), acetaminophen plus diclofenac (WMD, −1.11 cm [CI, −2.00 to −0.21 cm]; RD, 25%), and acetaminophen alone (WMD, −1.03 cm [CI, −1.82 to −0.24 cm]; RD, 23%) (Figure 1, Appendix Figure 1, and Supplement Table 13).

Low-certainty evidence suggested that compared with placebo, transbuccal fentanyl (WMD, −3.52 cm [CI, −4.99 to −2.04 cm]; RD, 57%) was the most effective treatment in reducing pain within 2 hours. Low-certainty evidence suggested that acetaminophen plus ibuprofen plus codeine (WMD, −1.36 cm [CI, −2.49 to −0.23 cm]; RD, 30%), transcutaneous electrical nerve stimulation (WMD, −1.94 cm [CI, −2.90 to −0.98 cm]; RD, 40%), specific acupressure (WMD, −1.59 cm [CI, −2.52 to −0.66 cm]; RD, 34%), and joint manipulation (WMD, −1.75 cm [CI, −2.68 to −0.81 cm]; RD, 37%) were more effective than placebo but less effective than fentanyl (Figure 1, Appendix Figure 1, and Supplement Table 13).

Pain Relief at 1 to 7 Days

Pain relief at 1 to 7 days was reported in 69 studies involving 10 829 patients (Supplement Figure 4) and including 33 direct comparisons, among which 11 had 2 or more studies available for conventional pairwise meta-analysis; heterogeneity was substantial in 8 comparisons ($I^2 \geq 56\%$) (Supplement Table 14). The design-by-treatment interaction model showed no evidence of incoherence; however, we observed incoherence in 3 loops of the evidence (Supplement Figure 5), in which the difference between direct and indirect comparison was statistically significant for acetaminophen plus opioids versus oral NSAIDs, acetaminophen plus opioids versus placebo, and oral NSAIDs versus transcutaneous electrical nerve stimulation (Supplement Table 14). We therefore used the direct estimate of effect from conventional meta-analysis, over the network estimate, for acetaminophen plus opioid versus placebo, which showed high-certainty evidence of improved pain relief (WMD, −1.71 cm [CI, −2.97 to −0.46 cm] on a 10-cm VAS for pain; MID of 1 cm; RD for achieving the MID, 19%).

Compared with placebo, moderate-certainty evidence showed that acetaminophen alone (WMD, −1.07 cm [CI, −1.89 to −0.24 cm]; RD, 15%), topical NSAIDs (WMD, −1.08 cm [CI, −1.40 to −0.75 cm]; RD, 15%), and oral NSAIDs (WMD, −0.99 cm [CI, −1.46 to −0.52 cm]; RD, 14%) were among the most effective treatments in reducing pain at 1 to 7 days. Low-certainty evidence showed no difference in pain relief at 1 to 7 days between acetaminophen plus opioids and NSAIDs (Figure 1, Appendix Figure 1, and Supplement Table 15).

Low-certainty evidence suggested that acetaminophen plus chlorzoxazone (WMD, −2.92 cm [CI, −5.41 to −0.43 cm]; RD, 24%), specific acupressure (WMD, −2.09 cm [CI, −3.86 to −0.32 cm]; RD, 21%), and transcutaneous electrical nerve stimulation (WMD, −1.18 cm [CI, −2.09 to −0.28 cm]; RD, 16%) were among the most effective treatments (Figure 1, Appendix Figure 1, and Supplement Table 15).

Physical Function

Thirty studies involving 3549 patients reported physical function (Supplement Figure 6) in 15 direct comparisons, among which 8 had 2 or more studies available for conventional pairwise meta-analysis; heterogeneity was substantial in 3 comparisons ($I^2 \geq 70\%$) (Supplement Table 16). We found no evidence of global or loop-specific incoherence (Supplement Figure 7).

Moderate-certainty evidence showed that compared with placebo, topical NSAIDs (WMD, 1.66 cm [CI, 1.16 to 2.16 cm] on a 10-cm VAS for physical function; MID of 1 cm; RD for achieving the MID, 15%) was the most effective treatment in improving physical function. Oral NSAIDs (WMD, 0.73 cm [CI, 0.17 to 1.30 cm]; RD, 9%) were inferior to topical NSAIDs but superior to placebo. Among the interventions supported by low- or very-low-certainty evidence, only specific acupressure (WMD, 1.51 cm [CI, 0.42 to 2.61 cm]; RD, 14%) improved physical function compared with placebo (Figure 1, Appendix Figure 1, and Supplement Table 17).

Patients' Satisfaction With Treatment

Seventeen studies involving 10 390 patients and addressing 15 direct comparisons reported treatment satisfaction (Supplement Figure 8 and Supplement Table 18). In 3 comparisons, 2 or more studies were available for conventional pairwise meta-analysis; the heterogeneity was substantial in 1 comparison ($I^2 = 89\%$) (Supplement Table 19). We found no evidence of global or loop-specific incoherence (Supplement Figure 9).

High-certainty evidence showed that compared with placebo, only topical NSAIDs (OR, 5.20 [CI, 2.03 to

13.33]; RD, 34%) demonstrated a statistically significant increase in the likelihood of treatment satisfaction (Figure 1 and Supplement Tables 20 and 21).

Symptom Relief

Symptom relief was reported in 26 studies involving 4067 patients (Supplement Figure 10 and Supplement Table 22) addressing 21 direct comparisons, among which 5 had 2 or more studies available for conventional pairwise meta-analysis. Heterogeneity was substantial in 1 comparison (I^2 = 82%) (Supplement Table 23). We found no evidence of global or loop-specific incoherence (Supplement Figure 11). Compared with placebo, moderate-certainty evidence showed that topical NSAIDs alone (OR, 6.39 [CI, 3.48 to 11.75]; RD, 40%), oral NSAIDs (OR, 3.10 [CI, 1.39 to 6.91]; RD, 17%), and acetaminophen plus diclofenac

Figure 1. NMA results, sorted based on GRADE certainty of evidence and effect estimate for the comparisons of active treatments versus placebo for effectiveness and harm outcomes.

Intervention	Effectiveness Outcomes					Harms Outcomes		
	Pain Relief ≤2 h After Tx: MD (95% CI)	Pain Relief 1–7 d After Tx: MD (95% CI)	Physical Function: MD (95% CI)	Treatment Satisfaction: OR (95% CI)	Symptom Relief: OR (95% CI)	GI-Related AEs: OR (95% CI)	Neurologic AEs: OR (95% CI)	Dermatologic AEs: OR (95% CI)
Topical NSAID	*−1.02 (−1.64 to −0.39)*	*−1.08 (−1.40 to −0.75)*	*1.66 (1.16 to 2.16)*	*5.20 (2.03 to 13.33)*	*6.39 (3.48 to 11.75)*	1.14 (0.65 to 2.01)	1.18 (0.51 to 2.74)	0.78 (0.52 to 1.15)
Oral NSAID	*−0.93 (−1.49 to −0.37)*	*−0.99 (−1.46 to −0.52)*	*0.73 (0.17 to 1.30)*	3.24 (0.43 to 24.70)	*3.10 (1.39 to 6.91)*	*1.77 (1.33 to 2.35)*	1.02 (0.65 to 1.59)	1.33 (0.43 to 4.09)
Acetaminophen	*−1.03 (−1.82 to −0.24)*	*−1.07 (−1.89 to −0.24)*	0.90 (−0.27 to 2.61)	2.43 (0.18 to 32.70)	2.73 (0.90 to 8.27)	0.50 (0.06 to 4.38)	–	–
Acetaminophen + Diclofenac	*−1.11 (−2.00 to −0.21)*	−1.09 (−2.20 to 0.01)	–	3.45 (0.18 to 66.96)	*3.72 (1.02 to 13.52)*	–	–	–
Topical NSAID + Menthol Gel	*−1.68 (−0.27 to −3.09)*	−0.89 (−2.33 to 0.54)	–	–	*13.34 (3.30 to 53.92)*	2.35 (0.04 to 124.85)	1.22 (0.02 to 69.98)	0.53 (0.05 to 6.29)
TENS	*−1.94 (−2.90 to −0.98)*	*−1.18 (−2.09 to −0.28)*	0.68 (−0.20 to 1.57)	–	6.00 (0.78 to 46.36)	1.25 (0.14 to 11.01)	1.12 (0.13 to 9.98)	1.18 (0.13 to 11.03)
Specific Acupressure*	*−1.59 (−2.52 to −0.66)*	*−2.09 (−3.86 to −0.32)*	*1.51 (0.42 to 2.61)*	0.50 (0.04 to 6.49)	2.54 (0.52 to 12.38)	0.80 (0.02 to 41.67)	0.80 (0.01 to 42.60)	0.80 (0.01 to 45.60)
Joint manipulation	*−1.75 (−2.68 to −0.81)*	0.40 (−1.71 to 2.51)	0.09 (−1.06 to 0.87)	–	*167.71 (6.67 to 4217.10)*	0.50 (0.01 to 31.30)	1.41 (0.03 to 78.76)	–
Acetaminophen + Chlorzoxazone	–	*−2.92 (−5.41 to −0.43)*	–	–	–	0.35 (0.01 to 10.59)	–	–
Laser Therapy	–	−1.04 (−2.28 to 0.19)	–	–	*32.08 (4.93 to 208.60)*	0.49 (0.01 to 24.85)	0.49 (0.01 to 25.41)	0.49 (0.01 to 27.21)
Mobilization	–	3.40 (−0.05 to 6.85)	0.12 (−0.59 to 0.83)	2.07 (0.07 to 58.49)	*7.99 (1.29 to 49.41)*	0.93 (0.02 to 47.12)	0.93 (0.02 to 48.18)	0.93 (0.02 to 51.60)
Acetaminophen + Opioid†	−0.52 (−1.47 to 0.43)	*−1.71 (−2.97 to −0.46)*	–	2.50 (0.14 to 44.86)	1.47 (0.55 to 3.91)	*5.63 (2.84 to 11.16)*	*3.53 (1.92 to 6.49)*	–
Acetaminophen, Ibuprofen + Codeine	*−1.36 (−2.49 to −0.23)*	–	–	–	–	–	–	–
Acetaminophen + Ibuprofen	−0.70 (−1.62 to 0.22)	−1.18 (−2.74 to 0.38)	–	–	3.62 (0.99 to 13.14)	–	–	–
Nonspecific Acupressure	−0.05 (−0.99 to 0.89)	−0.18 (−1.91 to 1.55)	−0.18 (−1.32 to 0.96)	0.44 (0.03 to 5.76)	1.80 (0.36 to 9.03)	0.85 (0.02 to 44.76)	0.85 (0.02 to 45.76)	0.85 (0.01 to 48.97)
Exercise	–	−0.81 (−2.64 to 1.02)	−0.43 (−1.00 to 0.14)	3.50 (0.21 to 59.42)	0.84 (0.31 to 2.29)	1.04 (0.06 to 17.06)	1.08 (0.07 to 17.95)	1.08 (0.06 to 18.84)
Cyclobenzaprine	–	−2.03 (−4.11 to 0.06)	–	–	–	0.64 (0.03 to 15.74)	1.95 (0.20 to 18.88)	–
Supervised Rehab	–	0.96 (−0.35 to 2.27)	0.24 (−0.59 to 1.07)	2.25 (0.15 to 34.07)	5.09 (0.84 to 30.78)	1.06 (0.02 to 54.49)	1.06 (0.02 to 55.71)	1.06 (0.02 to 59.65)
Ibuprofen + Cyclobenzaprine	−1.05 (−2.63 to 0.53)	*−1.51 (−3.06 to 0.04)*	–	5.52 (0.21 to 147.01)	–	1.10 (0.13 to 9.42)	*4.91 (1.45 to 16.61)*	–
Menthol Gel	–	−1.14 (−2.28 to 0.00)	0.70 (−0.61 to 2.02)	–	–	–	–	1.00 (0.11 to 8.91)
Ultrasonography	–	−0.40 (−2.46 to 1.66)	–	–	–	–	–	–
Glucosamine	–	−0.10 (−1.89 to 1.69)	–	–	–	–	–	–
Phenyramidol	–	–	–	–	–	–	0.32 (0.01 to 8.45)	–
Massage Therapy	−0.70 (−1.90 to 0.50)	–	–	–	–	–	–	–
Education	–	–	0.10 (−0.67 to 0.87)	–	0.93 (0.39 to 2.24)	–	–	–
Acetaminophen, Ibuprofen + Oxycodone	−0.94 (−2.27 to 0.38)	–	–	–	–	–	–	–
Fentanyl	*−3.52 (−4.99 to −2.04)*	–	–	–	–	*59.38 (6.21 to 567.71)*	*5.73 (1.20 to 27.47)*	–
Tramadol	0.95 (−0.80 to 2.70)	–	–	–	–	5.98 (0.33 to 108.25)	*6.72 (1.24 to 36.39)*	–

Color Key:

Certainty of Evidence	Statistically Significant Difference With Placebo and ≥1 Other Tx	Statistically Significant Difference With Placebo	Statistically No Difference With Placebo
High or Moderate	Among the most effective	Inferior to the most effective, but superior to placebo	No more effective than placebo
	Among the most harmful	Less harmful than some alternatives, but more harmful than placebo	No more harmful than placebo
Low or Very Low	May be among the most effective (or harmful)	May be inferior to the most effective, but superior to placebo (or less harmful than some alternatives, but more harmful than placebo)	May be no more effective (or harmful) than placebo

Results are the MD on a scale of 0 to 10, or ORs, and associated 95% CI between the intervention and placebo from the NMA. For pain relief, scores range from 0 to 10 cm; lower is better (MID is 1 cm). For physical function, scores range from 0 to 10 cm; higher is better (MID is 1 cm). An OR greater than 1 for effectiveness outcomes indicates that the treatment is superior to placebo; an OR greater than 1 for adverse events indicates that the treatment is associated with a higher likelihood of harms compared with placebo. Numbers in italics represent statistically significant results. AE = adverse event; GI = gastrointestinal; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; MID = minimally important difference; NMA = network meta-analysis; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; Rehab = rehabilitation; TENS = transcutaneous electrical nerve stimulation; Tx = treatment.
* Intervention details among trials exploring specific acupressure are provided in Supplement Table 40.
† Because of incoherence, the effect estimate for pain relief (1 to 7 days after treatment) is from the direct comparison instead of the network estimate.

(OR, 3.72 [CI, 1.02 to 13.52]; RD, 21%) were the most effective treatments for symptom relief (**Figure 1** and **Supplement Tables 21** and **24**).

Low- to very-low-certainty evidence suggested that joint manipulation (OR, 167.71 [CI, 6.67 to 4217.10]; RD, 81%) was the most effective treatment for symptom relief, and that topical NSAIDs combined with menthol gel (OR, 13.34 [CI, 3.30 to 53.92]; RD, 54%), low-level laser therapy (OR, 32.08 [CI, 4.93 to 208.60]; RD, 59%), and mobilization (OR, 7.99 [CI, 1.29 to 49.41]; RD, 21%) were inferior to joint manipulation but superior to placebo (**Figure 1** and **Supplement Tables 21** and **24**).

Gastrointestinal Adverse Events

Gastrointestinal adverse events were reported in 45 studies involving 7070 patients (**Supplement Figure 12** and **Supplement Table 25**) addressing 24 direct comparisons, among which 5 had 2 or more studies available for conventional pairwise meta-analysis; there was no statistical heterogeneity in any of the comparisons (I^2 = 0%) (**Supplement Table 26**). We found no evidence of global or loop-specific incoherence (**Supplement Figure 13**).

Compared with placebo, moderate-certainty evidence showed that fentanyl (OR, 59.38 [CI, 6.21 to 567.71]; RD, 37%) and acetaminophen plus opioids (OR, 5.63 [CI, 2.84 to 11.16]; RD, 13%) were among the most harmful treatments, increasing the likelihood of gastrointestinal adverse events. Moderate-certainty evidence existed that oral NSAIDs significantly increased the likelihood of gastrointestinal adverse events (OR, 1.77 [CI, 1.33 to 2.35]; RD, 4%) compared with placebo but were less harmful than fentanyl or acetaminophen plus opioids (**Figure 1**, **Appendix Figure 2**, and **Supplement Table 27**).

Neurologic Adverse Events

Neurologic adverse events were reported in 37 studies involving 6245 patients (**Supplement Figure 14** and **Supplement Table 25**). Of the 22 available direct comparisons, 6 had 2 or more studies available for conventional pairwise meta-analysis, in which heterogeneity was low (I^2 < 40%) (**Supplement Table 28**). We found no evidence of global or loop-specific incoherence (**Supplement Figure 15**).

Relative to placebo, high- to moderate-certainty evidence showed that acetaminophen plus opioids (OR, 3.53 [CI, 1.92 to 6.49]; RD, 16%), fentanyl (OR, 5.73 [CI, 1.20 to 27.47] [moderate certainty]; RD, 22%), and tramadol (OR, 6.72 [CI, 1.24 to 36.39]; RD, 22%) caused greater harm due to neurologic events. Low-certainty evidence suggested that ibuprofen and cyclobenzaprine combination therapy increases the likelihood of neurologic adverse events (OR, 4.91 [CI, 1.45 to 16.61]; RD, 20%) (**Figure 1**, **Appendix Figure 2**, and **Supplement Table 29**).

Dermatologic Adverse Events

Thirty-eight studies involving 7235 patients reported dermatologic adverse events (**Supplement Figure 16** and **Supplement Table 25**, available at Annals .org). Of the 13 available direct comparisons, 4 had 2 or more studies available for conventional pairwise meta-analysis, in which heterogeneity was low (I^2 < 40%) (**Supplement Table 30**). We found no evidence of global or loop-specific incoherence (**Supplement Figure 17**). Our analysis showed that no intervention caused any statistically significant dermatologic-related harm compared with placebo (**Supplement Table 31**).

Additional Analyses

Supplement Tables 32 to **34** and **Supplement Figures 18** to **25** provide details of rankings and values for surface under the cumulative ranking curve for all outcomes. We were unable to explore between-study heterogeneity based on clinical condition or injury severity, because most eligible trials enrolled mixed populations. We performed network metaregression to explore the impact of allocation concealment, blinding, missing participant data, and length of follow-up, and found no statistically significant coefficients for any of our outcomes; however, we rated down certainty of evidence for risk of bias (when present) because of concerns that our analyses may have been underpowered to detect associations. We were unable to explore associations between dose or intensity of treatment and age with treatment effects because of limited variability. **Supplement Tables 35** to **37** present summaries of findings for comparisons that were not included in any network. Sensitivity analyses using the Hartung–Knapp–Sidik–Jonkman method for pooling showed point estimates of effect consistent with the DerSimonian–Laird method; some associated measures of precision were wider; however, they would not alter our network estimates, because we assumed a common heterogeneity parameter (**Supplement Tables 38** and **39**).

DISCUSSION

In this network meta-analysis of RCTs in patients with acute pain from non–low back musculoskeletal injuries, we found high- to moderate-certainty evidence that topical NSAIDs, followed by oral NSAIDS, acetaminophen, and acetaminophen plus diclofenac, showed the most attractive benefit–harm ratio; fentanyl, tramadol, and opioid plus acetaminophen caused greater harm relative to placebo than other agents (**Figure 1**). Even the most effective interventions supported by high- or moderate-quality evidence achieved only modest benefits. Several nonpharmacologic interventions (such as transcutaneous electrical nerve stimulation, joint manipulation, and specific acupressure) may provide effective pain relief without risk for gastrointestinal, neurologic, or dermatologic adverse events but are supported by only low-certainty evidence. Most control participants had substantial pain relief by 1 to 7 days. These results may not apply to persons involved in litigation or receiving disability benefits.

Although oral NSAIDs have been a mainstay of treatment for acute pain, topical NSAIDs were licensed by the U.S. Food and Drug Administration only in 2007. We found that topical NSAIDs showed a magnitude of effect against placebo similar to that of oral NSAIDs,

without the gastrointestinal adverse events associated with oral NSAIDs (48).

Clinicians in the United States frequently use opioids for acute pain; this practice may lead to prolonged use and associated harms (49). An analysis of 15 344 U.S. visits for acute pain from 2001 to 2010 found that opioid prescribing increased from 10% to 16% (50). An analysis of 30 832 opioid-naive U.S. patients who received treatment for acute ankle sprains from 2011 to 2015 showed a median opioid-prescribing rate of 25%, with a median morphine equivalent dose of 100 mg/d (51). The 3 most commonly prescribed opioids for acute ankle pain in the United States are hydrocodone, tramadol, and oxycodone (52). Although a 2016 Centers for Disease Control and Prevention (CDC) guideline (53) and a 2019 CDC analysis (54) suggested up to 7 days of opioid therapy for patients presenting to primary care with acute pain, our findings do not support opioid therapy for acute pain from non–low back musculoskeletal injuries.

To our knowledge, no other NMA of all treatments for acute non–low back musculoskeletal injuries has been performed. The most recent systematic review exploring evidence for treatment of individual musculoskeletal injuries excluded opioid therapy and did not conduct meta-analyses or consider the overall certainty of evidence. Our review proves that several interventions concluded to be effective by that earlier review were supported by only low- or very-low-certainty evidence (8). Consistent with our findings, a 2020 systematic review and meta-analysis of analgesics to manage acute pain in the prehospital setting found low-certainty evidence that opioids provided similar pain relief, but carried a greater risk for adverse events, than acetaminophen or NSAIDs (55).

Strengths of our review include a comparative assessment of pharmacologic and nonpharmacologic interventions available to treat acute pain from non–low back musculoskeletal injuries. Collapsing all NSAIDs into topical or oral nodes, and all opioids plus acetaminophen into a single node, improved the precision of treatment effects and interpretation of NMA results. We used the GRADE approach to assess the certainty of evidence in NMA effect estimates and ranked interventions according to both the magnitude of effects across benefits and harms and the certainty of the supporting evidence.

Our review was limited to English-language trials; however, a recent meta-epidemiologic study found that excluding non-English publications from systematic reviews on clinical interventions had a minimal effect on overall conclusions (56). We found limited direct evidence to inform the effectiveness of some interventions versus placebo, including fentanyl, diclofenac plus menthol gel, and acetaminophen plus ibuprofen. Further, the evidence to inform effectiveness of most nonpharmacologic interventions proved to be of low or very low certainty. A key assumption of our review is that treatment effects are similar across different acute musculoskeletal injuries. The process of healing is consistent across musculoskeletal injuries; therefore, the effect of therapeutic interventions is probably similar. This was the conclusion of our technical expert panel and was supported by assessment of between-study variance within closed loops of interventions and networks. Moreover, 48% of the trials eligible for our review enrolled populations with diverse musculoskeletal injuries and reported aggregate results, indicating that trialists anticipated similar responses across different musculoskeletal injuries. Although litigation and wage replacement benefits probably influence treatment effects, data in the included trials were insufficient to form conclusions regarding these issues.

A March 2020 search of ClinicalTrials.gov identified 59 ongoing trials of interventions for acute pain from non–low back musculoskeletal injuries. The most common approaches under evaluation are physiotherapy or rehabilitation (n = 12), topical NSAIDs (n = 11), acupuncture (n = 5), electrical stimulation (n = 5), joint manipulation or mobilization (n = 5), oral NSAIDs (n = 5), and exercise (n = 4) (**Supplementary Appendix 2**).

Our review found high- to moderate-certainty evidence that compared with placebo, tramadol failed to achieve important benefits and opioids caused significantly more adverse events. Our results demonstrating that opioids fail to achieve important benefits beyond interventions with less harm provide compelling reasons to avoid opioid prescribing in the setting of acute non–low back musculoskeletal injury.

From McMaster University and the Chronic Pain Centre of Excellence for Canadian Veterans, Hamilton, Ontario, Canada (J.W.B.); McMaster University, Hamilton, Ontario, Canada (B.S., Y.O., E.C., S.A.R., P.E., S.T.N., W.Y., A.L., S.H.A., S.C., R.C., R.L.M., K.A., A.P., Y.S., A.D., G.H.G.); Stanford University, Stanford, California (A.G.); University of British Columbia, Vancouver, British Columbia, Canada (C.M.); University of Toronto, Toronto, Ontario, Canada (P.J.H., A.A., K.C.); McMaster University, Hamilton, and OrthoEvidence, Burlington, Ontario, Canada (Y.C.); McMaster University, Hamilton, Ontario, Canada, and University of Antioquia, Medellin, Colombia (I.D.F.); University at Buffalo, Buffalo, New York (S.B.); University of Limerick, Limerick, Ireland (L.S.); and Kerman University of Medical Sciences, Kerman, Iran (B.Z.).

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Corresponding Author: Jason W. Busse, DC, PhD, Department of Anesthesia, Michael G. DeGroote School of Medicine, McMaster University, HSC-2V9, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada; e-mail, bussejw@mcmaster.ca.

Current author addresses and author contributions are available at Annals.org.

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Current Author Addresses: Dr. Busse: Department of Anesthesia, Michael G. DeGroote School of Medicine, McMaster University, HSC-2V9, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada.
Drs. Sadeghirad, Chang, and Shergill; Ms. Craigie; and Ms. Couban: National Pain Centre, McMaster University, MDCL-2112, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada.
Dr. Oparin: 10 Mallard Marsh Crescent, Richmond Hill, ON L4E 4M2, Canada.
Mr. Chen: 11314 72 Avenue Northwest, Edmonton, AB T6G 0B6, Canada.
Ms. Goshua: 51 Dudley Lane, Apartment 412, Stanford, CA 94305.
Mr. May: 5311 No 8 Road, Richmond, BC V6V 1S4, Canada.
Dr. Hong: 3704-761 Bay Street, Toronto, ON M5G 2R2, Canada.
Dr. Agarwal: Department of Medicine, University of Toronto, C. David Naylor Building, 6 Queen's Park Crescent West, Third Floor, Toronto, ON M5S 3H2, Canada.
Drs. Ross and Guyatt and Ms. Noor: Department of Health, Evidence & Impact, McMaster University Medical Centre, 1280 Main Street West, 2C Area, Hamilton, ON L8S 4K1, Canada.
Dr. Emary: Langs Community Health Centre, 1145 Concession Road, Cambridge, ON N3H 4L5, Canada.
Dr. Florez: Department of Pediatrics, University of Antioquia, Calle 67 No. 51-27, Segundo Piso del Hospital Infantil San Vicente Fundacion, 050001 Medellın, Colombia.
Mr. Yao: 89 Carling Street, Hamilton, ON L8S 1N1, Canada.
Ms. Lok: 88 Dunmail Drive, Scarborough, ON M1V 1J5, Canada.
Dr. Ali: 7283 Highway 20, Smithville, ON L0R 2A0, Canada.
Dr. Morgan: McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada.
Ms. Culig: 1001 Bay Street, #1317, Toronto, ON M5S 3A6, Canada.
Dr. Brar: 157 Woodstream Drive, Grand Island, NY 14072.
Mr. Akbari-Kelachayeh: 53 Pinewood Drive, Thornhill, ON L4J 5N8, Canada.
Dr. Pozdnyakov: 1280 Main Street West, Michael DeGroote Centre for Learning and Discovery (MDCL) – 3010, Hamilton, ON L8S 4K1, Canada.
Ms. Sivananthan: Graduate Entry Medical School, University of Limerick, Castletroy, Co. Limerick V94 T9PX, Ireland.
Dr. Zihayat: Faculty of Pharmacy, Kerman University of Medical Sciences, 7 Avicenna Street, Kerman 76169, Iran.
Dr. Das: 68A Brenda Crescent, Toronto, ON M1K 3C6, Canada.

Author Contributions: Conception and design: J.W. Busse, B. Sadeghirad, S. Craigie.
Analysis and interpretation of the data: J.W. Busse, B. Sadeghirad, Y. Oparin, E. Chen, P.J. Hong, I.D. Florez, A. Lok, R.L. Morgan, Y. Shergill, A. Das.
Drafting of the article: J.W. Busse, B. Sadeghirad, Y. Oparin, S.T. Noor, W. Yao, S. Craigie, Y. Shergill.
Critical revision for important intellectual content: B. Sadeghirad, Y. Oparin, A. Agarwal, Y. Chang, P. Emary, I.D. Florez, S. Craigie, R.L. Morgan, G.H. Guyatt.
Final approval of the article: J.W. Busse, B. Sadeghirad, Y. Oparin, E. Chen, A. Goshua, C. May, P.J. Hong, A. Agarwal, Y. Chang, S.A. Ross, P. Emary, I.D. Florez, S.T. Noor, W. Yao, A. Lok, S.H. Ali, S. Craigie, R. Couban, R.L. Morgan, K. Culig, S. Brar, K. Akbari-Kelachayeh, A. Pozdnyakov, Y. Shergill, L. Sivananthan, B. Zihayat, A. Das, G.H. Guyatt.
Provision of study materials or patients: S. Craigie, B. Zihayat.
Statistical expertise: J.W. Busse, B. Sadeghirad.
Obtaining of funding: J.W. Busse.
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Appendix Figure 1. NMA results and SUCRA values sorted on the basis of GRADE certainty of evidence for the comparisons of active treatments versus placebo for pain relief and physical function.

Effectiveness Outcomes	Certainty of Evidence	Classification	Intervention	MD (95% CI)	SUCRA (95% CI)	RR of Achieving the MID of 1 cm	RD of Achieving the MID of 1 cm, %
Pain Relief* (≤2 h After Treatment)	High (moderate to high)	Among the most effective	Topical NSAID + menthol	−1.68 (−3.09 to −0.27)	73.0 (68.3 to 77.7)	1.93	36.0
			Acetaminophen + diclofenac	−1.11 (−2.00 to −0.21)	54.7 (51.2 to 58.2)	1.63	24.7
			Topical NSAID	−1.02 (−1.64 to −0.39)	49.6 (46.5 to 52.7)	1.59	22.7
			Acetaminophen	−1.03 (−1.82 to −0.24)	51.3 (48.2 to 54.4)	1.59	22.9
			Oral NSAID	−0.93 (−1.49 to −0.37)	44.9 (42.4 to 47.4)	1.53	20.8
		Among the least effective	Acetaminophen + ibuprofen + oxycodone	−0.94 (−2.27 to 0.38)	47.4 (43.7 to 51.1)	–	–
			Acetaminophen + opioid	−0.52 (−1.47 to 0.43)	28.9 (26.7 to 31.1)	–	–
			Tramadol	0.95 (−0.80 to 2.7)	3.5 (2.9 to 4.1)	–	–
	Low (low to very low)	May be the most effective	Fentanyl	−3.52 (−4.99 to −2.04)	98.3 (96.9 to 99.7)	2.46	56.8
		May be inferior to the most effective/superior than the least effective	TENS	−1.94 (−2.90 to −0.98)	82.4 (78.1 to 86.7)	2.04	40.4
			Joint manipulation	−1.75 (−2.68 to −0.81)	78.2 (74.1 to 82.3)	1.96	37.2
			Specific acupressure	−1.59 (−2.52 to −0.66)	72.4 (67.9 to 76.9)	1.88	34.3
			Acetaminophen + ibuprofen + codeine	−1.36 (−2.49 to −0.23)	65.6 (61.7 to 69.5)	1.77	29.8
		May be among the least effective	Ibuprofen + cyclobenzaprine	−1.05 (−2.63 to 0.53)	50.4 (46.5 to 54.3)	–	–
			Massage therapy	−0.70 (−1.90 to 0.50)	37.6 (34.7 to 40.5)	–	–
			Acetaminophen + ibuprofen	−0.70 (−1.62 to 0.22)	34.8 (32.3 to 37.3)	–	–
			Nonspecific acupressure	−0.05 (−0.99 to 0.89)	15.2 (13.8 to 16.6)	–	–
Pain Relief* (1–7 d After Treatment)	High (moderate to high)	Among the most effective	Topical NSAID	−1.08 (−1.40 to −0.75)	59.4 (55.9 to 62.9)	1.20	14.8
			Acetaminophen	−1.07 (−1.89 to −0.24)	58.5 (54.2 to 62.8)	1.19	14.7
			Oral NSAID	−0.99 (−1.46 to −0.52)	54.7 (51.4 to 58.0)	1.18	13.9
		Among the least effective	Acetaminophen + diclofenac	−1.09 (−2.20 to 0.01)	58.8 (53.9 to 63.7)	–	–
			Topical NSAID + menthol gel	−0.89 (−2.33 to 0.54)	51.9 (47.8 to 56.0)	–	–
			Ultrasonography	−0.40 (−2.46 to 1.66)	39.0 (34.9 to 43.1)	–	–
			Glucosamine	−0.10 (−1.89 to 1.69)	30.7 (28.0 to 33.4)	–	–
	Low (low to very low)	May be among the most effective	Acetaminophen + chlorzoxazone	−2.92 (−5.41 to −0.43)	92.5 (88.4 to 96.6)	1.31	23.6
			Specific acupressure	−2.09 (−3.86 to −0.32)	83.0 (78.1 to 87.9)	1.28	21.4
			TENS	−1.18 (−2.09 to −0.28)	62.9 (57.8 to 68.0)	1.21	15.7
		May be among the least effective	Cyclobenzaprine	−2.03 (−4.11 to 0.06)	79.9 (75.0 to 84.8)	–	–
			Ibuprofen + cyclobenzaprine	−1.51 (−3.06 to 0.04)	70.6 (65.7 to 75.5)	–	–
			Menthol gel	−1.14 (−2.28 to 0.00)	60.7 (56.0 to 65.4)	–	–
			Acetaminophen + ibuprofen	−1.18 (−2.74 to 0.38)	61.6 (56.5 to 66.7)	–	–
			Laser therapy	−1.04 (−2.28 to 0.19)	57.2 (53.1 to 61.3)	–	–
			Acetaminophen + opioid†	–	–	–	–
			Exercise	−0.81 (−2.64 to 1.02)	49.0 (44.9 to 53.1)	–	–
			Nonspecific acupressure	−0.18 (−1.91 to 1.55)	31.8 (28.7 to 34.9)	–	–
			Joint manipulation	0.40 (−1.71 to 2.51)	21.9 (19.2 to 24.6)	–	–
			Supervised rehab	0.96 (−0.35 to 2.27)	9.4 (9.0 to 9.8)	–	–
			Mobilization	3.40 (−0.05 to 6.85)	1.7 (1.5 to 1.9)	–	–
Improvement in Function‡ (Longest Follow-up)	High (moderate to high)	The most effective	Topical NSAID	1.66 (1.16 to 2.16)	94.5 (92.0 to 97.0)	1.17	14.5
		Inferior to the most effective/superior to the least effective	Oral NSAID	0.73 (0.17 to 1.30)	64.6 (61.7 to 67.5)	1.11	9.4
		The least effective	Menthol gel	0.70 (−0.61 to 2.02)	59.3 (55.8 to 62.8)	–	–
	Low (low to very low)	May be the most effective	Specific acupressure	1.51 (0.42 to 2.61)	88.4 (84.7 to 92.1)	1.17	14.0
		May be among the least effective	Acetaminophen	0.90 (−0.27 to 2.07)	67.8 (64.1 to 71.5)	–	–
			TENS	0.68 (−0.20 to 1.57)	60.7 (57.2 to 64.2)	–	–
			Exercise	0.43 (−0.14 to 1.00)	48.4 (45.5 to 51.3)	–	–
			Supervised rehab	0.24 (−0.59 to 1.07)	36.9 (34.4 to 39.4)	–	–
			Mobilization	0.12 (−0.59 to 0.83)	30.3 (28.3 to 32.3)	–	–
			Education	0.10 (−0.67 to 0.87)	29.2 (27.2 to 31.2)	–	–
			Joint manipulation	0.09 (−0.87 to 1.06)	30.0 (27.8 to 32.2)	–	–
			Nonspecific acupressure	−0.18 (−1.32 to 0.96)	19.2 (17.4 to 21.0)	–	–

Please refer to the key in **Figure 1** for colors and shading. GRADE = Grading of Recommendations Assessment, Development and Evaluation; MD = mean difference; MID = minimally important difference; NMA = network meta-analysis; NSAID = nonsteroidal anti-inflammatory drug; RD = risk difference; rehab = rehabilitation; RR = relative risk; SUCRA = surface under the cumulative ranking curve; TENS = transcutaneous electrical nerve stimulation; VAS = visual analogue scale.

* Pain relief is measured using a VAS; scores range from 0 to 10 cm, lower is better (the MID is 1 cm).

† Because of incoherence, we have prioritized the direct estimate of effect from conventional meta-analysis, over the network estimate, for acetaminophen plus opioid versus placebo.

‡ Physical function is measured by using a VAS. Scores range from 0 to 10 cm; higher is better (the MID is 1 cm).

Appendix Figure 2. NMA results and SUCRA values sorted on the basis of GRADE certainty of evidence for the comparisons of active treatments versus placebo for AEs.

Harm Outcomes	Certainty of Evidence	Classification	Intervention	OR (95% CI)	SUCRA (95% CI)	RD (95% CI)
GI-Related AEs	High (moderate to high)	Among the most harmful	Fentanyl	*59.38 (6.21 to 567.71)*	2.4 (2.2 to 2.6)	36.63 (19.03 to 54.23)
			Acetaminophen + opioid	*5.63 (2.84 to 11.16)*	18.3 (17.3 to 19.3)	13.3 (9.04 to 17.55)
		Inferior to the most harmful/superior to the least harmful	Oral NSAID	*1.77 (1.33 to 2.35)*	39.3 (36.9 to 41.7)	3.64 (2.16 to 5.12)
		Among the least harmful	Tramadol	5.98 (0.33 to 108.25)	24.3 (21.6 to 27)	13.47 (−4.37 to 22.57)
			Topical NSAID	1.14 (0.65 to 2.01)	53.3 (50.0 to 56.6)	0.47 (−0.97 to 1.91)
			Laser therapy	0.49 (0.01 to 24.85)	65.5 (60.8 to 70.2)	−0.35 (−2.49 to 1.78)
	Low (low to very low)	May be among the least harmful	Topical NSAID + menthol gel	2.35 (0.04 to 124.85)	40.7 (36.8 to 44.6)	0.90 (−2.04 to 3.83)
			TENS	1.25 (0.14 to 11.01)	50.7 (46.6 to 54.8)	1.74 (−2.4 to 5.87)
			Ibuprofen + cyclobenzaprine	1.10 (0.13 to 9.42)	53.4 (48.9 to 57.9)	2.57 (−3.82 to 8.95)
			Supervised rehab	1.06 (0.02 to 54.49)	52.8 (48.9 to 56.7)	0.06 (−3.74 to 3.85)
			Exercise	1.04 (0.06 to 17.06)	54.4 (50.3 to 58.5)	0.03 (−4.56 to 4.62)
			Mobilization	0.93 (0.02 to 47.12)	54.3 (50.2 to 58.4)	−0.04 (−1.9 to 1.83)
			Nonspecific acupressure	0.85 (0.02 to 44.76)	56.1 (51.6 to 60.6)	−0.3 (−7.83 to 7.23)
			Specific acupressure	0.80 (0.02 to 41.67)	57.2 (52.7 to 61.7)	−0.42 (−7.74 to 6.91)
			Cyclobenzaprine	0.64 (0.03 to 15.74)	61.2 (56.9 to 65.5)	1.5 (−8.18 to 11.18)
			Joint manipulation	0.50 (0.01 to 31.30)	66.1 (61.4 to 70.8)	−3.5 (−10.84 to 3.85)
			Acetaminophen	0.50 (0.06 to 4.38)	69.3 (64.8 to 73.8)	5.97 (−0.47 to 11.46)
			Acetaminophen + chlorzoxazone	0.35 (0.01 to 10.59)	72.9 (68.2 to 77.6)	−12.99 (−42.42 to 16.44)
CNS/Neurologic-Related AEs	High (moderate to high)	Among the most harmful	Tramadol	*6.72 (1.24 to 36.39)*	17.2 (15.4 to 19.0)	22.36 (6.23 to 38.5)
			Fentanyl	*5.73 (1.20 to 27.47)*	19.4 (17.8 to 21.0)	22.45 (3.02 to 41.88)
			Acetaminophen + opioid	*3.53 (1.92 to 6.49)*	28.2 (26.6 to 29.8)	15.78 (10.82 to 20.75)
		Among the least harmful	Oral NSAID	1.02 (0.65 to 1.59)	61.1 (57.6 to 64.6)	−0.11 (−1.44 to 1.22)
			Laser therapy	0.49 (0.01 to 25.41)	67.7 (63.2 to 72.2)	−0.35 (−2.49 to 1.78)
			Phenyramidol	0.32 (0.01 to 8.45)	75.4 (70.9 to 79.9)	−2.78 (−10.34 to 4.79)
	Low (low to very low)	May be the most harmful	Ibuprofen + cyclobenzaprine	*4.91 (1.45 to 16.61)*	21.1 (19.5 to 22.7)	19.84 (7.08 to 32.59)
		May be among the least harmful	Cyclobenzaprine	1.95 (0.20 to 18.88)	44.7 (41.0 to 48.4)	5.14 (−7.21 to 17.49)
			Topical NSAID + menthol gel	1.22 (0.02 to 69.98)	52.8 (48.5 to 57.1)	0.14 (−3.2 to 3.48)
			Topical NSAID	1.18 (0.51 to 2.74)	56.4 (52.9 to 59.9)	0.11 (−0.86 to 1.08)
			Exercise	1.08 (0.07 to 17.95)	55.7 (51.4 to 60.0)	0.06 (−3.41 to 3.53)
			Joint manipulation	1.41 (0.03 to 78.76)	48.8 (44.9 to 52.7)	9.72 (−4.53 to 23.97)
			TENS	1.12 (0.13 to 9.98)	57.0 (52.7 to 61.3)	0.26 (−3.86 to 4.39)
			Supervised rehab	1.06 (0.02 to 55.71)	54.8 (50.5 to 59.1)	0.06 (−3.74 to 3.85)
			Mobilization	0.93 (0.02 to 48.18)	59.2 (54.9 to 63.5)	−0.04 (−1.9 to 1.83)
			Nonspecific acupressure	0.85 (0.02 to 45.76)	58.7 (54.4 to 63.0)	−0.3 (−7.83 to 7.23)
			Specific acupressure	0.80 (0.01 to 42.60)	59.7 (55.4 to 64.0)	−0.42 (−7.74 to 6.91)
Dermatologic-related AEs	High (moderate to high)	Among the least harmful	Oral NSAID	1.33 (0.43 to 4.09)	37.2 (34.7 to 39.7)	0.14 (−0.26 to 0.54)
			Menthol gel	1.00 (0.11 to 8.91)	47.7 (47.6 to 52.0)	0 (−10.3 to 10.3)
			Topical NSAID	0.78 (0.52 to 1.15)	58.9 (51.7 to 57.9)	−0.73 (−1.75 to 0.3)
			Laser therapy	0.49 (0.01 to 27.21)	60.3 (58.9 to 65.1)	−0.35 (−2.49 to 1.78)
	Low (low to very low)	May be among the least harmful	TENS	1.18 (0.13 to 11.03)	43.6 (29.4 to 35.2)	0.36 (−3.74 to 4.46)
			Supervised rehab	1.06 (0.02 to 59.65)	46.9 (45.6 to 51.8)	0.06 (−3.74 to 3.85)
			Exercise	1.08 (0.06 to 18.84)	45.8 (45.2 to 51.0)	0.06 (−3.41 to 3.53)
			Mobilization	0.93 (0.02 to 51.60)	49.0 (47.2 to 53.0)	−0.04 (−1.9 to 1.83)
			Nonspecific acupressure	0.85 (0.01 to 48.97)	50.5 (47.8 to 54.0)	−0.3 (−7.83 to 7.23)
			Specific acupressure	0.80 (0.01 to 45.60)	52.3 (50.0 to 56.2)	−0.42 (−7.74 to 6.91)
			Topical NSAID + menthol gel	0.53 (0.05 to 6.29)	62.0 (59.8 to 64.6)	−1.49 (−5.9 to 2.92)

Please refer to the key in Figure 1 for colors and shading. Numbers in italics represent statistically significant results. AE = adverse event; CNS = central nervous system; GI = gastrointestinal; GRADE = Grading of Recommendations Assessment, Development and Evaluation; NMA = network meta-analysis; NSAID = nonsteroidal anti-inflammatory drug; OR = odds ratio; RD = risk difference; rehab = rehabilitation; SUCRA = surface under the cumulative ranking curve; TENS = transcutaneous electrical nerve stimulation.