

Drug-Free Interventions to Reduce Pain or Opioid Consumption After Total Knee Arthroplasty

A Systematic Review and Meta-analysis

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 Supplemental content

IMPORTANCE There is increased interest in nonpharmacological treatments to reduce pain after total knee arthroplasty. Yet, little consensus supports the effectiveness of these interventions.

OBJECTIVE To systematically review and meta-analyze evidence of nonpharmacological interventions for postoperative pain management after total knee arthroplasty.

DATA SOURCES Database searches of MEDLINE (PubMed), EMBASE (OVID), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Web of Science (ISI database), Physiotherapy Evidence (PEDRO) database, and ClinicalTrials.gov for the period between January 1946 and April 2016.

STUDY SELECTION Randomized clinical trials comparing nonpharmacological interventions with other interventions in combination with standard care were included.

DATA EXTRACTION AND SYNTHESIS Three reviewers independently extracted the data from selected articles using a standardized form and assessed the risk of bias. A random-effects model was used for the analyses.

MAIN OUTCOMES AND MEASURES Postoperative pain and consumption of opioids and analgesics.

RESULTS Of 5509 studies, 39 randomized clinical trials were included in the meta-analysis (2391 patients). The most commonly performed interventions included continuous passive motion, preoperative exercise, cryotherapy, electrotherapy, and acupuncture. Moderate-certainty evidence showed that electrotherapy reduced the use of opioids (mean difference, -3.50 ; 95% CI, -5.90 to -1.10 morphine equivalents in milligrams per kilogram per 48 hours; $P = .004$; $I^2 = 17\%$) and that acupuncture delayed opioid use (mean difference, 46.17 ; 95% CI, 20.84 to 71.50 minutes to the first patient-controlled analgesia; $P < .001$; $I^2 = 19\%$). There was low-certainty evidence that acupuncture improved pain (mean difference, -1.14 ; 95% CI, -1.90 to -0.38 on a visual analog scale at 2 days; $P = .003$; $I^2 = 0\%$). Very low-certainty evidence showed that cryotherapy was associated with a reduction in opioid consumption (mean difference, -0.13 ; 95% CI, -0.26 to -0.01 morphine equivalents in milligrams per kilogram per 48 hours; $P = .03$; $I^2 = 86\%$) and in pain improvement (mean difference, -0.51 ; 95% CI, -1.00 to -0.02 on the visual analog scale; $P < .05$; $I^2 = 62\%$). Low-certainty or very low-certainty evidence showed that continuous passive motion and preoperative exercise had no pain improvement and reduction in opioid consumption: for continuous passive motion, the mean differences were -0.05 (95% CI, -0.35 to 0.25) on the visual analog scale ($P = .74$; $I^2 = 52\%$) and 6.58 (95% CI, -6.33 to 19.49) opioid consumption at 1 and 2 weeks ($P = .32$, $I^2 = 87\%$), and for preoperative exercise, the mean difference was -0.14 (95% CI, -1.11 to 0.84) on the Western Ontario and McMaster Universities Arthritis Index Scale ($P = .78$, $I^2 = 65\%$).

CONCLUSIONS AND RELEVANCE In this meta-analysis, electrotherapy and acupuncture after total knee arthroplasty were associated with reduced and delayed opioid consumption.

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There are 234 million major surgical procedures performed every year worldwide, and most patients experience moderate to severe postoperative pain.^{1,2} Inadequate postoperative pain management has profound acute effects, including immune system suppression, decreased mobility that increases deep vein thrombosis and pulmonary embolism rates, myocardial infarction, and pneumonia.³ Long-term influences of poor pain management include transition to chronic pain and prolonged narcotic consumption,⁴ which can result in opioid dependence, an epidemic in the United States.⁵

First-line therapies to treat postoperative pain are pharmacological, including anesthetics, opioids, and acetaminophen.^{6,7} Recently, nonpharmacological approaches to pain management aimed at reducing the use of prescription medications have increased.⁸ Physiotherapy is effective in treating postoperative pain and quality-of-life improvement and is standard treatment.⁹ However, other commonly used interventions for pain management have conflicting evidence on their effectiveness.^{10,11} As opioid addiction becomes a national priority,⁹ the importance of using effective nonpharmacological strategies for postoperative pain is now a top scientific priority.¹²

Total knee arthroplasty (TKA) is one of the most frequently performed surgical procedures worldwide. It is used for patients with advanced knee osteoarthritis, and the goals of surgery are to decrease pain, restore mobility and function, and improve health-related quality of life.¹³ Total knee arthroplasty is associated with intense postoperative pain, and many patients report moderate to severe postoperative pain past the anticipated recovery period.¹⁴ Therefore, many nonpharmaceutical therapies are performed in this population.^{10,11,15,16} Ensuring effective therapies for postoperative pain management is an important part of TKA care.¹⁷

We undertook a systematic review and meta-analysis to evaluate the effectiveness of commonly used drug-free interventions for pain management after TKA. We gathered evidence from randomized clinical trials (RCTs) on postoperative pain as measured by established pain metrics and reduced analgesic consumption, including opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). This comprehensive analysis of nonpharmaceutical pain management therapies can inform practice and identify effective pain management regimens that could also potentially reduce the prescribing of opioids after surgery.

Methods

We conducted a systematic review and meta-analysis in accord with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁸ The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO).¹⁹

Search Strategy

Databases

In an academic medical setting, we searched electronic databases to identify relevant studies for the period between January 1946 and April 2016, including MEDLINE (PubMed),

Key Points

Question Which of the nonpharmacological interventions used for postoperative pain after total knee arthroplasty are effective?

Findings In a systematic review of 5509 studies, 39 randomized clinical trials were included in a meta-analysis (2391 patients) and demonstrated moderate-certainty evidence that electrotherapy and acupuncture reduce or delay opioid consumption, but there is low certainty or very low certainty that they improve pain. Continuous passive motion and preoperative exercise do not improve pain or reduce opioid consumption (low certainty or very low certainty), and cryotherapy reduces opioid consumption but does not improve pain (very low certainty).

Meaning After total knee arthroplasty, electrotherapy and acupuncture were associated with reduced and delayed opioid consumption.

EMBASE (OVID), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Web of Science (ISI database), Physiotherapy Evidence (PEDRO) database, and clinicaltrials.gov. We scanned reference lists of selected reviews, original articles, and textbooks to find additional articles. We conducted a gray literature search for other documents and hand searches of key conference proceedings, journals, professional organizations' websites, national joint replacement registries, and guideline clearing houses. Snowball technique was applied to the search strategy.²⁰

Search Criteria

Because our aim was to be as comprehensive as possible in the systematic review, we did not place time or publication status limits to the search except for restriction to the English language. Two Chinese studies with English abstracts were considered; however, translation resources were not available to include them. We used the following search string in each database: (*postoperative pain** OR *postoperative pain* OR *post-operative pain*) AND (*total knee** or *total knee arthroplasty* OR *total knee replacement* OR *TKA*). Asterisks are used to truncate words, so that every desinence after the asterisks will be searched. To achieve the highest sensitivity, we used a combination of keywords and indexed terms (eg, PubMed Medical Subject Headings).

Patients, Interventions, Comparators, and Outcomes

Our primary search objective addressed the PICO (patients, interventions, comparators, and outcomes) question. These targets included (*P*) patients undergoing primary TKA, (*I*) nonpharmacological treatments for pain management (plus usual analgesic therapy), (*C*) other nonpharmacological intervention or no intervention (plus usual analgesic therapy), and (*O*) postoperative pain relief, and opioid and NSAID consumption.

Study Selection

Design

Postoperative pain management is generally layered, including pharmacological and nonpharmacological interventions. Hence, we selected studies comparing nonpharmacological interventions with routine pharmacological treatment either with

other nonpharmacological approaches or with only routine pharmacological treatments. We restricted our meta-analysis to RCTs in which patients were 18 years or older and had elective primary surgical procedures that included all forms of fixation (cemented, hybrid, or cementless), surgical approaches (medial, lateral, parapatellar, or minimally invasive), and types of prostheses (constrained, semiconstrained, or mobile platform).

Outcomes of Interest

Three of us (D.T., D.G., and K.R.D.) independently screened all identified articles by scanning abstracts or portions of the text to determine if they met the inclusion criteria. Any disagreements were resolved through discussion and consensus between the reviewers. Postoperative pain relief was defined as the mean difference in scores on the visual analog scale (VAS) or the Western Ontario and McMaster Universities Arthritis Index Scale (WOMAC). Opioid and other analgesic consumption was evaluated in terms of the mean difference in consumption of morphine equivalents in milligrams per kilogram per 48 hours, while other analgesic consumption was evaluated as the mean difference in the number of tablets per day. Time to first request for analgesia (patient-controlled analgesia [PCA]) in the acupuncture group was defined as minutes from the end of the intervention to the first PCA.

Information about quality of life was not systematically provided in the studies. Therefore, it was not included.

Intervention

We restricted our focus to commonly studied postoperative pain interventions. These included continuous passive motion (CPM), preoperative exercise, cryotherapy, electrotherapy, and acupuncture.

Continuous passive motion consists of using an external machine to provide regular movement to the knee using a predetermined range of motion (ROM). Theoretically, the repeated movements help increase ROM, while simultaneously improving pain.²¹

Preoperative exercise (or prehabilitation) involves sessions performed by the patients in the weeks preceding surgery. This regimen enables them to cope better with the physical stress associated with the surgical procedure and aids postoperative rehabilitation efforts.²²

Cryotherapy is based on applying cold to the surgical site either through ice bags or cooled water to minimize tissue trauma. The theory is that application of cooler substances reduces intra-articular temperatures, which interferes with the conduction of nerve signals and reduces local blood flow. These changes lead to decreased swelling and perceived pain.²³

Electrotherapy (based on electrophysical agents) aims to reduce pain and improve function through an energy transfer to the body. These modalities include transcutaneous electrical nerve stimulation and pulsed electromagnetic fields.²⁴

Acupuncture is a form of traditional Chinese medicine that requires the insertion of needles at specific points on the body to alleviate pain and other ailments. The plausible mechanism of acupuncture analgesia is its effect on the central

nervous system, particularly a short-term and long-term effect on μ -opioid receptors, and consequent regulation of neurotransmitters and hormones.^{25,26}

Study Quality Assessment

Two of us (D.T. and D.G.) independently assessed the risk of bias of included studies using the parameters defined by the *Cochrane Handbook for Systematic Reviews of Interventions* criteria.²⁷ Disagreement was resolved through discussion and consensus between the reviewers. Based on the information provided from included studies, each item was recorded as low risk of bias, high risk of bias, or unclear (lack of information or unknown risk of bias).

Two of us (D.T. and D.G.) independently assessed the quality of the body of evidence for the different outcomes considered through the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, a validated and widely implemented tool to rate the quality of scientific evidence.²⁸ According to the GRADE approach, we assessed 5 domains, grading the strength of evidence for each outcome.

Data Analysis and Synthesis

Three of us (D.T., D.G., and K.R.D.) independently extracted the data from included articles. Key information was gathered systematically using a standardized form. These variables included country, year of publication, number of participants, intervention, age, sex, study design, duration of intervention, outcome time points, statistical method, postoperative pain, opioid or analgesic consumption, and summary of the results.

For the pain scores, we standardized the results to a single scale by converting outcomes reported on a numerical rating scale to a 10-point VAS. Where possible, the results were extracted manually from the published figures. Data in other forms (ie, median, interquartile range, and mean [95% CI]) were converted to means (SDs) according to the *Cochrane Handbook for Systematic Reviews of Interventions*.²⁷ If data (eg, SDs and SEs) were not presented in the original article, corresponding authors were contacted to acquire the missing data, although no responses were received. We also normalized data for pain relief and analgesic consumption, opioid and other analgesic consumption, and time before the first analgesic treatment. Specifically, all data on opioid consumption were converted to milligrams per kilogram per 48 hours, other analgesic consumption was converted to the number of tablets per day, and time before the first analgesic treatment was converted to minutes.

We examined the evidence tables for clinical (participants, interventions, controls, outcomes, and measurement tools) and methodological heterogeneity to determine whether the studies were similar enough to perform a meta-analysis.²⁹ Where appropriate to pool the results, we used weighted mean differences for continuous data using the same measurement scales and standardized mean differences for continuous outcomes using different scales. We pooled both sets of summary statistics using the inverse variance method, which included studies from different time points, and we conducted sensitivity analyses by single time point.

We tested statistical heterogeneity to determine if it was appropriate to combine the studies for meta-analysis. We examined heterogeneity graphically using forest plots and statistically by calculating the I^2 statistic, which describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). We considered an I^2 statistic greater than 50% to be substantially heterogeneous. According to the *Cochrane Handbook for Systematic Reviews of Interventions*,²⁷ in cases where the number of studies was less than 5 or studies were substantially heterogeneous, we used a random-effects model. We calculated the random-effects estimates for the corresponding statistics using the method by DerSimonian and Laird.³⁰ Forest plots were created to display effect estimates with 95% CIs for individual trials and pooled results. For all data analysis, we used a software program (RevMan, version 5.3; The Cochrane Collaboration).

Results

Search Findings

Supplementary information is provided in eTables 1, 2, and 3 in the [Supplement](#) and in eFigures 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, and 42 in the [Supplement](#). Our search yielded 5509 studies, of which 120 (112 from selection and 8 added by hand and snowball searching) were appropriate for further assessment. Of the 77 RCTs we read in extenso, we extracted the data from 39 RCTs for our meta-analysis (eFigure 1 in the [Supplement](#)). Included studies were published between 1991 and 2015.

Study Characteristics

A pooled total of 2391 patients were examined in the RCTs ([Table 1](#)). We categorized the 39 RCTs based on 2 outcomes (pain relief and analgesic consumption, including different measures and types) and 5 interventions, including 18 studies in the CPM group (14 on pain and 5 on analgesics), 3 studies in the preoperative exercise group (all on pain), 12 studies in the cryotherapy group (8 on pain and 10 on analgesics), 4 studies in the electrotherapy group (2 on pain and 2 on analgesics), and 4 studies in the acupuncture group (2 on pain and 3 on analgesics). One study⁴⁸ recurred in 3 different categories owing to multiple comparison groups within the article. For the studies that did not provide sufficient data, we attempted to contact authors but received no response.

Quality Assessment

All studies were assessed for the risk of bias (eTable 1 in the [Supplement](#)). The methodological heterogeneity reflects the different range of interventions we examined. We identified that the highest bias in studies was due to improper or absent masking during the study (31 of 39 RCTs). In 2 studies^{54,58} on cryotherapy, masking was adequately achieved. Studies also showed high risk of bias for selective outcome reporting in 13 cases, particularly in those testing the effectiveness of CPM, cryotherapy, and electrotherapy RCTs.^{32,35,37,40,41,43,53,55,57,58,63,65,68} There was also high risk of bias due to improper or absent random sequenc-

ing methods in 8 studies.^{33,34,42,44,45,47,57,59} Last, a study⁶⁵ in the electrotherapy group showed high risk of bias for incomplete outcome data. We conducted sensitivity subgroup analyses for all the outcomes considered, classifying for sequence generation and allocation concealment availability, and no significant differences were shown (eFigures 10, 11, 12, 13, 14, 15, 16, 17, 18, and 19 in the [Supplement](#)). The GRADE quality of evidence certainty level of evidence assessment is reported in detail below in the Assessed Outcomes and Evidence Synthesis subsection, in [Table 2](#), and in eTable 2 in the [Supplement](#).

Publication Bias

To address publication bias, we created funnel plots for all analyses. No asymmetric patterns were seen (eFigures 24, 25, 26, 27, 28, and 29 in the [Supplement](#)).

Interventions

The key findings of the meta-analysis are summarized in [Table 2](#) for 2 types of pain scales and for 3 types of analgesic outcomes. [Figure 1](#) and [Figure 2](#) show the meta-analyses that reported statistically significant results.

Assessed Outcomes and Evidence Synthesis

Pain Relief and Analgesic Consumption

We found that the quality of evidence was of low certainty or very low certainty for pain improvement in all examined interventions ([Table 2](#)). Meta-analysis of 2 pain relief studies (189 patients) suggested a significant improvement in experimental groups vs controls with electrotherapy, with mean differences of -1.95 (95% CI, -2.68 to -1.22 ; $P < .001$; $I^2 = 17%$) on the VAS at 1 month, -2.34 (95% CI, -4.49 to -0.19 ; $P = .03$; $I^2 = 94%$) on the VAS at 2 months, and -2.60 (95% CI, -5.12 to -0.08 ; $P = .04$; $I^2 = 83%$) on the VAS at 6 months ([Figure 1A](#)). Meta-analysis of 3 studies (230 patients) suggested a significant improvement in experimental groups vs controls with acupuncture, with a mean difference of -1.14 (95% CI, -1.90 to -0.38 ; $P = .003$; $I^2 = 0%$) on the VAS at 6 months ([Figure 1B](#)). Meta-analysis of 8 studies (1383 patients) showed a mean difference with cryotherapy of -0.51 (95% CI, -1.00 to -0.02 ; $P < .05$; $I^2 = 62%$), but all subgroup analyses showed no statistically significant mean differences (eFigure 2 in the [Supplement](#)). Meta-analysis of 9 studies (1025 patients) suggested no significant improvement in experimental groups vs controls with CPM (mean differences, -0.05 ; 95% CI, -0.35 to 0.25 ; $P = .74$; $I^2 = 52%$ on the VAS at 1 week and 6 months and -0.20 ; 95% CI, -0.62 to 0.23 ; $P = .54$; $I^2 = 0%$ on the CPM WOMAC at 6 weeks and 6 months) (eFigure 3 and eFigure 4 in the [Supplement](#)) or with preoperative exercise (mean difference, -0.14 ; 95% CI, -1.11 to 0.84 ; $P = .78$; $I^2 = 65%$ on the WOMAC at 6 and 12 weeks) (eFigure 5 in the [Supplement](#)).

To address possible overestimation that could originate from the study design (ie, pain as a primary or secondary outcome), we conducted sensitivity subgroup analyses. No significant differences were found (eFigures 20, 21, 22, and 23 in the [Supplement](#)).

Opioid and Other Analgesic Consumption

Meta-analysis of 2 studies (99 patients) showed moderate-certainty reduction in opioid consumption for electrotherapy

Table 1. Characteristics of Randomized Clinical Trials of Nonpharmacological Postoperative Pain Management After Total Knee Arthroplasty

Source	Country	No. of Participants in Per-Protocol Analysis	Intervention	Age, Mean (SD) or Median (Range), y	Female, %
CPM					
Beaupré et al, ³¹ 2001	Canada	120	T1: CPM	T1: 68 (9)	T1: 30
			T2: Slider board	T2: 68 (9)	T2: 50
			C: Standard exercise	C: 69 (8)	C: 52.5
Bennett et al, ³² 2005	Australia	147	T1: Standard CPM	T1: 70.7	T1: 72.3
			T2: Early flexion CPM	T2: 71.4	T2: 64.6
			C: No CPM	C: 71.7	C: 67.3
Bruun-Olsen et al, ³³ 2009	Norway	63	T: CPM plus active exercise	68 (10)	T: 73
			C: Active exercise	71 (10)	C: 67
Chen et al, ³⁴ 2013	Taiwan	107	T: CPM plus basic rehabilitation	T: 69.3 (6.8)	NA
			C: Basic rehabilitation	C: 69.5 (8.2)	NA
Colwell and Morris ³⁵ 1992	United States	22	T: CPM plus standard rehabilitation	T: 73	T: 67
			C: Immobilization in a posterior splint plus standard rehabilitation	C: 74	C: 70
Denis et al, ³⁶ 2006	Canada	81	T1: Low-intensity CPM plus conventional physical therapy	T1: 69.6 (6.7)	T1: 61.5
			T2: High-intensity CPM plus conventional physical therapy	T2: 68.4 (7.4)	T2: 46.4
			C: Conventional physical therapy	C: 67.1 (7.6)	C: 51.9
Harms and Engstrom, ³⁷ 1991	United Kingdom	113	T: CPM plus standardized exercise	T1: 69 (9)	T1: 78
			C: Standardized exercise	C: 71 (10)	C: 93
Kim et al, ³⁸ 2009	South Korea	100	T: Regular PROME plus standard exercise	67.9 (53-83)	100
			C: Standard exercise (no PROME)	NA	NA
Lenssen et al, ³⁹ 2003	The Netherlands	40	T: CPM plus physical therapy	T: 65 (9)	T: 71
			C: Physical therapy	C: 66 (10)	C: 63
Lenssen et al, ⁴⁰ 2008	The Netherlands	60	T: CPM plus physical therapy	T: 68.9 (6.1)	T: 60
			C: Physical therapy	C: 67.5 (8.9)	C: 70
MacDonald et al, ⁴¹ 2000	Canada	120	T1: CPM with ROM 0°-50°	NA	NA
			T2: CPM with ROM 70°-110°	NA	NA
			C: No CPM	NA	NA
Maniar et al, ⁴² 2012	India	86	T1: 1 d of CPM plus conventional physical therapy	T1: 66.8	T1: 89
			T2: 3 d of CPM plus conventional physical therapy	T2: 66	T2: 87
			C: Conventional physical therapy	C: 67.4	C: 92
May et al, ⁴³ 1999	United States	19	T: CPM plus physical therapy	T: 73 (4)	T: 67
			C: Lower limb mobility board plus physical therapy	C: 66 (9)	C: 71
McInnes et al, ⁴⁴ 1992	United States	93	T: CPM plus conventional rehabilitation	T: 65.7 (1.6)	T: 65
			C: Conventional rehabilitation	C: 70.2 (1.3)	C: 64

(continued)

Table 1. Characteristics of Randomized Clinical Trials of Nonpharmacological Postoperative Pain Management After Total Knee Arthroplasty (continued)

Source	Country	No. of Participants in Per-Protocol Analysis	Intervention	Age, Mean (SD) or Median (Range), y	Female, %
Montgomery and Eliasson, ⁴⁵ 1996	United Kingdom	60	T: CPM C: Active physical therapy	T: 74 (5) C: 76 (6)	T: 86 C: 75
Pope et al, ⁴⁶ 1997	Australia	53	T1: CPM 0°-40° ROM plus physical therapy T2: CPM 0°-70° ROM plus physical therapy C: Physical therapy	T1: 72.5 T2: 72.7 C: 72.2	T1: 64.7 T2: 50 C: 69.6
Sahin et al, ⁴⁷ 2006	Turkey	31	T: CPM plus physical therapy C: Physical therapy	T: 61 (6.0) C: 61.6 (7.5)	T: 86 C: 86
Walker et al, ⁴⁸ 1991	United States	22	T: CPM C: No CPM	T: 72.7 (61-83) C: 73.6 (65-82)	NA NA
Preoperative Exercise					
Calatayud et al, ⁴⁹ 2016	Spain	44	T: 8 wk of exercise training program 3 d per wk before surgery C: No intervention	T: 66.8 (4.8) NA	84 NA
Gstoettner et al, ⁵⁰ 2011	Austria	35	T: 6 wk of preoperative proprioceptive training program C: No intervention	T: 72.8 (65-78) C: 66.9 (61-75)	NA NA
McKay et al, ⁵¹ 2012	Canada	22	T: 6 wk of prehabilitation exercise training program C: No intervention	T: 60.58 (8.05) C: 63.5 (4.93)	T: 66.67 C: 50
Cryotherapy					
Albrecht et al, ⁵² 1997	Germany	98	T1: Intermittent ice blocks T2: Continuous cold therapy C: Standard postoperative care plus CPM	T1: 69.8 T2: 71.9 C: 73.8	NA NA NA
Gibbons et al, ⁵³ 2001	United Kingdom	60	T: Cold compression dressing C: Robert Jones modified bandage	T: 70 C: 71	T: 63 C: 53
Ivey et al, ⁵⁴ 1994	United States	88	T1: Hot ice thermal pads at 10°C T2: Hot ice thermal pads at 15.6°C C: Hot ice thermal pads at 21.1°C	T1: 64.5 T2: 64.2 C: 66.9	T1: 57 T2: 63 C: 73
Kullenberg et al, ⁵⁵ 2006	Sweden	83	T: Cold compression applied with the Cryo Cuff (Aircast Incorporated) C: Standard care	T: 68.1 (6) C: 68.9 (6.8)	T: 74 C: 70
Levy and Marmor, ⁵⁶ 1993	United States	80	T: Cold compression applied with the Cryo Cuff (Aircast Incorporated) C: No intervention	T: 74 C: 73	T: 82.5 C: 80
Morsi, ⁵⁷ 2002	Egypt	60	T: Cooling device C: Standard care	NA NA	NA NA
Radkowski et al, ⁵⁸ 2007	United States	64	T: Cryotherapy at 7.2°C continued until discharge plus elastic wrap C: Cryotherapy at 23.9°C continued until discharge plus elastic wrap	T: 63.7 C: 66.9	T: 54 C: 36
Smith et al, ⁵⁹ 2002	Australia	84	T: Cold therapy C: Compression bandage	T: 72.1 (7.8) C: 72 (7.1)	T: 54.8 C: 45.2

(continued)

Table 1. Characteristics of Randomized Clinical Trials of Nonpharmacological Postoperative Pain Management After Total Knee Arthroplasty (continued)

Source	Country	No. of Participants in Per-Protocol Analysis	Intervention	Age, Mean (SD) or Median (Range), y	Female, %
Su et al, ⁶⁰ 2012	United States	187	T: Cryopneumatic device C: Ice and static compression	NA NA	NA NA
Thienpont, ⁶¹ 2014	Belgium	100	T: Continuous cooling at 11°C C: Cold packs (conserved at -17°C)	T: 67.5 (10.5) C: 68.5 (10)	T: 70 C: 80
Webb et al, ⁶² 1998	United Kingdom	31	T: Cold compression with the Cryo Cuff (Aircast Incorporated) C: Standard care	T: 69.0 C: 70.9	NA NA
Walker et al, ⁴⁸ 1991	United States	30	Continuous cooling pad plus CPM CPM	T: 75.0 (58-87) C: 70.0 (56-82)	NA NA
Electrotherapy					
Adravanti et al, ⁶³ 2014	Italy	26	T: Pulsed electromagnetic fields plus standard rehabilitation C: Standard rehabilitation	T: 66 (13) C: 73 (5)	T: 62.5 C: 53
Borckardt et al, ⁶⁴ 2013	United States	40	T: Transcranial direct current stimulation C: Sham transcranial direct current stimulation	NA NA	NA NA
Moretti et al, ⁶⁵ 2012	Italy	30	T: Stimulation with pulsed electromagnetic fields 4 h per d for 60 d plus kinesiotherapy C: Kinesiotherapy	T: 70.5 (8.1) C: 70.0 (10.6)	NA NA
Walker et al, ⁴⁸ 1991	United States	48	T1: TENS plus CPM T2: Subthreshold TENS plus CPM C: CPM	T: 69.8 (61-69) T2: 73.9 (55-84) C: 73.9 (60-86)	NA NA NA
Acupuncture					
Chen et al, ⁶⁶ 2015	Taiwan	60	T: Auricular acupuncture under general anesthesia C: Sham auricular acupuncture under general anesthesia	T: 68.9 (9.0) C: 69.0 (8.6)	T: 90 C: 73
Mikashima et al, ⁶⁷ 2012	Japan	80	T: Acupuncture treatment plus standard rehabilitation C: Standard rehabilitation	T: 72 (7) C: 73 (5)	T: 75 C: 70
Tsang et al, ⁶⁸ 2007	Hong Kong	30	T: Acupuncture plus standard rehabilitation C: Sham acupuncture plus standard rehabilitation	T: 70.6 (5.8) C: 66.1 (7.5)	T: 80 C: 80
Tzeng et al, ⁶⁹ 2015	Taiwan	47	T1: Electroacupuncture T2: Sham electroacupuncture C: No intervention	T1: 70.1 (6.9) T2: 69.6 (5.6) C: 71.4 (7.3)	T1: 82 T2: 75 C: 71

Abbreviations: C, control group; CPM, continuous passive motion; NA, not available; PROME, passive ROM exercise; ROM, range of motion; T, treatment group; TENS, transcutaneous electrical nerve stimulation.

Table 2. Main Findings of the Meta-analysis of Nonpharmacological Postoperative Pain Management After Total Knee Arthroplasty^a

Variable	No. of Studies	No. of Participants	Effect Estimate (95% CI)	I ² Heterogeneity, %	GRADE
Pain Relief on the VAS					
CPM	9	1025	-0.05 (-0.35 to 0.25)	52	
1 wk	8	575	-0.27 (-0.70 to 0.16)	35	
2 wk	2	145	-0.81 (-3.30 to 1.68)	88	Very low
3 mo	2	170	0.50 (-0.30 to 1.29)	54	
6 mo	2	135	0.15 (-0.04 to 0.35)	0	
Cryotherapy	8	1382	-0.51 (-1.00 to -0.02)	62	
Day 1 after surgery	7	529	-0.21 (-0.89 to 0.48)	40	Very low
Day 2 after surgery	5	422	-1.00 (-2.01 to 0.02)	59	
Day 3 after surgery	6	431	-0.44 (-1.37 to 0.49)	75	
Electrotherapy	2	189	-2.11 (-2.74 to -1.47)	80	
1 mo	2	63	-1.95 (-2.68 to -1.22)	17	Very low
2 mo	2	63	-2.34 (-4.49 to -0.19)	94	
6 mo	2	63	-2.60 (-5.12 to -0.08)	83	
Acupuncture	3	230	-0.66 (-1.29 to -0.03)	69	
2 d	2	90	-1.14 (-1.90 to -0.38)	0	Low
8 d	2	140	-0.37 (-1.04 to 0.30)	72	
Pain Relief on the WOMAC					
CPM	5	578	0.03 (-0.19 to 0.24)	0	
6 wk	2	168	-0.66 (-2.12 to 0.81)	60	Low
3 mo	3	242	0.05 (-0.22 to 0.32)	0	
6 mo	2	168	-0.34 (-1.35 to 0.68)	0	
Preoperative exercise	3	132	-0.14 (-1.11 to 0.84)	65	
6 wk	2	60	0.34 (-0.32 to 0.99)	0	Low
12 wk	2	72	-0.78 (-1.63 to 0.07)	8	
Opioid Consumption^b					
CPM	5	313	6.58 (-6.33 to 19.49)	87	
1 wk	3	178	11.12 (-12.21 to 34.44)	80	Very low
2 wk	2	135	-3.78 (-7.67 to 0.11)	8	
Cryotherapy within 48 h	7	468	-0.13 (-0.26 to -0.01)	86	
Cryotherapy vs nothing	2	61	-0.18 (-0.30 to -0.06)	0	Very low
Cryotherapy vs compression	5	407	-0.12 (-0.28 to 0.04)	90	
Electrotherapy within 48 h	2	99	-3.50 (-5.90 to -1.10)	17	Moderate
Acupuncture within 48 h	2	123	-0.71 (-1.44 to 0.02)	64	
Acupuncture vs sham acupuncture	2	90	-0.92 (-2.19 to 0.35)	79	Low
Acupuncture vs nothing	1	33	-0.40 (-1.05 to 0.25)	NA	
NSAID Consumption					
Cryotherapy within 48 h	3	363	-0.75 (-1.63 to 0.12)	95	
Cryotherapy vs nothing	1	60	-1.90 (-2.25 to -1.55)	NA	Very low
Cryotherapy vs compression	2	303	-0.31 (-0.55 to -0.07)	0	
Time to First PCA^c					
Acupuncture	2	124	46.17 (20.84 to 71.50)	19	
Acupuncture vs sham acupuncture	2	91	34.58 (-12.61 to 81.77)	53	Moderate
Acupuncture vs nothing	1	33	57.90 (16.52 to 99.28)	NA	

Abbreviations: CPM, continuous passive motion; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; PCA, patient-controlled analgesia; VAS, visual analog scale (range, 0-10); WOMAC, Western Ontario and McMaster Universities Arthritis Index Scale (range, 0-20).

^a The inverse variance method was used for the statistical analyses.

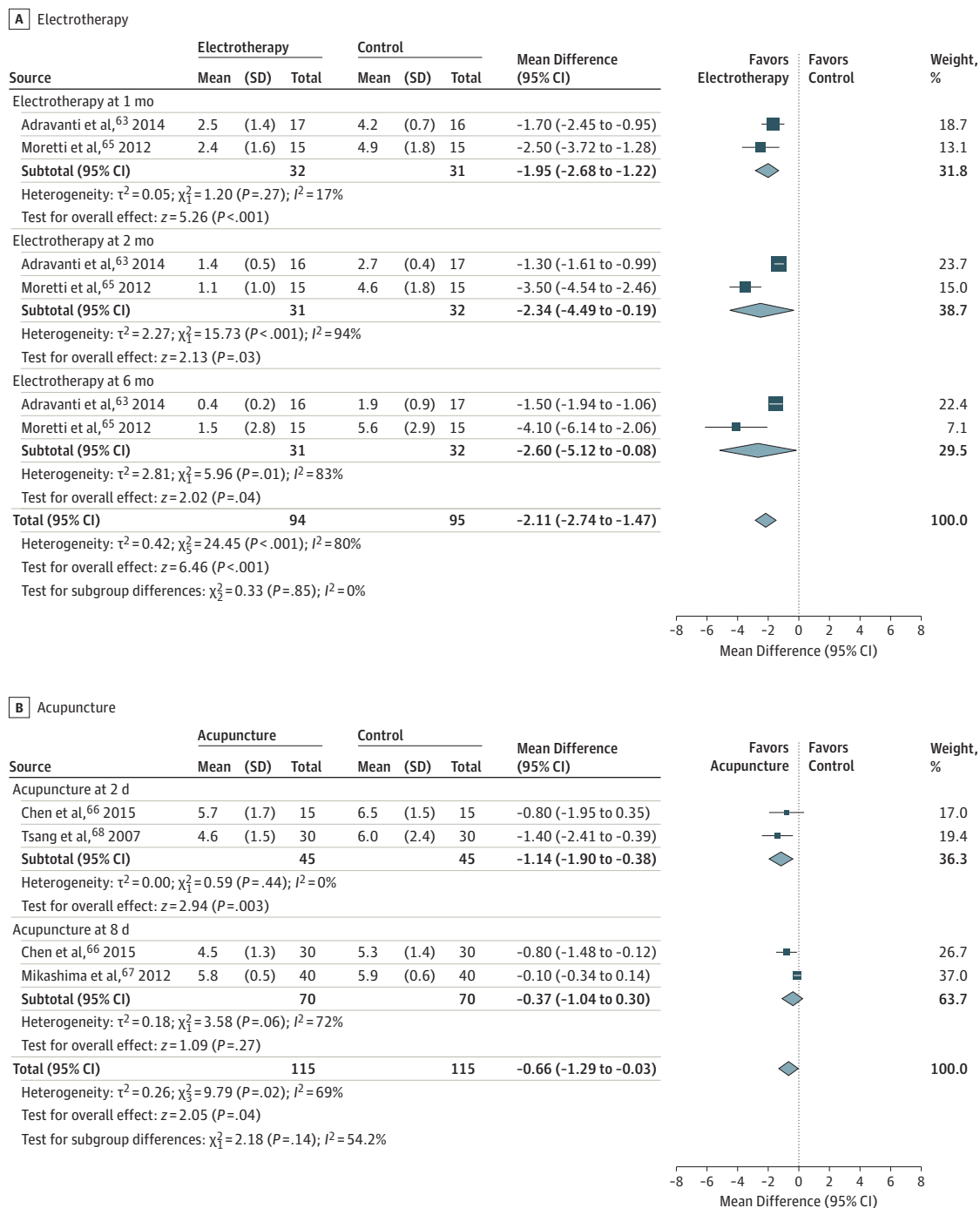
^b Units are the mean use of morphine equivalents in milligrams at 1 and 2 weeks for CPM, the number of tablets per 48 hours for cryotherapy, and morphine equivalents in milligrams per kilogram per 48 hours for all other variables under this heading.

^c Units are minutes after surgery.

(mean difference, -3.50; 95% CI, -5.90 to -1.10 opioids in milligrams per hour; *P* = .004; *I*² = 17%) (Figure 2A). Meta-analysis of 7 studies (468 patients) showed very low-certainty reduction in opioid consumption for cryotherapy (mean difference, -0.13; 95%

CI, -0.26 to -0.01 opioids in milligrams per hour; *P* = .03; *I*² = 86%) (Figure 2B). Meta-analysis of 3 studies (363 patients) showed very low-certainty nonreduction in nonsteroidal antiinflammatory drug (NSAID) consumption for cryotherapy (mean difference,

Figure 1. Pain Relief and Analgesic Consumption



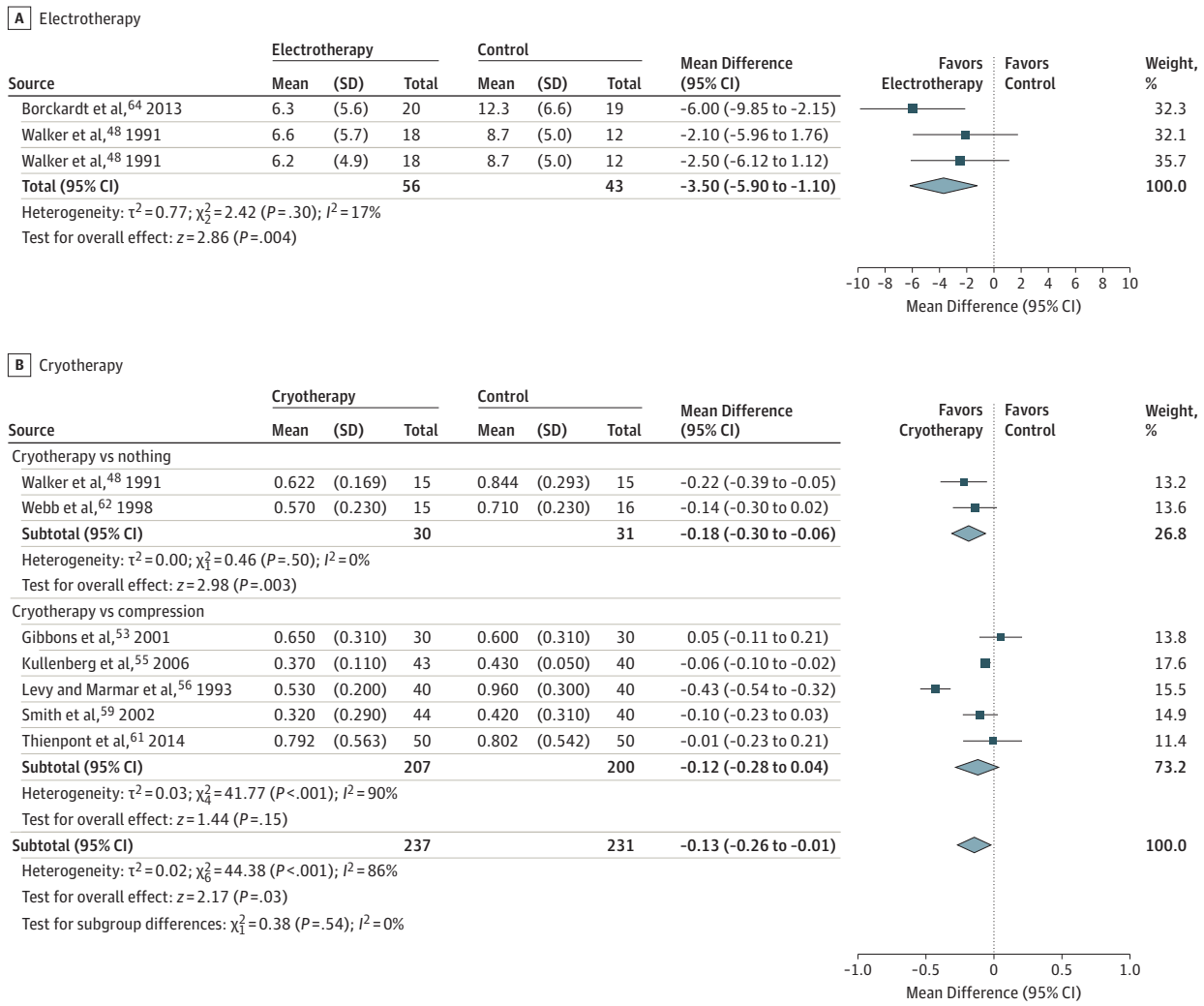
Shown are individual and pooled weighted mean differences in pain measured with a visual analog scale using the inverse variance method. A, The mean differences at 1, 2, and 6 months after surgery.^{63,65} B, The mean differences at 2

days and 8 days after surgery.⁶⁶⁻⁶⁸ A random-effects model was used to pool the data.

-0.75; 95% CI, -1.63 to 0.12 tablets per day; $P = .09$; $I^2 = 95\%$). Nevertheless, subgroup analyses showed a significant reduction in NSAID consumption, with mean differences of -1.90 (95% CI, -2.25 to -1.55 tablets per day; $P < .01$; $I^2 =$ not applicable) for cryotherapy vs nothing (1 study, with 60 patients) and -0.31 (95% CI, -0.55 to -0.07 tablet per day; $P = .01$; $I^2 = 0\%$) for cryotherapy vs

compression (2 studies, with 303 patients) (eFigure 6 in the Supplement). Acupuncture (2 studies, with 123 patients) and CPM (5 studies, with 313 patients) showed no significant differences between experimental groups and controls for amount of opioid consumed after surgery, with low-certainty and very low-certainty evidence, respectively: the mean differences were -0.71 (95% CI,

Figure 2. Opioid and Other Analgesic Consumption



Shown are individual and pooled weighted mean differences in opioid consumption within 48 hours after surgery (morphine equivalents in milligrams per kilogram per 48 hours) using the inverse variance method.

A, Electrotherapy.^{48,64} B, Cryotherapy.^{48,53,55,56,59,61,62} A random-effects model was used to pool the data.

-1.44 to 0.02 opioids in milligrams per hour; $P = .06$; $I^2 = 64\%$) for acupuncture (eFigure 7 in the Supplement) and 6.58 (95% CI, -6.33, to 19.49 opioids in milligrams per hour; $P = .32$; $I^2 = 87\%$) for CPM (eFigure 8 in the Supplement). Preoperative exercise studies did not report data on opioid consumption.

To address opioid consumption changes across the study period, we conducted sensitivity analyses stratifying for period (before or after 2000). The results were not significant (eFigure 39 and eFigure 40 in the Supplement).

Time Before the First Analgesic Treatment

In 2 studies (124 patients), we assessed time to first PCA in the acupuncture group and found moderate-certainty evidence that acupuncture significantly increases this period (mean difference, 46.17; 95% CI, 20.84-71.50 minutes; $P < .001$; $I^2 = 19\%$) (eFigure 9 in the Supplement). Also, a subgroup analysis carried out in 1 study⁶⁹ revealed a stronger difference in the acu-

puncture group compared with controls, with a mean difference of 57.90 (95% CI, 6.52-99.28 minutes; $P = .006$; $I^2 =$ not applicable).

Conflict of Interest of Included Studies

Authors of 7 studies reported at least 1 conflict of interest statement. Only 3 studies^{32,33,49} explicitly identified the funding sources (eTable 3 in the Supplement).

Discussion

This meta-analysis found moderate evidence that electrotherapy and acupuncture improved postoperative pain management and reduced opioid consumption. We found very low-certainty evidence that cryotherapy reduced opioid consumption, but there was no evidence that it improves perceived pain. The meta-

analysis suggests that CPM and preoperative exercise do not help alleviate pain (measured at different time points and using different scales) or reduce opioid consumption.

Electrotherapy and acupuncture are known to reduce postoperative pain. Electrotherapy is thought to decrease pain by stimulating the pain fibers with a nonpainful stimulus that blocks painful stimuli from reaching the brain and is free of adverse effects.¹⁰ One study⁷⁰ recommended electrotherapy to reduce analgesic use for various surgical procedures. Our findings suggest that electrotherapy may not only reduce early pain but also change the long-term trajectory of recovery from pain after TKA. We found evidence that electrotherapy changed pain severity at 1, 2, and 6 months, with increasing effect sizes over time. Hence, electrotherapy might be considered an effective nonpharmacological ancillary intervention to standard pharmacological therapy for long-term pain improvement. This finding is an important and underappreciated contribution to the literature that examines factors influencing the propensity to develop chronic pain after surgery, an area of significant general interest in clinical literature.⁴ However, because the quality of the studies analyzed for this outcome was very low, more high-quality RCTs on long-term pain improvement after electrotherapy are needed.

Our findings showed that acupuncture pain relief benefits concentrate in the early postoperative phase but are ineffective in the long run. A delay in opioid consumption can be considered a proxy of lower pain levels; high postoperative pain can lead to chronic pain.³ Our results suggest that acupuncture led to a modest delay in PCA requests, leading to possible benefits in this critical time window. Similarly, others have found that acupuncture provides significant pain improvement in patients undergoing TKA and total hip arthroplasty in the first 2 days after surgery.¹⁶ The acupuncture studies had less risk of bias than other modalities, so our conclusions regarding their benefit are more secure. If confirmed in future studies, our findings support the use of both electrotherapy and acupuncture after TKA.

We found less evidence that cryotherapy reduced opioid and NSAID consumption. While a Cochrane review article reported a small benefit of cryotherapy for pain at 2 days after surgery but not at 1 and 3 days,²³ our results demonstrated very low-certainty evidence for this intervention on postoperative analgesia after TKA. More research about this intervention could focus on opioid consumption effects.

The CPM results are particularly notable. Continuous passive motion is commonly used after TKA, with the 2 proposed benefits of improved function and reduced pain. However, recent work has not shown the usefulness of CPM in improving functionality and rehabilitation.¹¹ The RCTs included in our meta-analysis found very low-certainty evidence that CPM reduces opioid consumption during the early postoperative phase and found low-certainty or very low-certainty evidence that CPM provides no improvement in perceived pain. Our findings are consistent with a Cochrane review article that also found no benefits of CPM on function, pain, or quality of life after TKA.¹¹ These results need to be cautiously considered because CPM is not without risk.⁷¹ Also, CPM is an expensive and time-consuming procedure.^{33,71} Because

the results of other studies have suggested that CPM is ineffective in improving functionality¹¹ and that CPM is associated with increased hospital length of stay,⁷¹ careful consideration should be exercised before applying this treatment.

Our study also found little evidence to support that preoperative exercise improves postoperative pain and thus adds to conflicting literature. Several studies have reported that preoperative exercise had no significant benefit in improving functionality, quality of life, or pain for patients after TKA,^{72,73} whereas others found that the intervention improved postoperative pain, hospital length of stay, and physical function after various surgical procedures.⁷⁴ However, given the poor quality of the evidence, our results do not support the use of preoperative exercise for patients after TKA and advocate for further high-quality studies on this topic.

Limitations

Several limitations should be considered before interpreting these findings. First, for each intervention and outcome, we could only include a small number of studies in the analysis because of high heterogeneity in the timing and type of interventions. To address this issue, we pooled studies from different time points to obtain larger sample sizes, and subgroup analyses showed results similar to the overall findings (eFigures 30, 31, 32, 33, 34, 35, 36, 37, and 38 in the [Supplement](#)). Age and sex were not differently distributed in the groups (treatment vs control as shown in the meta-regressions) (eFigure 41 and eFigure 42 in the [Supplement](#)). Second, studies often showed a high risk or unclear risk of bias, which may have led to overestimations or underestimations of the reported effects. However, we assessed the quality of evidence through a validated tool and took into account the level of certainty of evidence for each outcome. Third, most studies did not achieve full masking, which also may have caused overestimation of effects in various meta-analyses conducted. Fourth, some studies lacked sufficient data to measure dispersion for the effect measurement (SD or SE). We attempted to address this problem by contacting authors but never obtained a response.

Conclusions

Although past studies^{8,10,11,16,23,73} have investigated individual nonpharmaceutical interventions for different postoperative outcomes after TKA, to our knowledge, this meta-analysis is the first comprehensive study to examine the most frequent treatments, adding new evidence on drug consumption. As prescription opioid use is under national scrutiny and because surgery has been identified as an avenue for addiction, it is important to recognize effective alternatives to standard pharmacological therapy, which remains the first option for treatment.^{5,12} Our study provides modest but clinically significant evidence that electrotherapy and acupuncture can potentially reduce and delay opioid consumption. However, strong supporting research is further needed. Evidence for other interventions, although limited by the quality of the underlying literature, had less support.

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Author Contributions: Dr Hernandez-Boussard had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Tedesco, Asch, Carroll, Curtin, McDonald, Fantini, Hernandez-Boussard.

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