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Pharmacologic Management of Acute Pain in Children
A Systematic Review and Network Meta-Analysis

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IMPORTANCE Several pharmacologic options exist for the management of acute pediatric pain; however, their comparative effectiveness remains uncertain.

OBJECTIVE To assess the relative benefits and harms of pharmacotherapy for acute pediatric pain through a network meta-analysis of randomized clinical trials.

DATA SOURCES Cochrane Database of Systematic Reviews, Medline, Embase, CINAHL, Web of Science, and Scopus to October 2023.

STUDY SELECTION Trials that enrolled children (aged <18 years) with acute pain and randomized them to receive a pharmacologic analgesic vs an alternate analgesic or placebo were included.

DATA EXTRACTION AND SYNTHESIS Pairs of reviewers independently reviewed abstracts, extracted data, and assessed risk of bias of eligible trials. A frequentist random-effects model was used for all meta-analyses, and the certainty of evidence was assessed for treatment effects using the Grading of Recommendations Assessment, Development, and Evaluation approach.

MAIN OUTCOMES The primary outcomes were pain severity (range, 0-10 cm using a visual analog scale; minimally important difference [MID], 1 cm), need for rescue medication, symptom relief, and adverse drug events.

RESULTS A total of 41 trials involving 4935 children were included. High- to moderate-certainty evidence found that compared with placebo, nonsteroidal anti-inflammatory drugs (NSAIDs) (weighted mean difference [WMD], −1.29; 95% CI, −1.89 to −0.70; modeled risk difference [RD] for achieving the MID, 16%), ketamine (WMD, −1.12; 95% CI, −2.09 to −0.14; modeled RD for achieving the MID, 14%), and mid-high potency opioids (WMD, −1.19; 95% CI, −1.83 to −0.55; modeled RD for achieving the MID, 15%) reduced pain. Only NSAIDs reduced the need for rescue medication (relative risk [RR], 0.31; 95% CI, 0.14 to 0.68; modeled RD, 16% fewer patients). Neither NSAIDs (RR, 0.69; 95% CI, 0.31 to 1.55) nor acetaminophen (RR, 0.63; 95% CI, 0.21 to 1.87) increased the risk of short-term gastrointestinal adverse events. All other comparisons showed moderate-certainty evidence of little to no difference from placebo or were supported by low/very low–certainty evidence.

CONCLUSIONS AND RELEVANCE Compared with placebo, NSAIDs, ketamine, and mid- to high-potency opioids are effective in reducing acute pediatric pain. NSAIDs provide the greatest benefits and least harm, suggesting that they should be the first-line therapy for acute painful conditions in children.

Supplemental content

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Acute pain is prevalent in children, reported in almost 60% of all pediatric emergency department (ED) encounters.[1-3] Pediatric guidelines emphasize multimodal therapy for pain care (ie, psychological, physical, pharmacologic),[4-7] including several analgesic medications as potential options.[5,6,8-10] Such recommendations are based on individual trials, conventional reviews, and expert opinions, in the absence of a comprehensive and up-to-date assessment of the effectiveness and associated harm of available analgesics.

The clinical management of acute pain remains variable, and opioids are often administered despite minimal and sometimes contradictory evidence regarding their efficacy.[11-14] In response, we conducted a systematic review and network meta-analysis (NMA) of randomized clinical trials (RCTs) to compare the effectiveness and safety of pharmacologic treatments. Our goal was to provide a comprehensive comparison of the safety and efficacy of the available analgesics to inform clinical guidelines and practice.

Key Points

Question In children with acute painful conditions, which pharmacologic interventions provide the most effective pain relief with the least risk of harm?

Findings This systematic review and network meta-analysis that included 41 trials and 4935 pediatric patients with acute pain found that compared with placebo, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and ketamine were effective for pain relief. NSAIDs were also effective in reducing the need for rescue analgesia and caused the least harm.

Meaning NSAIDs have an optimal benefit-harm ratio in children with acute pain due to several painful conditions.

Methods

Search Strategy and Selection Criteria

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline to report systematic reviews incorporating NMAs[15] and registered our protocol on the Open Science Framework platform.[16] We followed Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidance to communicate our findings.[17]

A medical librarian developed database-specific search strategies without language restrictions and searched the Cochrane Central Register of Controlled Trials (CENTRAL), Medline (via Ovid), Embase, CINAHL, Web of Science, and Scopus from inception until October 3, 2023 (eMethods 1 in Supplement 1). We reviewed the reference lists of eligible trials and related reviews[18-20] to identify additional eligible RCTs.[21,22]

Pairs of reviewers independently screened the titles and abstracts of identified studies and assessed the full-text articles of all potentially eligible studies, resolving discrepancies through discussion. Eligible trials enrolled children (<18 years) presenting with acute pain (<4 weeks) to the ED or urgent care or outpatient medical clinics and randomized them to receive a pharmacologic agent targeted at pain management vs another pharmacologic agent or placebo. We excluded trials from inpatient, dental, or perioperative settings and those that treated procedural pain. We excluded trials focused on migraine and sickle cell crises, as some of the pharmacologic interventions typically used for these populations (eg, triptans for migraines and morphine infusions for sickle cell crises) are not applicable to other acutely painful conditions (eMethods 2 in Supplement 1).

Data Abstraction and Risk-of-Bias Assessment

Pairs of reviewers extracted data and assessed the risk of bias using a modified Cochrane risk-of-bias instrument[23,24] that addressed the following issues: random sequence generation, allocation concealment, blinding of study participants, health care professionals, data collectors, or outcome assessors, incomplete outcome data (>20% was considered at high risk of bias), and other potential sources of bias (eMethods 2 in Supplement 1). Outcomes of interest were changes in baseline pain scores at the closest time point to 1 hour, need for rescue medication, symptom relief, and adverse drug events (ADEs) (eMethods 3-5 in Supplement 1).

Data Synthesis and Statistical Analysis

For changes in pain, we pooled each direct paired comparison reported in more than 1 study as the weighted mean difference (WMD) and associated 95% CI. We first transformed all measures of pain severity to a 10-cm visual analog scale using the method suggested by Thorlund et al.[25] We calculated the probability of children achieving the minimally important difference (MID) of a 1-cm[26] reduction in pain using the network mean differences for interventions and placebo groups.[25] For dichotomous outcomes, we calculated the pooled risk ratio (RR) and risk difference (RD) and their corresponding 95% CIs. We used the median risk from the placebo arms of the included trials as baseline risk to calculate absolute risk estimates.[27-29]

To pool effect estimates from direct comparisons informed by more than 1 RCT, we performed conventional pairwise meta-analyses using a DerSimonian-Laird random-effects model. When there were at least 10 trials contributing to a direct comparison, we assessed small-study effects through visual inspection of the funnel plot and calculation of an Egger test for continuous outcomes and Harbord test for binary outcomes.[30-32] For all direct comparisons, we assessed heterogeneity among RCTs using forest plots and the I^2 statistic, with heterogeneity classified as not important (0%-40%), moderate (30%-60%), substantial (50%-90%), or considerable (75%-100%).[33]

We performed random-effects frequentist NMA using the methodology of multivariate meta-analysis assuming a common-heterogeneity parameter with the automated network suite in Stata.[30,34,35] After consultation with methodologists and acute pain experts, we pooled results across all types of painful conditions (ie, musculoskeletal, abdominal, and otorhinolaryngologic), which is consistent with previous NMA of treatment for acute adult pain.[35]

To test the coherence assumption of the network, we used the "design-by-treatment" model (global test) and generated the *P* value for global incoherence.[36] We also used the side-splitting method to evaluate local (loop-specific) incoherence in each closed loop. All analyses were performed using Stata version 18 (StataCorp).[30,34]

We performed a prespecified subgroup analysis for route of medication administration (intranasal vs intramuscular vs intravenous vs oral vs sublingual/rectal) and used network meta-regression to explore associations of effect estimates with type of painful condition (musculoskeletal, abdominal pain, otorhinolaryngologic) and age. We performed sensitivity analysis by expanding the network of interventions with individual drugs as nodes (eMethods 2 in Supplement 1).

Assessing Certainty of the Evidence

We used the GRADE approach to assess the certainty of evidence for the direct, indirect, and network estimates.[37] Direct estimates from RCTs start as high-certainty evidence but may be rated down because of risk of bias, indirectness, inconsistency, or publication bias. Indirect estimates start at the lowest rating of indirect comparisons from the dominant lowest-order loop and can be further downgraded for intransitivity.[38,39] We assessed intransitivity by ensuring that all interventions in eligible trials included were jointly randomizable and assessing the distribution of potential effect modifiers (age, publication year, and funding) across direct comparisons in the networks and by performing network meta-regression for clinical condition and route of medication administration.

For GRADE ratings of network estimates, we started with the dominant direct or indirect estimate (whichever contributed >50%) and further rated down our certainty in evidence for incoherence and imprecision if applicable.[40,41] We judged imprecision based on whether 95% CIs crossed prespecified thresholds.[37,42] The decision threshold for pain intensity was half the MID (0.5 cm) and, for dichotomous outcomes, the null value (RR = 1). We did not rate down for imprecision if the confidence interval excluded the decision threshold unless the comparison was statistically significant, and the optimal information size was not met. If both intransitivity and incoherence were present, we only rated down 1 level, as these are related issues (eMethods in Supplement 1).[41]

Summary of Results GRADE Approach

We used a minimally contextualized GRADE approach to draw conclusions from the NMA.[17] We categorized interventions from most to least effective, based on the treatment effect estimates for benefits and harms obtained from the NMA and their associated certainty of evidence. For each effectiveness outcome, we created groups of interventions as follows: (1) the reference intervention (placebo) and interventions not different from placebo, which we refer to as "among the least effective"; (2) interventions superior to placebo but not superior to other interventions, (category 2 interventions); and (3) 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 but designated groups as follows: (1) no more harmful than placebo, (2) less harmful than some alternatives but more harmful than placebo, and (3) among the most harmful. We then categorized interventions as those supported by moderate or high certainty evidence and those supported by low or very low certainty evidence relative to placebo.

Results

Our search identified 27 893 records, of which 41 trials involving 4935 children were eligible for review (**Figure 1** and eResults 1 in Supplement 1). The median (IQR) of the mean age of patients was 9.7 years (7.98-11.68 years), and among 40 trials that provided this information, the median (SD) of the mean pain score at baseline was 6.9 (1.3) cm. Of the 41 RCTs, 25 trials (61%) enrolled participants with musculoskeletal pain (fracture, sprain/strain), 6 (15%) had otorhinolaryngologic pain (tonsillopharyngitis, mouth lesions, acute otitis media, and mucositis), 5 (12%) had abdominal pain, and 5 (12%) enrolled children with mixed types of painful conditions (eTables 1 and 2 in Supplement 1). Among the 41 trials, 35 (85%) were conducted in the ED, 29 (70%) had health care professionals administer the medication, and 34 (83%) had outcomes measured in hospital.

We grouped interventions as follows: (1) placebo; (2) acetaminophen (oral); (3) NSAIDs (ibuprofen [oral], ketoprofen [oral, topical], naproxen [oral], ketorolac [oral, sublingual, intravenous], nimesulide [oral], morniflumate [rectal], fentiazac [rectal], benzidamide [rectal]); (4) tramadol (sublingual); (5) codeine (oral); (6) mid- to high-potency opioids (morphine [oral, intramuscular, intravenous], diamorphine [intranasal]), oxycodone [oral], fentanyl [transmucosal, intranasal, intravenous]); (7) ketamine (intranasal, oral swish); and (8) combinations of interventions. **Figure 2** and eFigures 1 through 12 in Supplement 1 present the networks of eligible comparisons for each outcome. For 7 studies,[22,43-49] all treatment arms were from the same drug class and were thus excluded from our primary NMA.

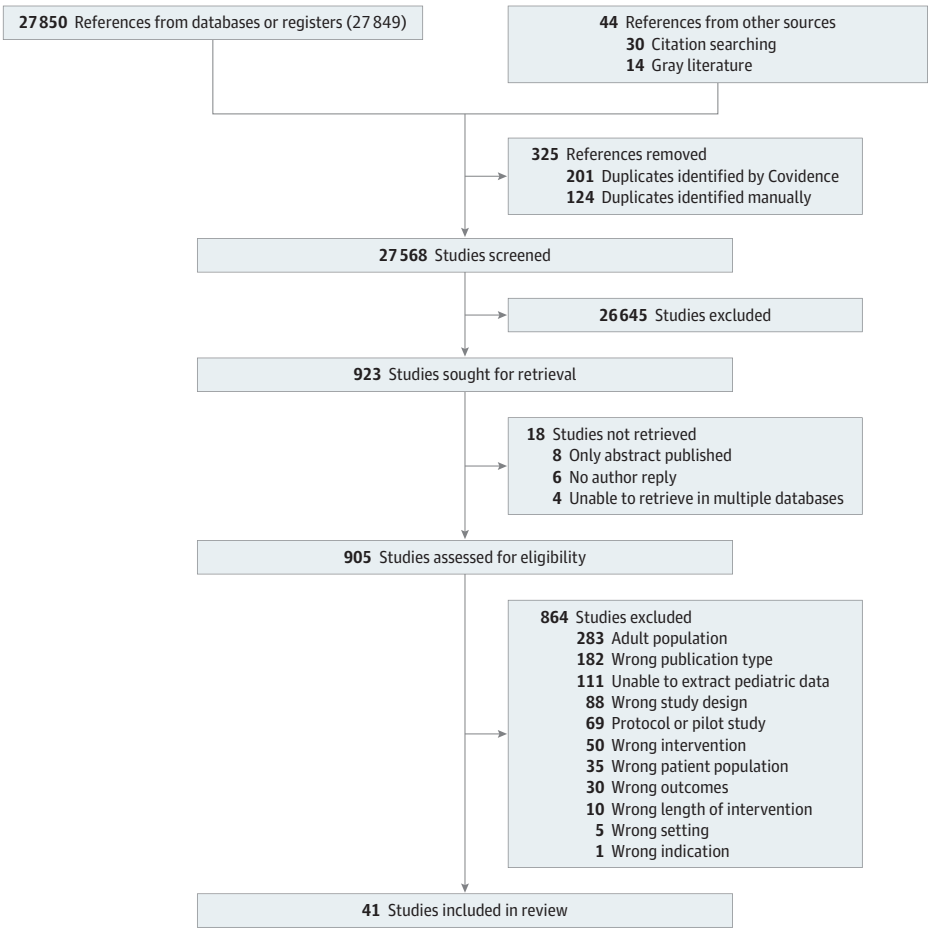
Risk of Bias

Of the 41 RCTs, 19 (46%) were at high risk of bias for at least 1 domain. Most trials (36 [88%]) adequately generated their randomization sequence, 30 (73%) ensured allocation concealment, 33 (80%) were blinded to patients, and 28 (68%) were blinded to health care professionals. Only 2 trials (5%) reported missing data of more than 20%. Most trials (30 [73%]) reported no funding or nonindustry funding (eTable 3 in Supplement 1).

Pain Relief Measured at or Near the 1-Hour Mark

Pain intensity was reported in 33 trials including 3482 patients. Of the 21 comparisons informed by direct evidence, 10 were informed by 2 or more studies and 1 comparison showed considerable heterogeneity (I^2 = 90%). There was no evidence of global (*P* = .69) or loop-specific incoherence (refer to incoherence plot 1 in eResults 2 of Supplement 1).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram for Study Selection



Moderate to high certainty evidence showed that, compared with placebo, NSAIDs (WMD, −1.29; 95% CI, −1.89 to −0.70; modeled RD for achieving the MID, 16%), ketamine (WMD, −1.12; 95% CI, −2.09 to −0.14; modeled RD for achieving the MID, 14%), and mid- to high-potency opioids (WMD, −1.19; 95% CI, −1.83 to −0.55; modeled RD for achieving the MID, 15%) reduced pain (**Table**). Across all interventions, only NSAIDs demonstrated superiority over codeine (WMD, −1.05; 95% CI, −2.08 to −0.03; moderate certainty).

Low certainty evidence suggests that tramadol, acetaminophen alone or in combination with NSAIDs or opioids, NSAIDs plus codeine or opioids, and midazolam plus opioids may reduce pain. In contrast, codeine alone may have little to no effect on pain compared with placebo. The effect of acetaminophen with codeine was supported by very low certainty evidence (eTable 4 in Supplement 1).

Need for Rescue Medication

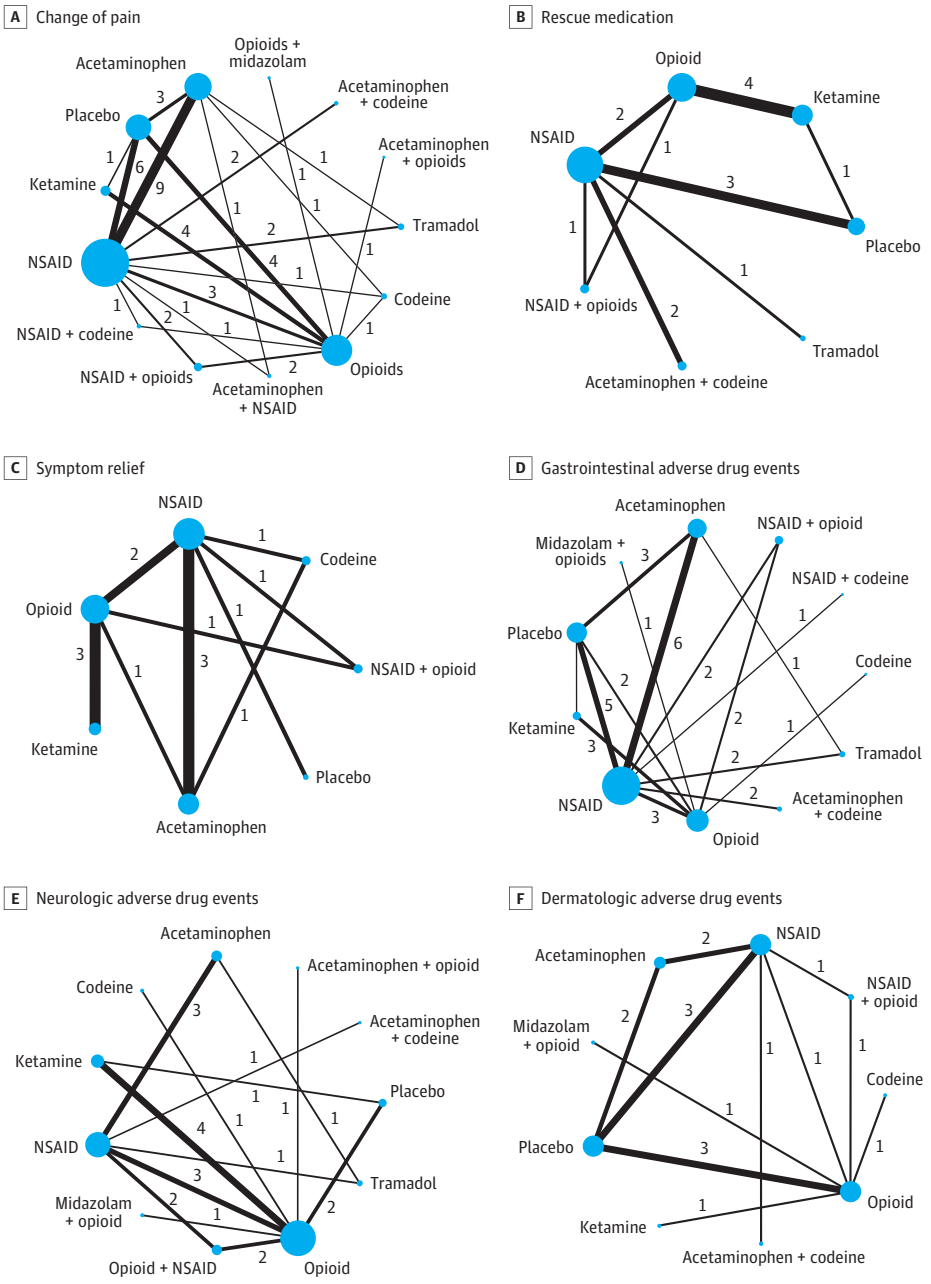
Thirteen trials including 1525 patients reported on need for rescue medication, with the definition of rescue medication in each trial provided in eMethods 3 in Supplement 1. Four of the 8 direct comparisons were informed by more than 1 study. No substantial heterogeneity was observed among conventional pairwise meta-analyses, nor did we find evidence of global (P = .18) or loop-specific incoherence (refer to incoherence plot 3 in eResults 2 in Supplement 1).

High certainty evidence found that NSAIDs reduced the need for rescue medication (RR, 0.31; 95% CI, 0.14 to 0.68; RD, 16% fewer patients; 95% CI, −8% to 21%) compared with placebo. Moderate certainty evidence suggested that ketamine (RR, 0.44; 95% CI, 0.18 to 1.11; RD, 13% fewer patients; 95% CI, −20% to 3%) and opioids (RR, 0.52; 95% CI, 0.2 to 1.27; RD, 12% fewer patients; 95% CI, −19% to 6%) probably make little to no difference in the use of rescue medication vs placebo. Low certainty evidence suggests that tramadol, NSAIDs plus opioids, and acetaminophen plus codeine may make little to no difference in the use of rescue medication vs placebo (**Figure 3**, **Figure 4**, and eTable 5 in Supplement 1).

Symptom Relief

Symptom relief, often defined as either complete pain relief or the achievement of mild pain, was reported in 8 trials that included 1310 patients. Three of the 9 direct comparisons were informed by more than 1 study. No substantial heterogeneity was observed among conventional pairwise meta-

Figure 2. Network of Eligible Comparisons



The size of the node corresponds to the number of children randomized to receive the intervention. The directly compared interventions are linked with a line; the thickness of the line corresponds to the number of studies that assessed the comparison. Panels A through F organize the comparisons by type of outcome or adverse drug event. NSAID indicates nonsteroidal anti-inflammatory drug.

analyses, nor did we find evidence of global (P = .47) or loop-specific incoherence (refer to incoherence plot 5 in eResults 2 in Supplement 1). Moderate certainty evidence showed that compared with placebo, NSAIDs (RR, 0.94; 95% CI, 0.39 to 2.29), NSAIDs plus opioids (RR, 0.77; 95% CI, 0.30 to 1.98), codeine (RR, 0.77; 95% CI, 0.30 to 1.99), acetaminophen (RR, 0.76; 95% CI, 0.31 to 1.90), and opioids (RR, 0.70; 95% CI, 0.28 to 1.75) provided little to no difference in symptom relief. Low certainty evidence suggests that ketamine may provide little to no difference in symptom relief compared with placebo (Table, Figure 3, Figure 4, and eTable 6 in Supplement 1).

Adverse Drug Events

ADEs were reported in 41 trials including 4935 patients. For dermatologic and neurologic ADEs, there was no evidence of global incoherence (P = .40 and P = .74, respectively) or loop-specific incoherence (incoherence plots 9 and 11 in eResults 2 in Supplement 1). For gastrointestinal ADEs, there was no evidence of global incoherence (P = .14); however, we found evidence of loop-specific incoherence in a single loop (placebo-ketamine-opioids) (incoherence plot 7 in eResults 2 in Supplement 1).

Moderate certainty evidence suggests that, compared with placebo, NSAIDs (RR, 0.69; 95% CI, 0.31 to 1.55; RD 1% fewer

Table. Network Meta-Analysis Results (Mean Difference and 95% CIs) Sorted Based on GRADE Certainty of Evidence for Comparisons of Active Interventions vs Placebo

Certainty of evidence	Classification	Intervention	Effect estimates (95% CI)	SUCRA	Risk difference, per 100[a]
Pain relief[b]					
Moderate to high	Among the most effective	NSAID	−1.29 (−1.89 to −0.70)	66.5	16.13 (9.83 to 20.71)
		Opioids	−1.19 (−1.83 to −0.55)	58.7	15.19 (7.93 to 20.33)
		Ketamine	−1.12 (−2.09 to −0.14)	53.0	14.50 (2.16 to 21.88)
Low to very low	May be among the most effective	Midazolam + opioid	−1.99 (−3.97 to −0.01)	80.3	21.31 (0.16 to 26.92)
		Tramadol	−1.20 (−2.33 to −0.06)	58.0	15.28 (0.94 to 23.06)
		Acetaminophen	−1.00 (−1.71 to −0.29)	46.0	13.26 (4.37 to 19.52)
	May be among the least effective	Acetaminophen + opioid	−1.41 (−3.11 to 0.28)	63.9	17.18 (−4.57 to 25.63)
		Acetaminophen + NSAID	−1.37 (−2.92 to 0.18)	65.8	16.84 (−2.90 to 25.16)
		NSAID + codeine	−1.19 (−2.57 to 0.19)	55.6	15.19 (−3.06 to 24.04)
		NSAID + opioid	−1.02 (−2.09 to 0.05)	46.8	13.47 (−0.79 to 21.88)
		Acetaminophen + codeine	−0.70 (−1.95 to 0.54)	33.1	9.83 (−9.06 to 21.08)
		Codeine	−0.24 (−1.35 to 0.87)	16.2	0.00 (−15.04 to 16.66)
Need for rescue medication					
Moderate to high	The most effective	NSAID	0.31 (0.14 to 0.67)	86.5	−16.48 (−21 to −8)
	Among the least effective	Ketamine	0.44 (0.18 to 1.11)	61.5	−13 (−20 to 3)
		Opioids	0.52 (0.21 to 1.27)	43.8	−12 (−19 to 6)
Low to very low	May be among the least effective	NSAID + opioids	0.30 (0.04 to 2.07)	68.9	−17 (−23 to 26)
		Acetaminophen + codeine	0.44 (0.18 to 1.09)	56.5	−13 (−20 to 2)
		Tramadol	1.13 (0.20 to 6.20)	18.6	3 (−19 to 125)
Symptom relief					
Moderate to high	Not better than placebo (or among the least effective)	NSAID	0.94 (0.39 to 2.29)	85.0	−1 (−10 to 22)
		NSAIDs + opioids	0.77 (0.30 to 1.98)	49.9	−4 (−12 to 17)
		Codeine	0.77 (0.30 to 1.99)	47.7	−4 (−12 to 17)
		Acetaminophen	0.76 (0.31 to 1.90)	44.9	−4 (−12 to 15)
		Opioids	0.70 (0.28 to 1.75)	28.5	−5 (−12 to 13)
Low to very low	May not be better than placebo (or may be among the least effective)	Ketamine	0.68 (0.26 to 1.74)	24.8	−5 (−13 to 13)
GI adverse events					
Moderate to high	Not more harmful than placebo	NSAID	0.69 (0.31 to 1.55)	20.8	−1.0 (−3.0 to 2.0)
		Acetaminophen	0.63 (0.21 to 1.87)	18.5	−1.0 (−3.0 to 3.0)
Low to very low	May be the most harmful	Ketamine	4.87 (1.52 to 15.65)	88.9	15.0 (2.0 to 59.0)
	May not be more harmful than placebo	Tramadol	3.61 (0.86 to 15.18)	78.4	10.0 (−1.0 to 57.0)
		Codeine	2.59 (0.64 to 10.43)	67.2	6.0 (−1.0 to 38.0)
		NSAID + opioid	2.34 (0.62 to 8.87)	64.8	5.0 (−2.0 to 31.0)
		Opioid	2.18 (0.78 to 6.11)	61.6	5.0 (−1.0 to 20.0)
		NSAID + codeine	2.03 (0.07 to 57.75)	55.6	4.0 (−4.0 to 227.0)
		Midazolam + opioid	1.17 (0.08 to 16.61)	42.5	1.0 (−4.0 to 62.0)
		Acetaminophen + codeine	0.59 (0.20 to 1.75)	15.6	−2.0 (−3.0 to 3.0)
Neurologic adverse events					
Low to very low	May be the most harmful	Midazolam + opioid	7.03 (1.02 to 48.55)	89.1	3.5 (0.0 to 24.0)
	May not be more harmful than placebo	Tramadol	10.35 (0.52 to 204.55)	85.0	9.0 (1.0 to 204.0)
		Ketamine	5.88 (0.97 to 35.75)	85.2	5.0 (0.0 to 35.0)
		Acetaminophen + codeine	2.97 (0.45 to 19.57)	58.0	2.0 (−1.0 to 19.0)
		Opioid	2.70 (0.45 to 16.27)	52.9	2.0 (−2.0 to 15.0)
		Codeine	2.63 (0.42 to 16.34)	50.4	2.0 (−1.0 to 15.0)
		NSAID + opioid	2.31 (0.31 to 17.41)	43.9	1.0 (−1.0 to 16.0)
		NSAID	1.82 (0.28 to 11.76)	28.9	1.0 (−1.0 to 11.0)
		Acetaminophen	1.20 (0.11 to 13.12)	23.0	0.0 (−1.0 to 12.0)
		Acetaminophen + opioid	0.39 (0.01 to 11.60)	12.4	−1.0 (−1.0 to 11.0)

(continued)

Table. Network Meta-Analysis Results (Mean Difference and 95% CIs) Sorted Based on GRADE Certainty of Evidence for Comparisons of Active Interventions vs Placebo (continued)

Certainty of evidence	Classification	Intervention	Effect estimates (95% CI)	SUCRA	Risk difference, per 100[a]
Dermatologic adverse events					
Low to very low	May not be more harmful than placebo	Midazolam + opioid	15.50 (0.55 to 439.17)	81.3	15.0 (0.0 to 438.0)
		Acetaminophen + codeine	6.84 (0.19 to 241.04)	67.0	6.0 (−1.0 to 240.0)
		Ketamine	6.07 (0.17 to 215.12)	64.0	5.0 (−1.0 to 214.0)
		NSAID + opioid	4.59 (0.50 to 41.95)	64.5	4.0 (0.0 to 41.0)
		Codeine	2.97 (0.47 to 18.80)	52.8	2.0 (−1.0 to 18.0)
		NSAID	2.15 (0.42 to 11.01)	42.6	1.0 (−1.0 to 10.0)
		Opioid	2.07 (0.41 to 10.58)	38.8	1.0 (−1.0 to 10.0)
		Acetaminophen	0.78 (0.06 to 9.52)	19.2	0.0 (−1.0 to 9.0)

Abbreviations: GI, gastrointestinal; MID, minimally important difference; NSAID, nonsteroidal anti-inflammatory drug; SUCRA, surface under the cumulative ranking curve.

[a] For pain relief, the risk difference was the modeled risk difference for achieving MID of 1 cm.

[b] Pain relief was measured using the mean difference visual analog scale; scores ranged from 0 to 10 cm, and lower was better (the MID was 1 cm).

Figure 3. Network Meta-Analysis Results Sorted Based on GRADE Certainty of Evidence and Effect Estimate for Comparisons of Active Treatments vs Placebo: Effectiveness Outcomes

Intervention	Pain relief, MD in VAS score (95% CI)	Need for rescue medication, RR (95% CI)	Symptom relief, RR (95% CI)
NSAID	−1.29 (−1.89 to −0.70)	0.31 (0.14 to 0.67)	0.94 (0.39 to 2.29)
Opioid	−1.19 (−1.83 to −0.55)	0.52 (0.21 to 1.27)	0.70 (0.28 to 1.75)
Ketamine	−1.12 (−2.09 to −0.14)	0.44 (0.18 to 1.11)	0.68 (0.26 to 1.74)
Acetaminophen	−1.00 (−1.71 to −0.29)	NA	0.76 (0.31 to 1.90)
Tramadol	−1.20 (−2.33 to −0.06)	1.13 (0.20 to 6.20)	NA
Acetaminophen + opioid	−1.41 (−3.11 to 0.28)	NA	NA
Acetaminophen + NSAID	−1.37 (−2.92 to 0.18)	NA	NA
NSAID + codeine	−1.19 (−2.57 to 0.19)	NA	NA
NSAID + opioid	−1.02 (−2.09 to 0.05)	0.30 (0.04 to 2.07)	0.77 (0.30 to 1.98)
Acetaminophen + codeine	−0.70 (−1.95 to 0.54)	0.44 (0.18 to 1.09	Insufficient[a]
Codeine	−0.24 (−1.35 to 0.87)	NA	0.77 (0.30 to 1.99)
Midazolam + opioid	−1.99 (−3.97 to −0.01)	NA	NA

	Statistically significant different from placebo	Statistically no difference from placebo
High or moderate certainty of evidence	Among the most effective	Among the least effective
Low or very low certainty of evidence	May be among the most effective	May be among the least effective

MD indicates mean difference; NA, not applicable; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk; VAS, visual analog scale.

[a]Insufficient observations/studies to run the network meta-analysis.

patients; 95% CI, −3% to 2%) and acetaminophen (RR, 0.63; 95% CI, 0.21 to 1.87; RD, 1% fewer patients; 95% CI, −3% to 3%) probably resulted in little to no difference in short-term gastrointestinal ADEs (ie, nausea, vomiting, pain, diarrhea, and constipation). Low certainty evidence suggests that opioids, codeine with or without acetaminophen, and tramadol may cause little to no difference in gastrointestinal events, vs placebo, and that ketamine may increase the risk of gastrointestinal ADEs. The effect of opioids with midazolam was supported by very low certainty evidence (eTable 7 in Supplement 1). The evidence for the effects of analgesics on neurologic or dermatologic ADEs was only of low or very low certainty and suggested little to no difference vs placebo (eTables 8 and 9 in Supplement 1). No trial reported overdose, the need for respiratory support, gastrointestinal bleeding or ulcers, renal dysfunction, or any serious or life-threatening ADEs.

Additional Analyses

Subgroup analysis of medication routes revealed that topical NSAIDs may be superior to alternative routes for pain relief. This subgroup effect has low credibility, as data from topical NSAIDs came from a single trial of 111 participants (subgroup analyses in eResults 3 in Supplement 1). We were not able to perform this analysis for other outcomes.

Network estimates using network meta-regression showed that NSAIDs (WMD, −2.32; 95% CI, −3.29 to −1.35; WMD, −0.79; 95% CI, −1.73 to 0.15) and opioids (WMD, −2.49; 95% CI, −3.68 to −1.29; WMD, −0.90; 95% CI, −1.67 to −0.12) may offer an in-

Figure 4. Network Meta-Analysis Results Sorted Based on GRADE Certainty of Evidence and Effect Estimate for the Comparisons of Active Treatments vs Placebo: Harm Outcomes

Intervention	RR (95% CI)		
	Gastrointestinal adverse drug events	Neurologic adverse drug events	Dermatologic adverse drug events
NSAID	0.69 (0.31 to 1.55)	1.82 (0.28 to 11.76)	2.15 (0.42 to 11.01)
Opioid	2.18 (0.78 to 6.11)	2.70 (0.45 to 16.27)	2.07 (0.41 to 10.58)
Ketamine	4.87 (1.52 to 15.65)	5.88 (0.97 to 35.75)	6.07 (0.17 to 215.12)
Acetaminophen	0.63 (0.21 to 1.87)	1.20 (0.11 to 13.12)	0.78 (0.06 to 9.52)
Tramadol	3.61 (0.86 to 15.18)	10.35 (0.52 to 204.55)	NA
Acetaminophen + opioid	NA	0.39 (0.01 to 11.60)	NA
Acetaminophen + NSAID	NA	NA	NA
NSAID + codeine	2.03 (0.07 to 57.75)	NA	NA
NSAID + opioid	2.34 (0.62 to 8.87)	2.31 (0.31 to 17.41)	4.59 (0.50 to 41.95)
Acetaminophen + codeine	0.59 (0.20 to 1.75)	2.97 (0.45 to 19.57)	6.84 (0.19 to 241.04)
Codeine	2.59 (0.64 to 10.43)	2.63 (0.42 to 16.34)	2.97 (0.47 to 18.80)
Midazolam + opioid	1.17 (0.08 to 16.61)	7.03 (1.02 to 48.55)	15.50 (0.55 to 439.17)

	Statistically significant different from placebo	Statistically no difference from placebo
High or moderate certainty of evidence	Among the most harmful	Not more harmful than placebo
Low or very low certainty of evidence	May be among the most harmful	May not be more harmful than placebo

NA indicates not applicable; NSAID, nonsteroidal anti-inflammatory drug; RR, relative risk.

creased reduction in musculoskeletal and abdominal pain when compared with otorhinolaryngologic pain (meta-regressions in eResults 4 in Supplement 1). Network meta-regression showed no other subgroup effects on any outcome. Sensitivity analysis for the expanded network of interventions, considering all interventions as separate nodes, found no evidence of clinically important superiority of any specific drug within drug classes. (League tables are in eResults 4, and probability rankings and SUCRA values are in eResults 5 in Supplement 1.)

Discussion

In this NMA of analgesic trials for children with acute pain, we found high to moderate certainty evidence that NSAIDs, mid- to high-potency opioids, and ketamine provide effective pain relief compared with placebo. However, the effects were modest, with reductions in pain severity approximating the MID (1 cm). We found moderate certainty evidence that compared with placebo, NSAIDs probably reduce the need for rescue medication, whereas mid- to high-potency opioids and ketamine probably do not. Furthermore, moderate certainty evidence suggests that NSAIDs and acetaminophen are probably no more likely to cause short-term gastrointestinal ADEs than placebo.

NSAIDs, particularly ibuprofen, are recommended in clinical guidelines[5,6,9] as a first-line therapy for pain management. This recommendation appears to be consistent with practice, as physician reports indicate that NSAIDs are the most commonly used class of analgesics in ED pediatric pain management.[50] Our findings align with a recent NMA examining oral analgesics for acute musculoskeletal pain in children, which found that ibuprofen with or without opioids, acetaminophen, and opioids were similarly effective for pain relief at 1-hour follow-up.[51]

However, the prior NMA only considered acute musculoskeletal pain; their network was informed by only 5 trials, and the certainty of evidence was low for all comparisons. Networks of treatments should be informed by 7 to 10 RCTs[52] and should have more trials than nodes; the prior NMA failed both criteria. Our review extends these findings to more types of acute pediatric pain, including 28 additional trials, establishes effects for opioids and NSAIDs as supported by high to moderate certainty evidence, identifies ketamine as effective for pain relief, and quantifies the magnitude of effects as both the mean improvement in pain severity and RD for achieving important pain relief.

In our subgroup analysis, topical NSAIDs were superior to oral NSAIDs; however, this finding was based on a single trial.[53] These results are consistent with an NMA of adult patients with non–low back acute musculoskeletal pain, involving 207 trials and more than 32 000 participants.[35] In the mentioned NMA, authors ranked topical NSAIDs followed by oral NSAIDs as the interventions with the best benefit-harm ratio, as topical administration avoided gastrointestinal harm. Notably, most trials in our NMA administered oral medications. Guidelines underscore the importance of tailoring the route of administration to a child's ease and comfort.[6] Given the potential advantages of the topical route, further studies are warranted to explore its efficacy and acceptability in pediatric populations.

Although mid- to high-potency opioids had a similar effect on pain relief as NSAIDs, they should be second-line agents because of their lack of reduction in the need for rescue analgesia and evidence regarding their associated harms compared with NSAIDs. These results complement the comparative syn-

thesis on the safety of 3 commonly used pharmacologic agents, which found that opioids present the highest risk of central nervous system ADEs and combination of a nonopioid and an opioid medication results in a lower risk compared with using opioids alone.[54] This aligns with international[5,6,9] and national[10] recommendations for the use of opioids as additional therapy when nonopioid medications alone are inadequate for pain relief. Despite existing literature on the undertreatment of pain or opioid administration in children from racial minority or marginalized groups,[2,55,56] the included RCTs did not provide enough data to conduct subgroup analysis based on race or ethnicity and how this may affect outcomes. Future pain trials should include reporting on race, ethnicity, gender, and other intersectional considerations in a standardized manner, to improve capability to systematically synthesize this information and support equitable care outcomes.

Subdissociative analgesic doses of ketamine have been proposed as a valuable adjunct in pain management.[57] In this NMA, 5 studies,[58-62] 4 of which included children with moderate to severe pain related to musculoskeletal injuries, explored the effects of ketamine on pain improvement. Although ketamine provided pain relief, it did not reduce the need for rescue analgesia and may have increased gastrointestinal ADEs. One trial[60] found intranasal ketamine to be noninferior to intranasal fentanyl for fractures; however, ketamine showed a considerably higher rate of ADEs, consistent with our overall NMA findings. Although ketamine shows promise for pain relief, its potential for ADEs necessitates cautious use and further research to optimize its indications and safety profile in pediatric pain management.

Strengths and Limitations

The strengths of this review include a comprehensive assessment of all pharmacologic interventions and the presentation of interpretable data by (1) converting all pain-relief scores to a 10-cm visual analog scale with an anchored MID and (2) presenting the absolute risk ratio of achieving the MID. This approach provides a clinically relevant ranking of interventions by comparing the magnitude of their benefits and harms, supported by the GRADE certainty of evidence. Despite these strengths, this NMA has several limitations. There is limited direct evidence to support many comparisons, and the evidence for several interventions is predominantly of low or very low certainty. Because of sparse data, when analyzing short-term harms, we were not able to assess whether there were any subgroup effects on ADEs across different analgesic routes. We could not assess long-term harms such as opioid misuse or severe ADEs such as gastrointestinal bleeding, as no trials reported these outcomes. Additionally, 85% of the trials were based in the ED, potentially limiting generalizability to non-ED outpatient clinics. Some drugs were excluded from analysis to avoid violating the network transitivity assumption, which ensures that participants across all trials could be jointly randomizable to any intervention in our NMA. These excluded drugs included an antispasmodic (drotaverine hydrochloride), antidepressants (citalopram, amitriptyline), anticholinergics (mebeverine, hyoscine butylbromide), an antihistamine (famotidine), a steroid (dexamethasone), topical anesthetics (lidocaine, ropivacaine), and nitrous oxide.

Conclusions

This NMA found that NSAIDs, mid- to high-potency opioids, and ketamine are effective in reducing acute pediatric pain compared with placebo, with NSAIDs providing the greatest benefits and least harm. Therefore, NSAIDs should be considered as first-line analgesic therapy for children with acute pain. Notably, even the most effective pharmacologic treatments provide only modest pain relief. Further pediatric studies are needed on alternative analgesic routes, such as topical NSAIDs and combination opioid/nonopioid therapies.

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