JAMA | Original Investigation

Acetaminophen (Paracetamol) or Opioid Analgesia Added to Ibuprofen for Children's Musculoskeletal Injury
Two Randomized Clinical Trials

Samina Ali, MD; Terry P. Klassen, MD, MSc; Patricia Candelaria, BScN; Maala Bhatt, MD, MSc; Scott Sawyer, MD; Antonia Stang, MD, MBA; Maryna Yaskina, PhD; Anna Heath, PhD; Petros Pechlivanoglou, PhD; Martin Offringa, MD, PhD; Amy L. Drendel, DO, MS; Serena Hickes, BA, DSW; Naveen Poonai, MD, MSc; for the KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Team

IMPORTANCE Ibuprofen is first-line therapy for musculoskeletal pain. However, two-thirds of children experience inadequate pain relief with ibuprofen monotherapy, and the efficacy of additive medications for moderate to severe musculoskeletal pain is unclear.

OBJECTIVE To determine whether treatment with an opioid (hydromorphone) plus ibuprofen or nonopioid (acetaminophen [paracetamol]) plus ibuprofen decreased pain scores compared with ibuprofen alone.

DESIGN, SETTING, AND PARTICIPANTS Two randomized, double-masked, placebo-controlled trials were conducted from April 2019 to March 2023 in 6 university-affiliated, tertiary care Canadian pediatric emergency departments. Children aged 6 to 17 years presenting with a nonoperative acute limb injury (<24 hours) and a verbal numerical rating scale (vNRS) pain score of 5 or more out of 10 were enrolled. Date of final follow-up was March 22, 2023.

INTERVENTIONS The opioid trial randomized participants to a single oral dose of ibuprofen plus hydromorphone, ibuprofen plus acetaminophen, or ibuprofen alone. The nonopioid trial randomized participants to a single oral dose of ibuprofen plus acetaminophen or ibuprofen alone. In all groups, ibuprofen was dosed at 10 mg/kg (maximum, 600 mg). The acetaminophen dose was 15 mg/kg (maximum, 1000 mg), and the hydromorphone dose was 0.05 mg/kg (maximum, 5 mg).

MAIN OUTCOMES AND MEASURES The primary efficacy outcome was self-reported vNRS pain score at 60 minutes post medication administration (score range, 0 [no pain] to 10 [worst pain]; minimal clinically important difference, 1.5). The primary safety end point was the proportion of children with any adverse event related to study drug administration.

RESULTS A total of 8098 children were screened for eligibility; 699 were randomized and 653 were included in the efficacy analyses. The opioid trial included 249 children: 110 randomized to ibuprofen plus hydromorphone, 70 to ibuprofen plus acetaminophen, and 69 to ibuprofen alone. The nonopioid trial included 450 children: 225 randomized to a single oral dose of ibuprofen plus acetaminophen and 225 randomized to ibuprofen alone. The mean (SD) age of children in the 2 trials was 11.5 (3.5) years and 47.4% were female. The mean (SD) vNRS score at recruitment was 6.4 (1.8). In pooled analyses, mean (SD) vNRS scores 60 minutes after drug administration were 4.8 (2.6) in the ibuprofen plus hydromorphone group, 4.6 (2.4) in the ibuprofen plus acetaminophen group, and 4.6 (2.3) in the ibuprofen alone group (P = .78). Any adverse event occurred at higher rates in the ibuprofen plus hydromorphone group (28.2%) compared with the ibuprofen plus acetaminophen (6.1%) or ibuprofen alone groups (5.8%). No serious adverse events occurred.

CONCLUSIONS AND RELEVANCE For children with acute nonoperative musculoskeletal injury, pain scores at 60 minutes after drug administration did not improve with ibuprofen plus acetaminophen or ibuprofen plus hydromorphone compared with ibuprofen alone. Adverse events were 4-fold more frequent with hydromorphone.

TRIAL REGISTRATION Clinicaltrials.gov Identifier: NCT03767933

JAMA. 2026;335(10):863-873. doi:10.1001/jama.2025.25033
Published online January 8, 2026.

Visual Abstract
Research Summary
Editorial page 856
Supplemental content
CME Quiz at jamacmelookup.com

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Team members are listed in Supplement 3.

Corresponding Author: Samina Ali, MD, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, 3-583 Dianne and Irving Kipnes Health Research Academy, 11405-87 Avenue, Edmonton, AB T6G 1C9, Canada (sali@ualberta.ca).

One in 5 children experience an acute injury annually, with one-third sustaining a fracture before the age of 17 years.[1,2] National guidelines,[3,4] supported by systematic review,[5-7] recommend that ibuprofen should be first-line therapy for acute musculoskeletal pain, but as many as two-thirds of children report suboptimal pain reduction with ibuprofen alone.[5,8] Untreated pain may have short- and long-term consequences for children, including school absence, poor sleep, and prolonged duration of healing.[8,9] In addition, persistent pain in children has negative effects on their caregivers, such as emotional distress and potentially needing to miss work. Despite its frequent use as combination therapy for children with fever and pain, limited evidence exists for combining acetaminophen (paracetamol) and ibuprofen for acute pain.[10,11] Further, federal warnings restricting codeine, hydrocodone, and tramadol use in children has left few oral opioid therapy options for moderate to severe pain.[12-14] In multiple trials, the combination of oral morphine with ibuprofen was no more effective and less safe than oral ibuprofen alone for children's musculoskeletal pain.[7,15-17] Similarly, oxycodone was no more effective and was associated with more adverse events (AEs) than ibuprofen.[8,18] Short-term ibuprofen use is well-tolerated in healthy children without kidney disease and has not been shown to affect fracture healing.[19] More recently, oral hydromorphone, which is a long-acting, potent opioid analgesic that is rapidly absorbed and has a mean systemic oral bioavailability of 17% to 62%,[20] has been suggested as an alternative to oral morphine, but evidence supporting its use in children is limited.[21,22]

Given the need for more comprehensive analgesia for children with musculoskeletal injury, combined with the importance of responsible opioid use in children,[23] 2 simultaneous trials were conducted to compare the effectiveness of ibuprofen plus hydromorphone and ibuprofen plus acetaminophen vs ibuprofen alone.

Key Points

Question Does addition of acetaminophen or hydromorphone to ibuprofen improve pain relief for children with nonoperative acute limb injury?

Findings In these 2 randomized clinical trials of 699 children who presented to an emergency department less than 24 hours after a nonoperative acute limb injury, addition of 1 dose of oral acetaminophen or hydromorphone to ibuprofen did not significantly reduce self-reported pain scores at 60 minutes. Use of hydromorphone resulted in a 4-fold increase in adverse events.

Meaning For children with acute nonoperative limb injuries, pain scores did not improve with addition of either acetaminophen or hydromorphone to ibuprofen; adverse events were higher with hydromorphone.

Methods

Trial Design and Oversight

This pair of multicenter, randomized, double-masked, placebo-controlled No OUCH trials was conducted at 6 Canadian tertiary care, pediatric emergency departments (EDs), which are all members of Pediatric Emergency Research Canada (PERC).

The No OUCH (Non-Steroidal or Opioid Analgesia Use for Children With Musculoskeletal Injuries) trials utilized a preference-informed complementary trial design that allowed the caregiver and child to decide whether to enroll in a 3-group opioid-inclusive trial (the opioid trial) or a 2-group nonopioid trial.[24,25] This method allowed for those with strong preferences regarding opioid use in children to still participate in this study. In the absence of clinical or statistical preclusionary evidence, the results of the 2 trials would be pooled.

The full study protocol and statistical analysis plan have been published and all prior versions of the protocol are available in Supplement 1.[24,26] No important changes were made to the protocol after initiation of data collection. This study was registered with ClinicalTrials.gov (NCT03767933).

Prior to commencing recruitment, approval was obtained from the human research ethics board at each site. The No OUCH trials were regulated and monitored by Health Canada and reside within the KidsCAN-PERC Innovative Pediatric Clinical Trials Network, which provided centralized data management and trial oversight.[27] Safety oversight was provided by an independent data and safety monitoring board that convened semiannually. Interim analyses for efficacy were not conducted. This report follows the CONSORT (Consolidated Standards of Reporting Trials) guideline.[28]

Patient Engagement

The study team's parent partner with lived experience of caring for a child with acute pain and parent advisory group members provided input on the study protocol and data collection tools, and provided feedback on the wording, readability, sensitivity, flow, and content of caregiver surveys.

Participants

Children aged 6 to 17 years, presenting with an acute limb injury (<24 hours) without obvious deformity or neurovascular compromise, and with a self-reported verbal numerical rating scale (vNRS) pain score of 5 or greater out of 10 were eligible (**Figure 1**). Exclusion criteria were (1) need for immediate intravenous or intranasal pain medications, (2) known hypersensitivity to study medications, (3) having received acetaminophen or nonsteroidal anti-inflammatory drugs within 3 hours of recruitment, (4) having received opioid medication within 1 hour of recruitment, (5) caregiver or child having cognitive impairment that precluded the ability to self-report pain and/or respond to study questions, (6) injury suspected to be due to child abuse, (7) suspected multilimb fracture, (8) chronic pain treated with daily analgesics, (9) hepatic or kidney disease or dysfunction, (10) bleeding disorder, (11) pregnancy, (12) vomiting that precluded the ability to take oral medications, (13) caregiver and/or child inability to communicate fluently in English or French in the absence of a native language interpreter, (14) caregiver unavailable for follow-up, and (15) previous enrollment in the study.

Figure 1. Flow Diagram of the No OUCH Trials

[a]There could be multiple reasons for exclusion.

[b]See Randomization subsection in the Methods section. Randomization was 1:1 and 1:1:1 until adjustment in July 2020, when changed to 1:1:2 in the opioid trial to avoid overrecruitment.

Randomization

Written informed consent was obtained from caregivers and mature minors (who were >14 years, unaccompanied by an adult caregiver, and judged by the research team, using a capacity to consent assessment tool, to have adequate judgment and understanding to make their own research participation decisions), and assent was obtained from children, when developmentally appropriate. Following this, family preference for study trial enrollment (ie, opioid or nonopioid) was elicited. If the family did not have trial preference, the child was enrolled in the opioid trial because it included 3 medication treatment groups. Randomization tables with random block sizes and a 1:1 (for the nonopioid trial) or 1:1:1 (for the opioid trial) trial group assignment stratified by site were used. To preserve the option of trial choice for families, recruitment was kept open for both trials until they each reached the required number of participants. To avoid significant overrecruitment, we monitored the recruitment rate of both trials through interim analysis after recruitment of 100 participants and adjusted the randomization of patients to the hydromorphone plus ibuprofen group from 1:1:1 to 1:1:2 in July 2020.[26]

An allocation list was sent to the research pharmacy at each site where research pharmacists prepared consecutively numbered kits for each trial. A standardized operating procedure ensured the placebo formulations were of similar taste, color, and consistency to the active drugs, and solutions were packaged in identical, labeled, amber-colored bottles. Kits were temperature monitored and securely stored in each site's pharmacy or ED. Participants, trial and clinical staff, and data analysts were unaware of trial group assignments.

Interventions

In the opioid trial, participants were randomized to 1 of 3 groups: (1) oral ibuprofen plus acetaminophen placebo plus oral hydromorphone (ibuprofen plus hydromorphone), (2) oral ibuprofen plus oral acetaminophen plus hydromorphone placebo (ibuprofen plus acetaminophen), or (3) oral ibuprofen plus acetaminophen placebo plus hydromorphone placebo (ibuprofen). In the nonopioid trial, participants were randomized to 1 of 2 groups: (1) oral ibuprofen plus oral acetaminophen (ibuprofen plus acetaminophen) or (2) oral ibuprofen plus acetaminophen placebo (ibuprofen). Ibuprofen was dosed as 10 mg/kg (maximum, 600 mg), acetaminophen as 15 mg/kg (maximum, 1000 mg), and oral hydromorphone as 0.05 mg/kg (maximum, 5 mg). All study medications and placebos were administered as a single oral dose in liquid form. No other medications were administered as part of the study. Enrolled patients were eligible to receive rescue analgesia at any time at the discretion of the clinical team. All cointerventions, including nonpharmacologic interventions (eg, ice, splinting) were documented.

The research nurses, who were all trained in study protocol, procedures, and tools, administered the medications according to the randomization scheme (eFigure 1 in Supplement 2), and monitored participants for up to 120 minutes, with safety and efficacy measures recorded at the time of recruitment, time of medication administration, as well as 30, 60, 90, and 120 minutes post medication administration, at the time of medical examination, and immediately following x-ray. The research nurse obtained pain scores from participants, recorded AEs and vital signs, and evaluated sedation level using the Ramsay Sedation Scale (RSS; score range, 1-6).[29] Prior to ED discharge, both the child and caregiver completed a brief survey. Two 10-minute follow-up digital surveys were completed by the caregiver at 1 to 3 days and 1 to 2 weeks post discharge to determine AEs and assess function (ie, sleep, school attendance, play).

Outcome

The primary efficacy outcome was self-reported vNRS pain score at 60 minutes post medication administration. The vNRS ranges from 0 (no pain) to 10 (worst pain) and is a validated and recommended pain measurement tool for children aged 6 to 17 years.[30] The 60-minute time point reflects the peak plasma concentration and analgesic efficacy for all 3 study medications.[21,31] The primary safety end point was the proportion of children with any AE related to study drug administration. There were 6 secondary efficacy outcomes including (1) the proportion of participants who achieved a mild pain score (defined as a vNRS score <3 by the World Health Organization) at 60 minutes post medication administration,[32] (2) pain scores at all study time points (30, 90, and 120 minutes post medication administration, immediately after x-ray, at the time of medical examination), (3) vNRS pain score reduction of at least 2 points at 60 minutes post medication administration, (4) ED length of stay, (5) rescue analgesic use in the 60 minutes following study drug administration, and (6) time to effective analgesia (ie, first vNRS score <3 post medication). There were 4 secondary safety outcomes including (1) any serious adverse events (SAEs) during the study period, (2) clinically important sedation (defined as an RSS score >3),[29] (3) each specific AE type (eg, nausea, dizziness, itchiness), and (4) missed fractures or dislocations. Adverse events were coded using Medical Dictionary for Regulatory Activities, version 22.0.

Statistical Analysis

A detailed statistical analysis plan for this trial has been previously published.[26] Sample size was determined based on a 2-sided level of .05, a power of 0.95, a minimally clinically important difference of 1.5 on the vNRS, an estimate of the SD of the difference of 2.7,[33] and a Bonferroni correction to adjust for the 3 treatment comparisons. Sample size for the 3-group opioid trial was 105 per group, for a total of 315. The sample size for the 2-group nonopioid trial was 85 per group, for a total of 170. Thus, the total sample size for the No OUCH trials was 485. To account for missing data for the primary outcome, the study planned to overrecruit by approximately 10%, for a target recruitment of approximately 540 patients. Based on previously conducted research,[34] an imbalance in recruitment pace between the 2 trials was anticipated, and in order to avoid compromising the key preference-based study design, both trials continued to recruit until the sample size was met for both. Study trials' recruitment rates were monitored and a planned update to the randomization strategy could be used

Table 1. Child Participant Characteristics[a]

Parameter	Ibuprofen plus hydromorphone (n = 110)	Ibuprofen plus acetaminophen (n = 295)	Ibuprofen only (n = 294)
Age, mean (SD), y	11.6 (3.0)	11.2 (3.0)	11.7 (3.0)
Age distribution, No. (%)			
6-11 y	51 (46.4)	168 (56.9)	141 (48.0)
12-17 y	59 (53.6)	127 (43.1)	153 (52.0)
Sex, No. (%)			
Male	58 (52.7)	150 (50.8)	160 (54.4)
Female	52 (47.3)	145 (49.2)	134 (45.6)
Mechanism of injury, No. (%)	n = 97	n = 276	n = 275
Slip, trip, or fall	33 (34.0)	67 (24.3)	68 (24.7)
Team sports injury	26 (26.8)	95 (34.4)	101 (36.7)
Trampoline	2 (2.0)	5 (1.8)	3 (1.1)
Bicycle, scooter, or skateboard	0	6 (2.2)	3 (1.1)
Motor vehicle collision/ road traffic crash	0	2 (0.7)	3 (1.1)
Other play or activity	35 (36.1)	95 (34.4)	95 (34.5)
Other mechanism	1 (1.0)	6 (2.2)	2 (0.7)
Injury location, No. (%)[b]			
Upper limb	69 (62.7)	165 (55.9)	162 (55.3)
Wrist	19 (17.3)	63 (21.4)	55 (18.7)
Single or multiple fingers	14 (12.7)	21 (7.1)	27 (9.2)
Forearm	10 (9.1)	23 (7.8)	24 (8.2)
Elbow	10 (9.1)	24 (8.1)	20 (6.8)
Hand	6 (5.5)	10 (3.4)	14 (4.8)
Shoulder	4 (3.6)	8 (2.7)	14 (4.8)
Clavicle	3 (2.7)	9 (3.1)	5 (1.7)
Upper arm	3 (2.7)	7 (2.4)	3 (1.0)
Lower limb	41 (37.3)	130 (44.1)	131 (44.7)
Ankle	17 (15.5)	62 (21.0)	67 (22.8)
Knee	11 (10.0)	22 (7.5)	31 (10.5)
Foot	8 (7.3)	30 (10.2)	22 (7.5)
Single or multiple toes	4 (3.6)	6 (2.0)	7 (2.4)
Hip/thigh	1 (0.9)	3 (1.0)	0
Lower leg	0	7 (2.4)	4 (1.4)
Missing	0	0	1 (0.3)
Verbal numerical rating scale (at recruitment), mean (SD) [range, 0-10]	6.5 (1.9)	6.4 (1.8)	6.4 (1.7)
Nonpharmacologic strategies in emergency department, No. (%)			
Splint	26 (23.6)	58 (19.7)	64 (21.8)
Cast	21 (19.1)	52 (17.6)	33 (11.2)
Ice	10 (9.1)	34 (11.5)	23 (7.8)
Distraction	8 (7.3)	14 (4.7)	11(3.7)
Sling	5 (4.5)	4 (1.4)	4 (1.1)
Crutches	3 (2.7)	11 (3.7)	15 (5.1)
Tensor bandage	0	10 (3.4)	9 (3.1)
Other	0	0	2 (0.5)
Injury type, No. (%)	n = 109	n = 293	n = 284
Soft tissue injury	60 (55.0)	178 (60.8)	172 (60.6)
Fracture	45 (41.3)	107 (36.5)	107 (37.7)
Dislocation/subluxation only	1 (0.9)	8 (2.7)	4 (1.4)

(continued)

Table 1. Child Participant Characteristics[a] (continued)

Parameter	Ibuprofen plus hydromorphone (n = 110)	Ibuprofen plus acetaminophen (n = 295)	Ibuprofen only (n = 294)
Discharge disposition, No. (%)			
Discharged	109 (99.1)	291 (98.6)	281 (95.6)
Admitted	1 (0.9)	3 (1.0)	3 (1.0)
Left prior to physician assessment	0	0	4 (0.7)
Missing/early withdrawal	0	1 (0.3)	6 (2.7)

[a] See eTable 4 in Supplement 2 for presentation of demographic characteristics by trial.

[b] Two participants in the ibuprofen plus hydromorphone group, 5 in the ibuprofen plus acetaminophen group, and 11 in the ibuprofen group had an additional same-limb digital injury present.

Table 2. Primary and Secondary Efficacy (Pain) Outcomes[a]

Parameter	Ibuprofen plus hydromorphone	Ibuprofen plus acetaminophen	Ibuprofen only
Primary outcome[b]	n = 107	n = 272	n = 274
vNRS at 60 min after administration, mean (SD)[c]	4.8 (2.6)	4.6 (2.4)	4.6 (2.3)
Secondary outcomes			
vNRS pain scores, mean (SD)[c]			
Time of medication administration (n = 684)	6.5 (1.9)	6.4 (1.8)	6.4 (1.7)
30 min post medication administration (n = 678)	5.4 (2.4)	5.3 (2.2)	5.3 (2.2)
90 min post medication administration (n = 367)	4.7 (2.5)	4.6 (2.6)	4.5 (2.4)
120 min post medication administration (n = 262)	5.0 (2.8)	4.6 (2.7)	4.3 (2.3)
At time of medical examination (n = 600)	6.6 (2.5)	6.2 (2.5)	6.0 (2.6)
Immediately after x-ray (n = 609)	6.2 (2.7)	5.9 (2.6)	6.0 (2.5)
Participants achieving an vNRS pain score <3 at 60 min after administration, No. (%)	25 (23.4)	54 (19.9)	53 (19.3)
Participants with vNRS pain score reduction of at least 2/10 at 60 min after administration, No. (%)	48 (44.9)	127 (47.0)	133 (48.7)
vNRS pain score reduction from baseline to 60 min after administration, mean (SD)[c]	1.8 (1.9)	1.9 (2.2)	1.7 (2.1)
Emergency department length of stay, median (IQR), h	2.8 (2.1-3.8)	2.7 (2.1-3.6)	2.8 (2.1-3.7)
Participants requiring rescue analgesia, No.	0	0	0

[a] See eTable 5 in Supplement 2 for presentation of efficacy outcomes by trial.

[b] Missing data for the primary outcome were imputed. All 10 imputed sets of scores at 60 minutes after medication administration were analyzed using linear mixed models conditional on baseline verbal numerical rating scale (vNRS) and treatment group. Site and trial were used as nested random effects in the model. The results of these analyses were combined for the final estimate. $P = .78$ for this primary outcome.

[c] vNRS scores range from 0 (no pain) to 10 (worst pain); minimal clinically important difference = 1.5.

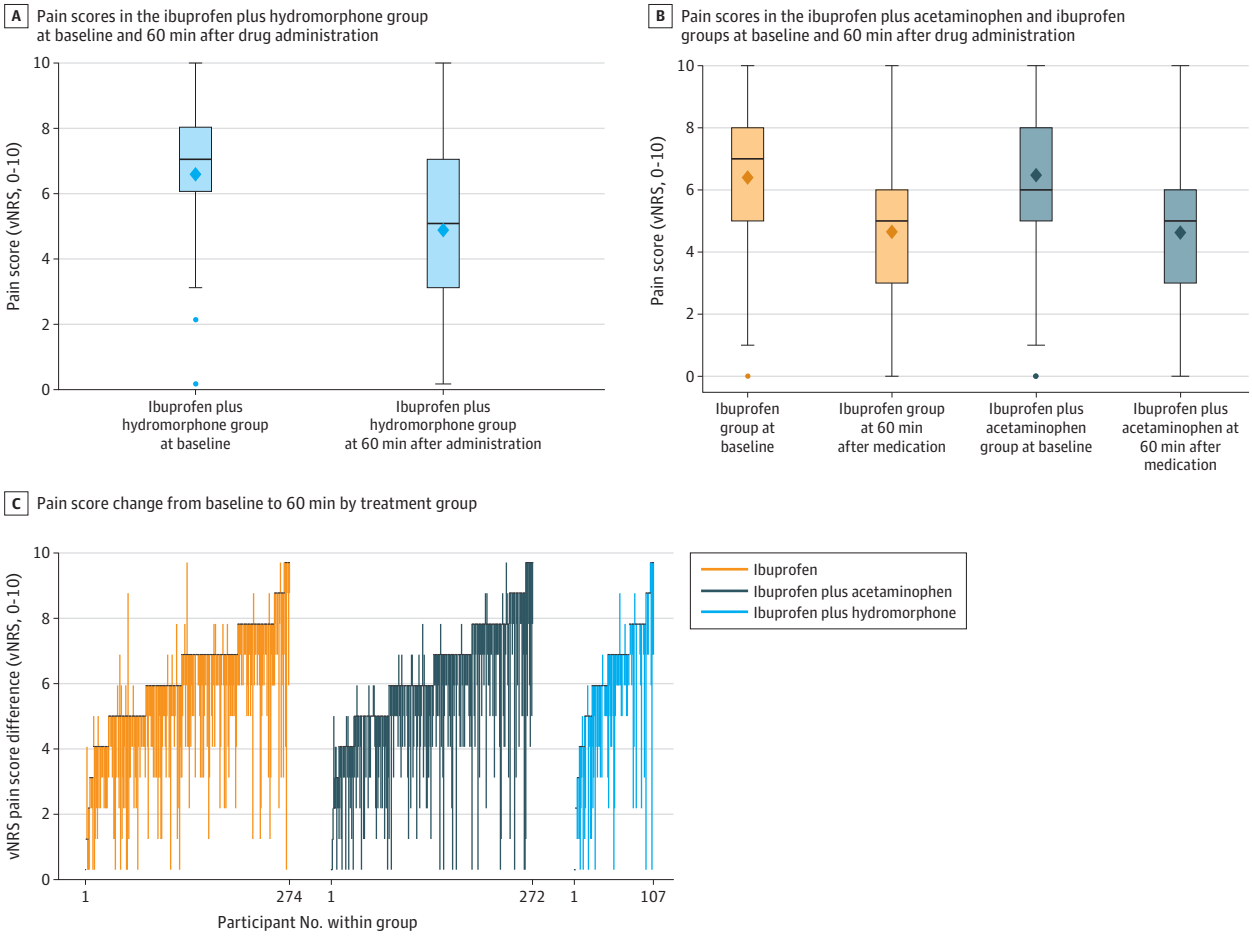
if there was an extreme overrecruitment for one of the trials. Ultimately, there was higher participation in the nonopioid trial, necessitating a change to the randomization ratio for the opioid trial from 1:1:1 to 1:1:2 in July 2020; this yielded some minor loss of power. Our choice of 0.95 for power allowed for accommodation of this loss without compromising the integrity of the study results.

Analyses were conducted using the intention-to-treat principle. Given homogeneity in the 2 trials' end points, we planned for a joint effectiveness analysis if the 2 populations were similar using prespecified decision rules.[26] Missing data for the primary outcome (vNRS at 60 minutes post medication administration) were addressed using multiple imputation with chained equations. All 10 imputed sets of vNRS scores at 60 minutes post medication administration were analyzed using linear mixed models conditional on baseline vNRS and treatment group. Site and trial were used as nested random effects in the model. The results of these analyses were combined for the final estimate. A likelihood ratio test determined whether there was statistical evidence of a differing treatment effect across the 2 trials.

Two nested linear mixed models for the vNRS score at 60 minutes post medication were fitted, adjusted for baseline vNRS score and site. The full model included a treatment-by-trial interaction term while the reduced model assumed constant treatment effect across the 2 trials. The likelihood ratio test was not statistically significant ($P = .29$). Therefore, the reduced model was used for the primary analysis (eTables 1 and 2 in Supplement 2).

We compared the proportion of children with a self-reported vNRS pain score less than 3 out of 10 at 60 minutes after medication administration across treatment groups using a logistic mixed model, adjusted for site and baseline pain. Because no children required a rescue analgesic by 60 minutes after medication, we did not run the planned model for this outcome. All other secondary outcomes were summarized

Figure 2. Parallel Line Plot of Verbal Numerical Rating Scale (vNRS) Score at 60 Minutes Post Medication Administration (Primary Outcome)



In panels A and B, the boxes represent the second and third quartiles; horizontal lines, medians; error bars, 1.5 × IQR; diamonds, means; and dots, outliers.

within treatment group using the appropriate descriptive statistics. Planned subgroup analyses were completed for age (6-11 vs 12-17 years) and injury type (fracture vs sprain vs dislocation). Analyses were performed with SAS software (version 9.4; SAS Institute).

Results

Trials' Characteristics

A combined analysis of the 2 trials was deemed appropriate because participants in the opioid and nonopioid trials had similar demographics (baseline pain scores, age, sex, injury location), and the likelihood ratio test described in the Statistical Analysis section was not statistically significant. Therefore, the reduced model (with baseline vNRS score and treatment group) was used for the primary analysis (eTables 1 and 2 in Supplement 2).

Participants

From April 2019 to March 2023, 699 participants were randomized, including 450 in the nonopioid trial and 249 in the opioid trial (Figure 1; eTable 3 in Supplement 2). Primary outcome data were obtained for 415 of 450 participants (92.2%) in the nonopioid trial and 238 of 249 participants (95.6%) in the opioid trial. Baseline demographic data and pain scores were similar across study groups and trials (**Table 1**; eTable 4 in Supplement 2).

Primary Outcome

The primary efficacy outcome of self-reported vNRS pain score at 60 minutes post medication administration was a mean (SD) of 4.8 (2.6) in the ibuprofen plus hydromorphone group, 4.6 (2.4) in the ibuprofen plus acetaminophen group, and 4.6 (2.3) in the ibuprofen group (P = .78) (**Table 2** and **Figure 2**). The primary outcome, presented by trial, can be found in eTable 5 and eFigures 2 and 3 in Supplement 2. Results were consistent with complete-case analyses, with both approaches showing no statistically significant difference between groups (P = .78) (eTable 1 in Supplement 2).

The primary safety outcome of the proportion of children with any AE related to study drug administration was 28.2% in the ibuprofen plus hydromorphone group, 6.1% in the ibuprofen plus acetaminophen group, and 5.8% in the ibuprofen group.

Table 3. Primary and Secondary Safety Outcomes[a]

Adverse event	No. (%)		
	Ibuprofen plus hydromorphone (n = 110)	Ibuprofen plus acetaminophen (n = 295)	Ibuprofen only (n = 294)
Primary safety outcome			
Adverse event (any) (primary safety end point)[b]	31 (28.2)	18 (6.1)	17 (5.8)
Secondary safety outcomes			
Central nervous system	17 (15.5)	8 (2.7)	12 (4.1)
Dizziness	9	0	2
Somnolence/fatigue	6	6	9
Agitation/anxiety	2	0	0
Numbness	0	2	0
Headache	0	0	1
Gastrointestinal	10 (9.1)	6 (2.0)	4 (1.4)
Nausea	5	2	2
Vomiting	4	0	1
Abdominal pain	1	4	1
Cutaneous	3 (2.7)	0	1 (0.3)
Sweating	1	0	0
Pallor	1	0	0
Itching	1	0	0
Rash	0	0	1
Other	1 (0.9)	4 (1.4)	0
Blurred vision	1	0	0
Chills	0	2	0
Tinnitus	0	1	0
Dyspnea	0	1	0
Ramsay Sedation Scale score >3[c]			
Time of medication administration	0	0	0
30 min post medication administration	0	1	1
60 min post medication administration	0	0	1
90 min post medication administration	0	0	1
120 min post medication administration	0	0	0
Missed fractures, No. (%)[d]	2 (1.8)	2 (0.7)	5 (1.7)

[a] There were no serious adverse events (any untoward medical occurrence that results in death, is life-threatening, requires hospitalization/prolongs existing hospitalization, or results in persistent/significant disability or incapacity) during the study period.

[b] Each participant could report multiple adverse events; this table presents the number of participants experiencing each adverse event.

[c] Ramsay Sedation Scale is scored from 1 (anxious, agitated) to 6 (unrousable); scores >3 correspond to a sleeping state and were considered clinically significant sedation.

[d] An injury that was diagnosed as something other than fracture by the treating physician at the time of emergency discharge (typically sprain) but was identified as a fracture through final radiology report.

Secondary Outcomes

There were no differences in any of the 6 prespecified secondary efficacy outcomes. The proportion of children who achieved mild pain (ie, vNRS score <3) was 23.4% in the ibuprofen plus hydromorphone group, 19.9% in the ibuprofen plus acetaminophen group, and 19.3% in the ibuprofen group (P = .95). Odds ratios for achieving a pain score less than 3 out of 10 were 1.10 (95% CI, 0.56-2.13) for ibuprofen plus hydromorphone and 1.06 (95% CI, 0.67-1.67) for ibuprofen plus acetaminophen compared with ibuprofen. Time to achieve effective analgesia was not calculated, given the small overall proportion of participants (20.2%) who achieved this outcome (defined as vNRS score at 60 minutes after medication administration <3). Pain reduction of at least 2 points on the vNRS at 60 minutes was achieved by 44.9% in the ibuprofen plus hydromorphone group, 47.0% in the ibuprofen plus acetaminophen group, and 48.7% in the ibuprofen group. Length of ED stay was a median of 2.8 hours (IQR, 2.1-3.8) in the ibuprofen plus hydromorphone group, 2.7 hours (IQR, 2.1-3.6) in the ibuprofen plus acetaminophen group, and 2.8 hours (IQR, 2.1-3.7) in the ibuprofen group. No participants required rescue analgesia in the 60 minutes after study drug administration (Table 2).

With regard to the prespecified secondary safety outcomes, there were no SAEs or deaths. There were no participants with clinically important sedation (RSS score >3) at baseline, 2 at 30 minutes, 1 at 60 minutes, 1 at 90 minutes, and none at 120 minutes after study drug administration; no participants with an RSS score greater than 3 received ibuprofen plus hydromorphone. Missed fractures were reported in 2 participants (1.8%) in the ibuprofen plus hydromorphone group, 2 (0.7%) in the ibuprofen plus acetaminophen group, and 5 (1.7%) in the ibuprofen only group. Central nervous system-related (ie, somnolence, fatigue, dizziness) and gastrointestinal-related (abdominal pain, nausea, vomiting) AEs were most frequent, representing 56.1% and 30.3% of AEs, respectively. All AEs in the ibuprofen and ibuprofen plus acetaminophen groups were rated as mild in severity; 19.4% (6/31) of AEs in the ibuprofen plus hydromorphone group were rated as moderate, with the remaining 80.4% reported as mild (**Table 3**).

Subgroup Analyses

No clinically important difference was noted across any subgroups. The self-reported mean (SD) pain scores at 60 minutes after medication administration by age group (6-11 vs 12-17 years) and by type of injury (fracture vs sprain vs isolated dislocation/subluxation) are presented in eTable 6 in Supplement 2.

Discussion

The American Academy of Pediatrics and the Canadian Paediatric Society currently recommend ibuprofen, acetaminophen, and oral opioids as effective analgesia for children with acute pain.[3,4] For musculoskeletal injury, current best evidence supports ibuprofen as the optimal first-line analgesic,[35,36] and national statements support combining ibuprofen with nonpharmacologic (ie, physical [ice, splinting]; psychological [distraction]) interventions for acute pain care.[3,4,37,38]

Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), has both analgesic and anti-inflammatory effects, making it particularly effective for musculoskeletal injuries.[39] In 2010, a systematic review of 85 RCTs included 54 trials whose data supported ibuprofen analgesic efficacy over acetaminophen.[38] A 2025 systematic review and network meta-analysis about pharmacologic management of acute pain in children that included 41 RCTs and 4935 children concluded that NSAIDs such as ibuprofen provide the greatest benefit and least harm.[5] Notably, 61% of these trials enrolled children with fractures and sprains; however, none of them studied hydromorphone.[5] These studies support ibuprofen as first-line treatment for acute musculoskeletal injury-related pain of all intensities in children, except for those who require immediate intranasal or intravenous opioids for severe pain.

Acetaminophen, although commonly used in pediatrics, has demonstrated similar or inferior efficacy compared with ibuprofen for treatment of acute musculoskeletal pain. Systematic reviews of musculoskeletal injury pain care for children demonstrated similar efficacy for ibuprofen and acetaminophen,[37] with comparable frequency of AEs.[40] A systematic review and network meta-analysis that included 8 RCTs and 1645 children with acute musculoskeletal injuries found that ibuprofen (with or without opioids), acetaminophen, and opioids were similarly effective for pain relief at 60 minutes post administration.[39] Another meta-analysis, which included 18 pediatric trials, reported an overall weighted estimate for standard mean difference in pain relief as 0.28 (95% CI, 0.10-0.46), indicating superior pain relief in ibuprofen-treated children 2 hours after dosing.[38]

Historically, oral opioids have been used to treat pediatric acute musculoskeletal pain.[7,17,18,41] However, more recent evidence suggests opioids offer no significant pain reduction over ibuprofen, perhaps related to a lack of anti-inflammatory action, and are associated with higher rates of AEs. An RCT of 336 children with acute arm fractures demonstrated that ibuprofen provided similar pain relief and better functional outcomes compared with acetaminophen with codeine.[41] Further, an observational cohort study of 329 children receiving ibuprofen or oxycodone for fracture pain found similar analgesic effectiveness but reported that 20% more children had AEs and 11% had worse functional outcomes (ie, poor sleep, lower activity, more missed school) with oxycodone.[9] Multiple systematic reviews have confirmed that opioids provide no additional benefit over NSAIDs for acute pain relief in children.[5,35,37] Furthermore, opioids can cause respiratory depression, nausea, and vomiting and potentially lead to opioid diversion and opioid use disorders, underscoring the need to limit opioid use to more severe pain.[42,43]

The No OUCH trials found that addition of acetaminophen or hydromorphone to ibuprofen provided no additional analgesic benefit compared with ibuprofen monotherapy for moderate to severe musculoskeletal injury-related pain in children. However, ibuprofen alone only adequately relieved pain in 20% of children, suggesting further studies of adjuvant topical and nonpharmacological therapies, as well as novel drugs, are still needed.

A strength of the No OUCH studies was the preference-informed complementary trial design, which allowed families with strong opinions about opioid medications to be included in one of the trials.[34] In addition, the opioid trial included the upper limit of dosing for the most potent oral opioid available in liquid form.

Limitations

The trial has several limitations. First, only children with nonoperative injuries were included. Therefore, results may not be applicable to postoperative settings. Second, although age and sex were reported, data about race and ethnicity and other equity-related factors such as gender, socioeconomic status, and preferred language were not captured. Third, although the participants in the 2 No OUCH trials had similar characteristics (eg, baseline pain score, age, sex, injury type), pooling may have introduced bias due to unmeasured differences between the trial populations.

Conclusions

For children with acute nonoperative musculoskeletal injury, pain scores at 60 minutes after drug administration were not improved with use of ibuprofen and acetaminophen or ibuprofen and hydromorphone compared with ibuprofen alone. Adverse events were 4-fold more frequent with hydromorphone use.

ARTICLE INFORMATION

Accepted for Publication: November 30, 2025.

Published Online: January 8, 2026. doi:10.1001/jama.2025.25033

Author Affiliations: Department of Pediatrics, Stollery Children's Hospital, University of Alberta, Edmonton, Alberta, Canada (Ali, Candelaria); Women and Children's Health Research Institute, University of Alberta, Edmonton, Alberta, Canada (Ali, Yaskina); Department of Pediatrics, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada (Klassen); Jim Pattison Children's Hospital, Saskatoon, Saskatchewan, Canada (Klassen); Department of Pediatrics,

University of Ottawa, Ottawa, Ontario, Canada (Bhatt); Emergency Medicine, Children's Hospital of Eastern Ontario, Ottawa, Ontario, Canada (Bhatt); Departments of Pediatrics and Emergency Medicine, HSC Winnipeg Children's Hospital, Winnipeg, Manitoba, Canada (Sawyer); Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, Manitoba, Canada (Sawyer, Hickes); Department of Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, Alberta, Canada (Stang); Alberta Children's Hospital Research Institute, Calgary, Alberta, Canada (Stang); Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada (Heath, Pechlivanoglou); Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada (Heath, Pechlivanoglou, Offringa); Department of Statistical Science, University College London, London, United Kingdom (Heath); Department of Pediatrics, Medical College of Wisconsin, Milwaukee (Drendel); Departments of Pediatrics and Epidemiology & Biostatistics, Western University, London, Ontario, Canada (Poonai).

Author Contributions: Drs Ali and Yaskina had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Ali, Klassen, Sawyer, Stang, Yaskina, Heath, Pechlivanoglou, Offringa, Drendel, Hickes, Poonai.
Acquisition, analysis, or interpretation of data: Candelaria, Bhatt, Sawyer, Stang, Yaskina, Offringa, Poonai.
Drafting of the manuscript: Ali, Candelaria, Stang, Yaskina, Drendel, Hickes, Poonai.
Critical review of the manuscript for important intellectual content: Ali, Klassen, Candelaria, Bhatt, Sawyer, Stang, Yaskina, Heath, Pechlivanoglou, Offringa, Drendel, Poonai.
Statistical analysis: Ali, Candelaria, Yaskina, Heath, Offringa.
Obtained funding: Ali, Klassen, Candelaria, Stang, Pechlivanoglou, Offringa, Poonai.
Administrative, technical, or material support: Ali, Candelaria, Bhatt, Sawyer, Stang, Hickes, Poonai.
Supervision: Ali, Candelaria, Sawyer, Stang.

Conflict of Interest Disclosures: None reported.

Funding/Support: This research was supported by an Innovative Clinical Trials Multi-year Grant from the Canadian Institutes of Health Research (funding reference No. MYG-151207; 2017–2020), as part of the Strategy for Patient-Oriented Research and the Children's Hospital Research Institute of Manitoba, the Centre Hospitalier Universitaire Sainte-Justine, the Department of Pediatrics, University of Western Ontario, the Alberta Children's Hospital Research Institute, the Women and Children's Health Research Institute, the Children's Hospital of Eastern Ontario Research Institute, and the Hospital for Sick Children Research Institute. This research has been facilitated by the Women and Children's Health Research Institute Data Coordinating Centre through the generous support of the Stollery Children's Hospital Foundation. This study was sponsored by the Governors of the University of Alberta.

Role of the Funder/Sponsor: The funders 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; and decision to submit the manuscript for publication.

Group Information: The KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Team members are listed in Supplement 3.

Data Sharing Statement: See Supplement 4.

Additional Contributions: The No OUCH study resides within the KidsCAN-PERC iPCT network, a Canadian trials network with centralized infrastructure for data management and trial oversight. We thank the members of the data and safety monitoring board of the KidsCAN PERC Innovative Pediatric Clinical Trials group for their unpaid contribution: Garth Meckler, MD, MSHS (chair, BC Children's Hospital, British Columbia, Canada), Mark Roback, MD (Children's Hospital Colorado), Anupam Kharbanda, MD, MS (Children's Minnesota Hospital, Minneapolis), Eyal Cohen, MD, MSc (Hospital for Sick Children, Ontario, Canada), and Lise Nigrovic, MD, MPH (Boston Children's Hospital, Massachusetts). We thank the Pediatric Emergency Research Canada network of health care professionals and the KidsCAN Trials Network for their contribution and support to this project and pediatric clinical research in Canada. We thank patients and their families for entrusting us to conduct this study, and study investigators and support staff across all sites for their commitment to the successful and diligent conduct of this trial. We also thank the emergency department physicians, nurses, and ancillary staff at all study sites for their assistance with identifying and connecting research team members with potentially eligible study participants. Finally, we extend our thanks to Miranda Holliday, BA (University of Alberta), for paid administrative support for this study.

REFERENCES

1. Spady DW, Saunders DL, Schopflocher DP, Svenson LW. Patterns of injury in children: a population-based approach. *Pediatrics*. 2004;113(3, pt 1):522-529. doi:10.1542/peds.113.3.522

2. Giffin NA, Liedtke R, Poonai N, Holmes A, Wright B, Ali S. Prevalence of pain-related presentations in Canadian pediatric emergency departments. *CJEM*. 2024;26(9):650-657. doi:10.1007/s43678-024-00729-w

3. Hadland SE, Agarwal R, Raman SR, et al. Opioid prescribing for acute pain management in children and adolescents in outpatient settings: clinical practice guideline. *Pediatrics*. Published online September 30, 2024. doi:10.1542/peds.2024-068752

4. Trottier ED, Ali S, Doré-Bergeron MJ, Chauvin-Kimoff L. Best practices in pain assessment and management for children. *Paediatr Child Health*. 2022;27(7):429-448. doi:10.1093/pch/pxac048

5. Olejnik L, Lima JP, Sadeghirad B, et al. Pharmacologic management of acute pain in children: a systematic review and network meta-analysis. *JAMA Pediatr*. 2025;179(4):407-417. doi:10.1001/jamapediatrics.2024.5920

6. Utsumi S, Amagasa S, Moriwaki T, Uematsu S. Oral analgesic for musculoskeletal injuries in children: a systematic review and network meta-analysis. *Acad Emerg Med*. 2024;31(1):61-70. doi:10.1111/acem.14803

7. Sin B, Sikorska G, YauLin J, Bonitto RA, Motov SM. Comparing nonopioids versus opioids for acute pain in the emergency department: a literature review. *Am J Ther*. 2019;28(1):e52-e86. doi:10.1097/MJT.0000000000001098

8. Le May S, Ali S, Plint AC, et al; Pediatric Emergency Research Canada (PERC). Oral analgesics utilization for children with musculoskeletal injury (OUCH Trial): an RCT. *Pediatrics*. 2017;140(5):e20170186. doi:10.1542/peds.2017-0186

9. Ali S, Manaloor R, Johnson DW, et al; Pediatric Emergency Research Canada. An observational cohort study comparing ibuprofen and oxycodone in children with fractures. *PLoS One*. 2021;16(9):e0257021. doi:10.1371/journal.pone.0257021

10. de Sévaux JLH, Damoiseaux RA, van de Pol AC, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database Syst Rev*. 2023;8(8):CD011534.

11. Wong T, Stang AS, Ganshorn H, et al. Combined and alternating paracetamol and ibuprofen therapy for febrile children. *Cochrane Database Syst Rev*. 2013;2013(10):CD009572. doi:10.1002/14651858.CD009572.pub2

12. FDA drug safety communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. US Food and Drug Administration. Published April 20, 2017. Accessed November 18, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and

13. Summary safety review - hydrocodone-containing products - assessing the risk of serious breathing problems (respiratory depression) in children and adolescents. Government of Canada. Published July 28, 2016. Accessed November 18, 2025. https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/safety-reviews/summary-safety-review-hydrocodone-containing-products-assessing-risk-serious-breathing.html

14. Navin L. FDA Drug Safety Podcast: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. January 14, 2022. Accessed November 18, 2025. https://www.fda.gov/drugs/fda-drug-safety-podcasts/fda-drug-safety-podcast-fda-restricts-use-prescription-codeine-pain-and-cough-medicines-and-tramadol

15. Rieder MJ, Jong G. The use of oral opioids to control children's pain in the post-codeine era. *Paediatr Child Health*. 2021;26(2):120-127. doi:10.1093/pch/pxaa133

16. Poonai N, Datoo N, Ali S, et al. Oral morphine versus ibuprofen administered at home for postoperative orthopedic pain in children: a randomized controlled trial. *CMAJ*. 2017;189(40):E1252-E1258. doi:10.1503/cmaj.170017

17. Poonai N, Bhullar G, Lin K, et al. Oral administration of morphine versus ibuprofen to manage postfracture pain in children: a randomized trial. *CMAJ*. 2014;186(18):1358-1363. doi:10.1503/cmaj.140907

18. Koller DM, Myers AB, Lorenz D, Godambe SA. Effectiveness of oxycodone, ibuprofen, or the

combination in the initial management of orthopedic injury-related pain in children. *Pediatr Emerg Care*. 2007;23(9):627-633. doi:10.1097/PEC.0b013e31814a6a39

19. Choo S, Nuelle JAV. NSAID use and effects on pediatric bone healing: a review of current literature. *Children (Basel)*. 2021;8(9):821. doi:10.3390/children8090821

20. Drover DR, Angst MS, Valle M, et al. Input characteristics and bioavailability after administration of immediate and a new extended-release formulation of hydromorphone in healthy volunteers. *Anesthesiology*. 2002;97(4):827-836. doi:10.1097/00000542-200210000-00013

21. Rodieux F, Ivanyuk A, Besson M, Desmeules J, Samer CF. Hydromorphone prescription for pain in children—what place in clinical practice? *Front Pediatr*. 2022;10:842454. doi:10.3389/fped.2022.842454

22. Quigley C. Hydromorphone for acute and chronic pain. *Cochrane Database Syst Rev*. 2002;(1):CD003447.

23. Chumpitazi CE, Chang C, Atanelov Z, et al; ACEP Pediatric Emergency Medicine Committee. Managing acute pain in children presenting to the emergency department without opioids. *J Am Coll Emerg Physicians Open*. 2022;3(2):e12664. doi:10.1002/emp2.12664

24. Ali S, Rajagopal M, Klassen T, et al; KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Team. Study protocol for two complementary trials of non-steroidal or opioid analgesia use for children aged 6 to 17 years with musculoskeletal injuries (the No OUCH study). *BMJ Open*. 2020;10(6):e035177. doi:10.1136/bmjopen-2019-035177

25. Ali S, Hopkin G, Poonai N, et al; KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Group; KidsCAN PERC Innovative Pediatric Clinical Trials Methods Core. A novel preference-informed complementary trial (PICT) design for clinical trial research influenced by strong patient preferences. *Trials*. 2021;22(1):206. doi:10.1186/s13063-021-05164-1

26. Heath A, Yaskina M, Hopkin G, et al; KidsCAN PERC Innovative Pediatric Clinical Trials No OUCH Study Group. Non-steroidal or opioid analgesia use for children with musculoskeletal injuries (the No OUCH study): statistical analysis plan. *Trials*. 2020;21(1):759. doi:10.1186/s13063-020-04503-y

27. Kelly LE, Richer L, Ali S, et al. Innovative approaches to investigator-initiated, multicentre paediatric clinical trials in Canada. *BMJ Open*. 2019;9(6):e029024. doi:10.1136/bmjopen-2019-029024

28. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomized trials. *JAMA*. 2025;333(22):1998-2005. doi:10.1001/jama.2025.4347

29. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *BMJ*. 1974;2(5920):656-659. doi:10.1136/bmj.2.5920.656

30. Birnie KA, Hundert AS, Lalloo C, Nguyen C, Stinson JN. Recommendations for selection of self-report pain intensity measures in children and adolescents: a systematic review and quality assessment of measurement properties. *Pain*. 2019;160(1):5-18. doi:10.1097/j.pain.0000000000001377

31. Vallner JJ, Stewart JT, Kotzan JA, Kirsten EB, Honigberg IL. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *J Clin Pharmacol*. 1981;21(4):152-156. doi:10.1002/j.1552-4604.1981.tb05693.x

32. World Health Organization. Persisting pain in children package: WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. 2012. Accessed August 8, 2025. https://iris.who.int/handle/10665/44540

33. Tsze DS, Hirschfeld G, von Baeyer CL, Suarez LE, Dayan PS. Changes in pain score associated with clinically meaningful outcomes in children with acute pain. *Acad Emerg Med*. 2019;26(9):1002-1013. doi:10.1111/acem.13683

34. Jun E, Ali S, Yaskina M, et al; Pediatric Emergency Research Canada. A two-centre survey of caregiver perspectives on opioid use for children's acute pain management. *Paediatr Child Health*. 2019;26(1):19-26. doi:10.1093/pch/pxz162

35. Parri N, Lazzeri S. Efficacy of ibuprofen in musculoskeletal post-traumatic pain in children: a systematic review. *PLoS One*. 2020;15(12):e0243314. doi:10.1371/journal.pone.0243314

36. Korownyk C, Young J, Michael Allan G. Optimal pain relief for pediatric MSK injury. *Can Fam Physician*. 2015;61(6):e276.

37. Ngo VTH, Bajaj T. Ibuprofen. In: *StatPearls*. StatPearls Publishing; 2025.

38. Pierce CA, Voss B. Efficacy and safety of ibuprofen and acetaminophen in children and adults: a meta-analysis and qualitative review. *Ann Pharmacother*. 2010;44(3):489-506. doi:10.1345/aph.1M332

39. Le May S, Ali S, Khadra C, et al. Pain management of pediatric musculoskeletal injury in the emergency department: a systematic review. *Pain Res Manag*. 2016;2016:4809394. doi:10.1155/2016/4809394

40. Hartling L, Ali S, Dryden DM, et al. How safe are common analgesics for the treatment of acute pain for children? a systematic review. *Pain Res Manag*. 2016;2016:5346819. doi:10.1155/2016/5346819

41. Drendel AL, Gorelick MH, Weisman SJ, Lyon R, Brousseau DC, Kim MK. A randomized clinical trial of ibuprofen versus acetaminophen with codeine for acute pediatric arm fracture pain. *Ann Emerg Med*. 2009;54(4):553-560. doi:10.1016/j.annemergmed.2009.06.005

42. Dyson MP, Dong K, Sevcik W, et al. Quantifying unused opioids following emergency and ambulatory care: a systematic review and meta-analysis. *J Am Coll Emerg Physicians Open*. 2022;3(5):e12822. doi:10.1002/emp2.12822

43. Ahrari M, Ali S, Hartling L, et al. Nonmedical opioid use after short-term therapeutic exposure in children: a systematic review. *Pediatrics*. 2021;148(6):e2021051927. doi:10.1542/peds.2021-051927