There is ample evidence that analgesia is underused, underprescribed, delayed in its administration and suboptimally dosed in clinical settings. Children are particularly susceptible to suboptimal pain management and are less likely to receive opioid analgesia. Untreated pain in childhood has been reported to lead to short-term problems such as slower healing and to long-term issues such as anxiety, needle phobia, hyperesthesia and fear of medical care. The American Academy of Pediatrics has reaffirmed its advocacy for the appropriate use of analgesia for children with acute pain. Fractures constitute between 10% and 25% of all injuries. The most severe pain after an injury occurs within the first 48 hours, with more than 80% of children showing compromise in at least 1 functional area. Low rates of analgesia have been reported after discharge from hospital. Recent warnings from Health Canada regarding codeine for children have led to increased use of nonsteroidal anti-inflammatory drugs and morphine for common injuries such as fractures. Our objective was to determine whether morphine administered orally has superior efficacy to ibuprofen in fracture-related pain.

Methods: We used a parallel group, randomized, blinded superiority design. Children who presented to the emergency department with an uncomplicated extremity fracture were randomly assigned to receive either morphine (0.5 mg/kg orally) or ibuprofen (10 mg/kg) for 24 hours after discharge. Our primary outcome was the change in pain score using the Faces Pain Scale — Revised (FPS-R). Participants were asked to record pain scores immediately before and 30 minutes after receiving each dose.

Results: We analyzed data from 66 participants in the morphine group and 68 participants in the ibuprofen group. For both morphine and ibuprofen, we found a reduction in pain scores (mean pre–post difference ± standard deviation for dose 1: morphine 1.5 ± 1.2, ibuprofen 1.3 ± 1.0, between-group difference [δ] 0.2 [95% confidence interval (CI) –0.2 to 0.6]; dose 2: morphine 1.3 ± 1.3, ibuprofen 1.3 ± 0.9, δ 0 [95% CI –0.4 to 0.4]; dose 3: morphine 1.3 ± 1.4, ibuprofen 1.4 ± 1.1, δ –0.1 [95% CI –0.7 to 0.4]; and dose 4: morphine 1.5 ± 1.4, ibuprofen 1.1 ± 1.2, δ 0.4 [95% CI –0.2 to 1.1]). We found no significant differences in the change in pain scores between morphine and ibuprofen between groups at any of the 4 time points (p = 0.6). Participants in the morphine group had significantly more adverse effects than those in the ibuprofen group (56.1% v. 30.9%, p < 0.01).

Interpretation: We found no significant difference in analgesic efficacy between orally administered morphine and ibuprofen. However, morphine was associated with a significantly greater number of adverse effects. Our results suggest that ibuprofen remains safe and effective for outpatient pain management in children with uncomplicated fractures.

Trial registration: ClinicalTrials.gov, no. NCT01690780.
evidence for the oral administration of morphine in acute pain management is limited.\textsuperscript{20,21} Thus, additional studies are needed to address this gap in knowledge and provide a scientific basis for outpatient analgesic choices in children. Our objective was to assess if orally administered morphine is superior to ibuprofen in relieving pain in children with nonoperative fractures.

Methods

Design and setting
We conducted a parallel-group, randomized, blinded superiority trial designed to test the hypothesis that orally administered morphine is superior to ibuprofen for outpatient analgesia in children with extremity fractures. We recruited participants from September 2012 to February 2014 from the pediatric emergency department of the Children’s Hospital, London Health Sciences Centre, in London, Ontario. This emergency department treats about 40 000 children each year, 1900 of whom present with fractures. We received approval for the trial from the Office of Research Ethics on behalf of Western University’s Research Ethics Board.

Participants
We included all children aged 5–17 years who presented to the pediatric emergency department with a nonoperative, radiographically evident extremity fracture sustained within the preceding 24 hours. Our exclusion criteria were known hypersensitivity to either ibuprofen or morphine, chronic use of nonsteroidal anti-inflammatory drugs (NSAIDS) or opioids, associated injuries requiring analgesia, known renal disease, bleeding disorders, poor fluency in English, sleep apnea and pregnancy. The participants consisted of a convenience sample screened consecutively for eligibility for 20 hours/week, between the hours of 1200 and 2300. Written, informed consent and assent were obtained from all patients or their legal guardians.

A trained research assistant assessed eligibility, took participants’ informed consent or assent, and performed all other correspondence with participants. The research assistant was invited to assess eligibility after the attending physician’s interpretation of the radiograph.

Interventions
Randomization and concealment of allocation were pharmacy-controlled by use of a computer-based random number generator (www-users.york.ac.uk/~mb55/soft/soft.htm). Eligible participants were randomly assigned in a 1:1 allocation ratio with a stratified block design using a block size of 6 to receive either normal-release morphine (ratio-MORPHINE; Ratiopharm, 0.5 mg/kg, max. 10 mg) or ibuprofen (Advil; Pfizer Canada, 10 mg/kg, max. 600 mg) every 6 hours as needed for pain for 24 hours after discharge (max. 4 doses). Concealment of allocation was performed by use of sequentially numbered, opaque sealed envelopes. The interventions were kept in identically appearing, nontranslucent sealed containers. They were prepared by our hospital pharmacy as opaque oral suspensions, identical in appearance, and presented to participants in identical white plastic vials by a research assistant. However, because the interventions differed in taste and consistency, we employed a double-dummy setup whereby each participant was given 4 prepackaged doses consisting of 2 vials, only 1 of which was the active agent. A protocol for unmasking was available on an emergency basis. Participants were counselled to take acetaminophen at a dose of 15 mg/kg (max. 975 mg) for breakthrough pain.

Participants were given a data collection form immediately before their discharge from the emergency department, on which they were asked to record pain using the Faces Pain Scale — Revised (FPS-R) immediately before and 30 minutes after each dose. The FPS-R is a 6-item self-report measure to assess the intensity of pain. It has been validated with sound psychometric properties\textsuperscript{24} for use in children at least 4 years of age.\textsuperscript{25} The scale is scored from 0 (no pain) to 5 (maximum amount of pain) by circling the appropriate face on a horizontal axis.

Participants were also asked to record any adverse effects that occurred within 72 hours of the first dose and the number of acetaminophen doses taken for breakthrough pain. We chose 30 minutes because the peak plasma concentration of morphine taken orally is reached at 30 minutes,\textsuperscript{22} and the peak plasma concentration for ibuprofen is reached between 30 and 60 minutes.\textsuperscript{23} Participants returned the data forms using a stamped, self-addressed envelope. All participants received a phone call 24 hours after discharge to remind them to return the forms, to enquire about serious complications and to verify compliance. We contacted participants who returned forms with unclear information for clarification. Participants, investigators, the biostatistician and all research assistants were blinded to allocation.

Outcome measures
Our primary outcome was the difference in pain scale scores before and after the first dose of analgesic. Our secondary outcomes included the type and frequency of adverse effects and the number of participants who required acetaminophen.
**Statistical analysis**

A between-group difference in pain intensity scores of 1 face has been shown to be a minimal clinically important difference. Assuming a standard deviation of 2 faces, we needed 63 participants in each group to be able to detect a 1-face between-group difference at 80% power with a 2-sided level of significance of 0.05.

Our analysis was based on a modified intention-to-treat principle and included all participants who took at least 1 dose of the intervention. We used means and standard deviations (SDs), medians and interquartile ranges (IQRs) or frequencies and percentages, as appropriate, to summarize baseline characteristics. We assessed comparisons between participants who did and did not take analgesia using an unpaired t test for continuous variables and a Pearson χ² test for categorical variables. We used an unpaired t test to assess the primary end point. Similarly, for the second, third and fourth doses, we used unpaired t tests to compare the 2 groups. We used a mixed linear regression model with an unstructured covariance matrix to assess the between-group differences across all 4 doses. We used analysis of variance and a test of interaction to perform a prespecified subgroup analysis involving only those patients who underwent closed reduction. We used a Pearson χ² to evaluate between-group differences in the proportions of participants who required breakthrough analgesia and had adverse effects.

We used the SPSS statistical software package (version 19) for data analysis. We considered p values less than 0.05 to be significant.

**Results**

**Participants**

Of the 183 participants who underwent randomization, 134 (73.2%) took at least 1 dose of the intervention and were included in our analysis (66 participants from the morphine group and 68 from the ibuprofen group) (Table 1, Figure 1). All of the participants who did not take any of the study drugs reported that they did not feel pain severe enough to require an analgesic. There were no significant differences between participants who did take analgesia and those who did not with respect to age (10.7 ± 3.3 v. 10.8 ± 3.1, p = 0.09), sex (49 girls [74.2%] v. 43 girls [63.2%, p = 0.8], median pain score on discharge (2 [IQR 1–3] v. 2 [IQR 1–3], p < 1.0) or number of closed reductions (32 [48.5%] v. 26 [38.2%] or number of closed reductions (56 [42%] v. 20 [41%], p = 0.45).

**Primary outcome**

Both morphine and ibuprofen resulted in a decrease in pain scores at each dose administration. The between-group difference in pre–post changes in pain scores was not significant (Table 2).

**Secondary outcomes**

Between-group differences for the second, third and fourth doses were not significant (Table 2). We found no evidence that the differences in pain scores changed over time (p = 0.3). For each of the 4 doses, tests for heterogeneity were nonsignificant whether or not the participant had a closed reduction (p = 0.4, 0.4, 0.6 and 0.4, respectively).

There were no significant differences in the percentage of participants requiring acetaminophen for breakthrough pain in the morphine or ibuprofen groups (17 [25.7%] v. 10 [14.7%], p = 0.1). No severe adverse drug reactions (e.g., immune-mediated hypersensitivity) were reported by any of the participants, and there were no deaths. Significantly more participants in the morphine group had adverse effects, the most common of which was drowsiness (more than 1/3 of participants in the morphine group, Table 3).

| Table 1: Characteristics of participants and their fractures, by study drug |
|-----------------|-----------------|-----------------|
| Characteristic   | Morphine n = 66 | Ibuprofen n = 68 |
| Age, yr, mean ± SD | 10.7 ± 3.3 | 10.8 ± 3.1 |
| Female sex, no. (%) | 49 (74.2) | 43 (63.2) |
| Discharge pain score, median (IQR) | 2 (1–3) | 2 (1–3) |
| Closed reduction, no. (%) | 32 (48.5) | 26 (38.2) |
| Type of fracture, no. | | |
| Transverse | 63 | 66 |
| Torus | 3 | 2 |
| Location of fracture | | |
| Radius | 30 | 26 |
| Ulna | 1 | 2 |
| Radius + ulna | 13 | 20 |
| Clavicle | 8 | 7 |
| Humerus | 5 | 5 |
| Elbow | 1 | 1 |
| Forearm | 2 | 0 |
| Tibia or fibula | 6 | 7 |
| Type of immobilization | | |
| Circular cast | 48 | 48 |
| Splint | 5 | 12 |
| Sling | 9 | 5 |
| Collar and cuff | 2 | 1 |
| None | 2 | 2 |

Note: IQR = interquartile range, SD = standard deviation.
Interpretation

In this randomized controlled study involving children with nonoperative fractures, we show that both morphine taken orally and ibuprofen resulted in improved pain scores with no significant difference in analgesic efficacy. However, morphine was associated with a greater frequency of adverse effects.

Concerns surrounding the safety of codeine in children has left a void in the choices of opioid therapy available for moderate to severe pain. As a possible consequence, some evidence suggests that the use of oral morphine is increasing. However, our results suggest that ibuprofen remains a relatively safe and effective analgesic agent for children who have sustained a nonoperative extremity fracture.

Two studies have investigated the use of morphine to relieve pain in pediatric fractures. In a single-arm trial, 0.5 mg/kg morphine administered orally decreased pain scores at 30 minutes. In an observational study comparing morphine administered intravenously with morphine administered orally, intravenous administration (0.2–0.4 mg/kg) resulted in greater pain reduction as assessed by a 5-item faces pain scale. We found children in the morphine group had significantly more adverse effects. Previous studies have described similar frequencies of nausea, vomiting and drowsiness, consistent with the expected adverse effects of morphine.

Our finding of a lack of analgesic superiority of morphine over ibuprofen is consistent with several studies involving children with orthopedic injuries. Ibuprofen has been found to be more efficacious than either acetaminophen or codeine, equivalent to an acetaminophen–codeine combination and equivalent to oxycodeone. In the only study of outpatient analgesia involving children with fractures, ibuprofen was

### Table 2: Mean pre–post differences in pain scores* between groups†

| Dose | Oral morphine |  | Ibuprofen |  | Between-group difference (95% CI) | p value‡ |
|------|---------------|---|------------|---|-----------------------------------|---------|
|      | No. of        | Pre–post difference, mean ± SD | No. of        | Pre–post difference, mean ± SD |                                   |         |
|      | participants  |                            | participants  |                            |                                   |         |
| 1    | 66            | 1.5 ± 1.2                   | 68            | 1.3 ± 1.0                   | 0.2 (−0.2 to 0.6)                  | 0.3     |
| 2    | 55            | 1.3 ± 1.3                   | 54            | 1.3 ± 0.9                   | 0.0 (−0.4 to 0.4)                  | 0.9     |
| 3    | 41            | 1.3 ± 1.4                   | 48            | 1.4 ± 1.1                   | −0.1 (−0.7 to 0.4)                 | 0.6     |
| 4    | 34            | 1.5 ± 1.4                   | 36            | 1.1 ± 1.2                   | 0.4 (−0.2 to 1.1)                  | 0.2     |

Note: SD = standard deviation, CI = confidence interval.
* Determined using the Faces Pain Scale — Revised.
† Reflects the number of participants taking the dose of each medication at the corresponding time interval.
‡ Unpaired t test.
Table 3: Proportion of participants with adverse effects between groups

| Adverse effect* | Patient group, no. (%) |  | p value† |
|-----------------|------------------------|--|---------|
|                 | Morphine n = 66        | Ibuprofen n = 68 |
| Any             | 37 (56.1)              | 21 (30.9)       | < 0.01  |
| Nausea          | 18 (27.3)              | 4 (5.9)         | < 0.01  |
| Vomiting        | 8 (12.1)               | 2 (2.9)         | 0.04    |
| Drowsiness      | 23 (34.8)              | 14 (20.6)       | 0.07    |
| Dizziness       | 8 (12.1)               | 6 (8.8)         | 0.5     |
| Constipation    | 4 (6.1)                | 1 (1.5)         | 0.2     |
| Other‡          | 8 (12.1)               | 3 (4.4)         | 0.1     |

*Some patients had more than 1 adverse effect.
†Pearson χ² test.
‡Includes headache, abdominal pain, irritability and hyperactivity.

associated with less impairment in functional outcomes and was more tolerable than acetaminophen plus codeine. Studies involving both adults and children with a variety of painful conditions have shown that ibuprofen’s efficacy is comparable with or superior to that of opioids.18,28,32,33 The possibility of comparable efficacy for musculoskeletal pain between NSAIDs and opioids as drug classes is evidenced by other studies that have shown ketorolac to be superior to morphine34 and equivalent to tramadol.35 Given ibuprofen’s and morphine’s similar and inexpensive prices, in addition to these results and ours, ibuprofen should be the initial drug of choice for acutely painful musculoskeletal trauma in children.

Limitations

To preserve blinding, participants took the intervention no more frequently than every 6 hours. However, the duration of action of normal-release morphine taken orally is 2 to 4 hours.22 Acetaminophen for breakthrough pain may have decreased the preintervention pain scores in the morphine group, providing a more conservative estimate of effect size.

Our study design favoured the pragmatic end of the Pragmatic–Explanatory Continuum Indicator Summary.36 Our intent was to determine the effects of analgesia under typical outpatient conditions. However, broad inclusion criteria may have added substantial between-subject variability, thereby decreasing power. We allowed participants to take analgesia on an as-needed basis because analgesic requirements after fracture immobilization are not universal, and fixed dosing may have led to noncompliance13 without benefiting short-term functional outcomes.12 Although as-needed dosing may have under-
analgesia for fracture pain. *Ann Emerg Med* 2003;42:197-205.
6. Ali S, Drendel AL, Janeva Kircher B, et al. Pain management of musculoskeletal injuries in children. *Pediatr Emerg Care* 2010; 26:518-24, quiz 525-8.
7. Taddio A, McGrath P, Finlay A. Effects of early pain experience: the human literature. In: McGrath PJ, Finlay GA, editors. Chronic and recurrent pain in children and adolescents. Vol. 13 in Progress in Pain Research and Management. Seattle: IASP Press; 1999. p. 57-74.
8. Weismann SJ, Bernstein B, Schechter NL. Consequences of inadequate analgesia during painful procedures in children. *Arch Pediatr Adolesc Med* 1998;152:147-9.
9. Pate JT, Blount RL, Cohen LL, et al. Childhood medical experience and temperament as predictors of adult functioning in medical situations. *Child Health Care* 1996;25:281-98.
10. Fein JA, Zempsky WT, O'Connor IP, Committee on Pediatric Emergency Medicine and Section on Anesthesiology and Pain Medicine, American Academy of Pediatrics. Relief of pain and anxiety in pediatric patients in emergency medical systems. *Acad Emerg Med* 2005;12:161-71.
11. Landin LA. Epidemiology of children’s fractures. *J Pediatr Orthop B* 1997;6:79-83.
12. Drendel AL, Lyon R, Bergholte J, et al. Outpatient pediatric pain management practices for fractures. *Pediatr Emerg Care* 2006;22:94-9.
13. Kircher J, Drendel AL, Newton AS, et al. Pediatric musculoskeletal pain in the emergency department: A medical record review. *CJM* 2013;15:1-5.
14. Ciszkowski C, Madadi P, Phillips MS, et al. Codeine use in certain children after tonsillectomy and/or adenoidectomy: a genetic variant — an ultra-rapid metabolizer. *Paediatr Anaesth* 2007;17:684-7.
15. Voronov P, Przybyle HJ, Jagannathan N. Apnea in a child after oral codeine: a genetic variant — an ultra-rapid metabolizer. *Paediatr Anaesth* 2013;23:1247-51.
16. Food and Drug Administration; 2013. Available: www.fda.gov/Safety/MeDWatch/SafetyInformatiomanızSafetyAlertsforHuman-MedicalProducts/ucm315627.htm (2014 Apr. 14).
17. Health Canada. Health Canada’s review recommends codeine only be used in patients aged 12 and over. Silver Spring (MD): U.S. Food and Drug Administration; 2013. Available: www.fda.gov/Safety/MeDWatch/SafetyInformatiomanızSafetyAlertsforHuman-MedicalProducts.
18. Friday JH, Kanegaye JT, McCaslin I, et al. Ibuprofen provides analgesia equivalent to acetaminophen–codeine in the treatment of acute pain in children with extremity injuries: a randomized clinical trial. *Acad Emerg Med* 2009;16:711-6.
19. Lewis ET, Cucciare MA, Trafton JA. What do patients do with unused opioid medications? *Clin J Pain* 2014;30:654-62.
20. Wille C, Bocquet N, Cojocaru B, et al. Oral morphine administration for pain management in children with musculoskeletal trauma. *Pediatrics* 2007;119:460-7.
21. Hasselström J, Eriksson S, Persson A, et al. The metabolism and bioavailability of morphine in patients with severe liver cirrhosis. *Br J Clin Pharmacol* 1990;29:289-97.
22. Friday JH, Kanegaye JT, McCaslin I, et al. Ibuprofen provides analgesia equivalent to acetaminophen–codeine in the treatment of acute pain in children with extremity injuries: a randomized clinical trial. *Acad Emerg Med* 2009;16:711-6.
23. Koller DM, Myers AB, Lorenz D, et al. Effectiveness of oxycode, ibuprofen, or the combination in the initial management of orthopedic injury-related pain in children. *Pediatr Emerg Care* 2007;23:627-33.
24. Taddio A, McGrath P, Finley A. Effects of early pain experience: the human literature. In: McGrath PJ, Finlay GA, editors. Chronic and recurrent pain in children and adolescents. Vol. 13 in Progress in Pain Research and Management. Seattle: IASP Press; 1999. p. 57-74.
25. Tucci Ji, Bandiera E, Darwiche R, et al. Paracetamol and ibuprofen for paediatric pain and fever. *J Pharm Pract Res* 2009; 39:223-5.
26. Hicks CL, von Baeyer CL, Spafford PA, et al. The Faces Pain Scale–Revised: toward a common metric in pediatric pain measurement. *Pain* 2001;93:173-83.
27. Paracetamol and ibuprofen for paediatric pain and fever. *J Pharm Pract Res* 2009; 39:223-5.
28. Retherford KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009;62:464-75.

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**Contributors:** Navleen Poonai is the primary investigator and was responsible for designing the study, interpreting and analyzing the data and writing the manuscript. Gina Bhullar was responsible for data entry and writing the manuscript. Kangrui Lin, Adam Papini, Jocelyn Howard, Michelle Bile, David Mainprize, John Teefy and Cindy Langford were responsible for writing the manuscript. Samina Ali and Rod Lim revised the manuscript for important intellectual content. Larry Stitt performed the statistical analysis and revised the manuscript for important intellectual content. Michael Rieder assisted with the study design and drafting and revising of the article. All of the authors approved the final version of the manuscript submitted for publication and have agreed to act as guarantors of the work.

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**Data sharing:** Data available on request to the corresponding author. Data can be accessed after a signed data transfer agreement is in place. Data will be transferred electronically through a secure network in a password-protected file.