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Nonopioid vs opioid analgesics after impacted third-molar extractions

The Opioid Analgesic Reduction Study randomized clinical trial

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ABSTRACT

Background. Opioids are still being prescribed to manage acute postsurgical pain. Unnecessary opioid prescriptions can lead to addiction and death, as unused tablets are easily diverted.

Methods. To determine whether combination nonopioid analgesics are at least as good as opioid analgesics, a multisite, double-blind, randomized, stratified, noninferiority comparative effectiveness trial was conducted, which examined patient-centered outcomes after impacted mandibular third-molar extraction surgery. Participants were randomized to receive 5 mg of hydrocodone with 300 mg of acetaminophen (opioid) or 400 mg of ibuprofen and 500 mg of acetaminophen (nonopioid). After an initial dose, analgesic was taken every 4 through 6 hours as needed for pain.

Results. In this randomized multisite clinical trial (n = 1,815 adults), those not taking opioids experienced significantly less pain (numeric rating scale ranging from 0 [no pain] through 10 [worst pain imaginable]) for first day and night (mean difference, –0.70; 95% CI, –0.94 to –0.45; $P < .001$) and second day and night (mean difference, –0.28; 95% CI, –0.52 to –0.04; $P = .015$), and experienced no more pain than participants taking opioids over the entire postoperative period (mean difference, –0.20; 98.75% CI, –0.45 to 0.05; $P = .172$). Participants not taking opioids had higher overall satisfaction at the postoperative visit (85.3% extremely satisfied or satisfied vs 78.9%; 95% CI, 1.21 to 1.98; $P = .006$).

Conclusions. The ibuprofen and acetaminophen combination managed pain better for the first 2 days and led to greater satisfaction over the entire postoperative period than hydrocodone with acetaminophen. At no time did hydrocodone outperform the nonopioid.

Practical Implications. Routine opioid prescribing after dental surgery is not supported. The results of this study confirmed the American Dental Association's recommendations that ibuprofen and acetaminophen in combination should be the first-line therapy for acute pain management. This clinical trial was registered at ClinicalTrials.gov. The registration number is NCT04452344.

Key Words. Pain management; opioids; impacted mandibular third-molar extraction; nonopioids; ibuprofen and acetaminophen; addiction.

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Opioid-associated morbidity and mortality have had a negative impact on families and communities.[1] Dentists are among the leading prescribers of opioid analgesics,[2-6] accounting for 8,910,437 opioid prescriptions in 2022.[7] An estimated 5 million opioid-naïve young adults are exposed each year to opioids after third-molar extractions. Unnecessary opioids prescriptions can lead to addiction, as unused tablets are easily diverted.[8] Young adults who receive opioid prescriptions are more likely than those who do not to eventually misuse opioids, contributing to an upsurge in deaths.[9,10] If nonopioid combinations provide comparable pain

relief with similar or greater satisfaction than opioid analgesia, the routine prescribing of opioids after third-molar extraction surgery could be eliminated.

Although results of systematic reviews have shown a combination of acetaminophen and ibuprofen is more efficacious than either alone,[11-13] few researchers directly compared the effectiveness of this combination with opioids for acute postsurgical pain.[14,15] Clinical trial designs rarely account for surgical or patient compliance variations, often test a single dose,[16] or provide initial analgesic dosing after onset of considerable pain. Sex differences are rarely considered,[17] and sample sizes are frequently small, limiting generalizability of results. Patient-centered outcomes, including pain interference and sleep quality, are often not included.

In this quasi-pragmatic, randomized clinical trial, we compared analgesic effectiveness using the dental impaction pain model, which relies on predictable postoperative pain after extraction of 1 or more bony impacted mandibular third molars.[18] We hypothesized that the nonopioid combination (400 mg of ibuprofen and 500 mg of acetaminophen) would be at least noninferior, and possibly even superior, to the most commonly prescribed opioid (5 mg of hydrocodone with 300 mg of acetaminophen) for average acute postoperative pain for the first day and night, second day and night, third day and night, and entire postoperative period and the nonopioid combination would be better than the opioid combination in overall satisfaction at the postoperative visit. We also tested these hypotheses in male and female participants as subgroup analyses due to differences in pain tolerance and analgesic metabolism.[17,19,20]

METHODS

Trial oversight

Rutgers University Institutional Review Board served as the single institutional review board of record (protocol 2020002299). All participants provided written informed consent. The ClinicalTrials.gov study record was first submitted on April 7, 2020, and posted on June 30, 2020. The first patient consented and was randomized on January 7, 2021. The National Institute of Dental and Craniofacial Research, National Institutes of Health appointed a Data and Safety Monitoring Board and contracted a clinical monitoring agency for trial oversight. Data sharing information can be found in the eBox available online at the end of this article.

Trial design and intervention

The Opioid Analgesic Reduction Study was a multisite, double-blind, prospective, stratified, noninferiority, randomized clinical trial that compared patient-centered outcomes using 2 analgesic regimens after impacted partial or full bony mandibular third-molar extraction surgery.[21] Our noninferiority design used similar populations (healthy young adults), surgical procedures (dental impaction pain model),[22] common analgesic comparators, and pain outcomes as used in previous efficacy studies (based on a numeric rating scale [NRS][23]). Clinical sites were selected on the basis of patient and provider diversity. As the study was pragmatic in nature, surgical technique and use of pharmaceuticals during surgery were at the surgeons' discretion. Before study initiation, randomization sequences for each site according to sex were generated by the chief statistician (S.-E.L.) using R software Version 3.6.1. (The R Project for Statistical Computing) at a 1:1 ratio, in blocks of 4, to either the nonopioid or opioid treatment arm.

Our analgesic comparators, which are US Food and Drug Administration (FDA)–approved and readily available, include opioid (5 mg hydrocodone with 300 mg acetaminophen)[14,24-32] and nonopioid (a combination of 400 mg of ibuprofen and 500 mg of acetaminophen).[11-13,15,16,33-47] Both were taken as needed for pain. Hydrocodone is the most commonly prescribed opioid analgesic in dental practice today.[4-6,48-51] Nonopioids are commonly used over-the-counter analgesics which, alone and in combination, have been shown to be effective against acute pain.[11-13,15,16,33-47] The comparators are recognized by the American Dental Association[24,52] and others[53-55] for managing severe postoperative dental pain. Furthermore, results of studies on ibuprofen and acetaminophen have shown no additional analgesic effect at higher dosages[34,56] and a combination of ibuprofen and acetaminophen is better than either one taken alone.[11-13,16,34-36]

After generation of the randomization sequence, study kits were prepared in sequence at the Rutgers Clinical Coordinating Core. A nonopioid dose consisted of 2 overencapsulated capsules: 1 brown capsule that contained 400 mg of ibuprofen and 1 white capsule that contained 500 mg of

ABBREVIATION KEY

AE: Adverse event.
FDA: US Food and Drug Administration.
NA: Not applicable.
NRS: Numeric rating scale.
PDMP: Prescription Drug Monitoring Program.

Table 1. Study drug administration* and postoperative instructions.†

ANALGESIC	NATIONAL DRUG CODE	NO. OF DOSES	CAPSULE SIZE	CAPSULE COLOR
Opioid				
5 mg of hydrocodone with 300 mg of acetaminophen	0406-0376-05	20	AA	Brown
Placebo	PROSOLV EASYTab SP (JRS Pharma)	20	0	White
Nonopioid				
400 mg of ibuprofen	67877-319-05	20	AA	Brown
500 mg of acetaminophen	50580-937-07 or 50580-499-36	20	0	White

* Investigational product administration comparator justification for hydrocodone with acetaminophen: hydrocodone is the most frequently prescribed opioid. Adolescents and young adults received more than 11% of dentist-prescribed opioids during the same period. This finding of opioid-prescribing prevalence for adolescents is consistent with other studies and the assessment of acute opioid prescriptions for youth using Prescription Drug Monitoring Program data. The US Food and Drug Administration limits acetaminophen doses to 300-325 mg to limit the possibility of liver toxicity. It was therefore decided the opioid would be 5 mg of hydrocodone with 300 mg of acetaminophen. Comparator justification for ibuprofen and acetaminophen: nonopioid was selected as researchers in single-dose studies suggest that the combination of ibuprofen and acetaminophen could be at least as effective as opioid in managing moderate through severe pain. In selecting dosages, the maximum recommended daily dose by the US Food and Drug Administration (3,200 mg of ibuprofen and 3,000 mg of acetaminophen) was taken into account along with the most common tablets available in patients' homes (ie, 200 mg of ibuprofen and 500 mg of acetaminophen). Consideration was also given to pill size, as the overencapsulation of 325-mg tablets of acetaminophen would not yield as manageable a capsule size as the 500-mg caplet. † Participant instructions: 1 dose (1 brown capsule and 1 white capsule) taken immediately after surgery completion if escorted to appointment or immediately on returning home if unescorted. After initial dose, additional doses were taken every 4-6 hours as needed for pain, not to exceed 6 doses taken per 24-hour period. If pain relief was insufficient, 2 additional doses per 24-period could be taken after consultation with surgeon. If rescue pain relief was required, 5 mg of oxycodone was prescribed with instructions to take rescue medication every 6 hours as needed for pain. At patient's discretion, 2 over-the-counter 200-mg ibuprofen tablets could be taken in lieu of investigational analgesic after the first dose was taken postsurgery.

acetaminophen. The opioid dose also consisted of 2 overencapsulated capsules: 1 brown capsule that contained 5 mg of hydrocodone with 300 mg of acetaminophen and 1 white capsule, which contained the placebo. As both nonopioid and opioid kits contained 2 medication bottles, 1 with brown capsules and 1 with white capsules, the analgesic was blinded to both participants and clinical site personnel (Table 1). For both treatment arms, 20 doses of study analgesic were provided. Each blinded kit contained a study identification for which assignment was known only to the chief statistician and clinical coordinating core (personnel who packed and shipped participant kits to the sites); no site personnel at any of the sites had knowledge of group assignments.

Patients

Patients, 18 years or older with treatment planned for partial or full bony impacted mandibular third-molar extraction, were recruited from outpatient clinics at University of Illinois at Chicago, University of Maryland, University of Michigan, University of Rochester, and Rutgers University. Participants were enrolled after informed consent was provided and eligibility determination. Key exclusion criteria included medical contraindications for taking ibuprofen, acetaminophen, or opioids, and social history of addiction or substance abuse. A full listing of inclusion and exclusion criteria can be found in eTable 1 (available online at the end of this article). Patients participated in the study from the day of surgery through their postoperative visit. Additional information can be found in the Appendix (available online at the end of this article).

Study visits

Patients having impacted mandibular third-molar extraction surgery provided consent, and their initial eligibility was determined (visit 0) (Figure 1). Demographic information and baseline characteristics were collected. On the day of surgery (visit 1), final eligibility (eTable 1) was determined by means of a negative pregnancy test (if female) and a Prescription Data Monitoring Program (PDMP) check for prior opioid prescriptions. Before surgery, the research coordinator provided the study kit to the participant to ensure understanding of study instructions without influence of sedation or general anesthesia. Surgery was performed by senior oral and maxillofacial

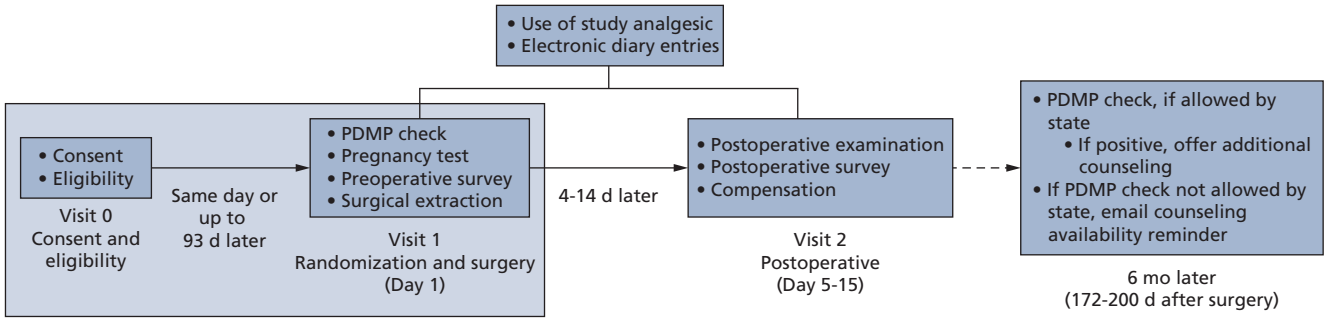

Figure 1. Participant flow diagram. Patients with treatment planned for impacted mandibular third-molar extraction provided consent and preliminary eligibility was determined (visit 0). That same day or up to 93 days later, final eligibility was determined by means of Prescription Drug Monitoring Program (PDMP) check and a negative pregnancy test for female participants. Once final eligibility was determined, a preoperative questionnaire was completed and third molars were extracted (visit 1). During the postoperative period, participants took blinded analgesic as needed for pain and completed morning and evening electronic diary entries for 7 days and nights or up until postoperative visit, whichever came first. Up to 15 days later, patients returned for a postoperative visit when a clinical examination and postoperative questionnaire were completed (visit 2). Six months later, a PDMP check was performed, if permitted by state law, to determine whether a new opioid prescription was written. Addiction counseling was offered to any participant with a positive PDMP query or participants in states that did not allow the PDMP query.

residents and attendings. After surgery, surgical data were collected and participants took their first dose of medication before leaving the office (if escorted) or when arriving home. Participants were instructed to continue to take their study analgesic every 4 through 6 hours as needed for pain (maximum of 6 doses per day), with the option to substitute 400 mg of ibuprofen in place of study analgesic. During the period between surgery and the postoperative visit, participants took the study analgesic as needed and completed twice-daily electronic diaries (assessing pain experience, pain interference, sleep quality, adverse effects, satisfaction, and medication use). If pain relief was inadequate, the participant contacted the study team members and rescue medication (5 mg of oxycodone) was prescribed. Participants returned 4 through 14 days later for a postoperative visit (visit 2), which included a clinical examination, questionnaire (evaluating pain intensity, pain interference, sleep, and overall satisfaction), and study materials return (pill bottles with unused medication). Six months after surgery, a new PDMP search was conducted, if permitted by the state PDMP (New Jersey and Illinois), to assess postoperative opioid use and offer addiction counseling. The full protocol is available at ClinicalTrials.gov, registration NCT04452344. There were no material changes in the protocol from the first to the last participant.

Outcomes

Data collection details and timing of outcome measures are detailed in eTable 2 (available online at the end of this article).

Primary Outcomes

Primary outcomes included pain experience and participant satisfaction with medication. For pain, we reported the composite pain experience rating derived from the pain items of the Brief Pain Inventory,[57,58] averaging 4 items (ie, worst, least, average, and now pain; Cronbach α, 0.91-0.96) (eTable 3, available online at the end of this article) obtained from the participants' electronic diaries, collected on the morning and evening each day from the day of surgery until the post-operative visit. These items used an NRS[59] (from 0 [no pain]-10 [worst pain imaginable]). As pain is greatest during the first 72 hours postsurgery,[60] we examined the first day and evening, second day and evening, and third day and evening as well as the entire postoperative period. Satisfaction was initially measured at the postoperative visit using a 5-point Likert scale ranging from 1 (very satisfied) through 5 (very dissatisfied).[61] It was later dichotomized into the following 2 categories: very satisfied and satisfied combined vs the remaining 3 categories to enhance clinician interpretation.

Secondary Outcomes

Secondary outcomes included the need for rescue medication,[62] composite pain interference rating (mean of 6 questions modeled after the Patient Reported Outcomes Measurement Information System-Pain Interference Short Form 6b; 5-point Likert scale, from 1 [not at all]-5 [very much];

Cronbach α 0.94-0.97) (eTable 3),[58,63] overall sleep quality using the NRS (from 0 [excellent]-10 [very poor]), adverse events (AEs) (frequency and severity of emergent clinical visit and eletronic diary self-report on 3-point Likert scale (from 1 [mild]-3 [severe]),[64] number of opioid tablets returned,[65] and future opioid prescription within 6 months of extraction surgery.

Statistical analysis

All statistical analyses were performed on an intent-to-treat basis. To test whether nonopioid medication was noninferior to opioids for pain, we used mixed-model analysis with pain modeled as a function of treatment (nonopioid vs opioid), day and day by treatment interactions as fixed-effects independent variables, and participants and clinical sites as random effects. We followed the recommendations[66,67] that suggested a difference of 13 mm on a visual analog scale, approximately equivalent to 1.3 on an NRS, as the clinically significant difference, and determined the noninferiority margin (d) as 1.0 on the 10-point NRS (from 0-10). Linear contrasts were constructed to compare the mean differences between treatment groups. The noninferiority of nonopioids was tested on the basis of 4 time comparisons for first day and night, second day and night, third day and night, and the entire postoperative period using the 2-sided 98.75% CI of mean $(\mu)_{\text{NONOPIOID}}$ to μ_{OPIOID} for each comparison, after the Bonferroni adjustment. If the entire CI was completely below d equals 1.0, we concluded the noninferiority of the nonopioid. *P* values were reported on the basis of testing the 1-sided hypotheses: H_0: $(\mu_{\text{NONOPIOID, t}}\text{-}\mu_{\text{OPIOID, t}}) \geq$ d vs H_1: $(\mu_{\text{NONOPIOID, t}}\text{-}\mu_{\text{OPIOID, t}}) <$ d, in which t equals first day and night, second day and night, third day and night, and the entire postoperative period, after Bonferroni adjustment to control overall α at 2.5% (1-sided). If noninferiority was established, we assessed superiority; if the CI completely laid below 0, we then concluded (statistical) superiority of the nonopioid analgesics at the 1.25% level (2-sided).[68] At the postoperative visit, satisfaction was treated as a categorical variable and compared between nonopioid vs opioid groups using random-effects logistic regression analysis, with the clinical site as a random effect. Secondary outcomes were compared using the generalized linear mixed-model analysis, with both participant and site or just site as the random effects, when appropriate. Prespecified subgroup analyses were performed to compare pain and satisfaction between nonopioid and opioid groups in male and female participants separately. Site differences were examined for the outcomes of pain and satisfaction. Missing data analysis was performed using the multiple imputation method.[69] Only pain was assessed using the noninferiority tests; satisfaction and all secondary outcomes were tested using conventional rules, that is, superiority tests, not as noninferiority tests. Statistical significance was defined as 2-sided α equals .05 for each outcome. Bonferroni multiple testing adjustment was also applied to analyses for the 4 times' comparisons for pain interference and sleep quality as more conservative statistical tests. All statistical analyses were performed using SAS software, Version 9.4 (SAS Institute).

Power and sample size considerations

To test noninferiority of nonopioids for pain, we determined the sample size on the basis of data from Chang and colleagues[14] (SD, 3.6), the noninferiority margin d equals 1.0 was established before the start of the trial, and applied the Bonferroni adjustment for 4 times to control the overall α at 1-sided 2.5% (2-sided 5% equivalent) with 90% power in the full sample analysis and greater than 80% power in the subgroup analysis according to sex. To account for 15% through 20% loss of follow-up and missing data, and other factors not included in the sample size estimation, we planned to recruit 1,800 participants, with 450 participants in each group (2 analgesic groups × 2 sex subgroups (male and female participants). To compare participant satisfaction, we assumed the proportion of positive ratings (extremely satisfied, satisfied) for the nonopioid group is 82%, similar to Daniels and colleagues,[15] powering our full study for 90% to detect a minimal difference of 7% (82% vs 75%) and an 11% difference (82% vs 71%) in the sex subgroup analysis (2-sided $\alpha = 2.5\%$).

RESULTS

Trial participants

Of the 2,102 patients screened for eligibility from January 2021 through June 2023, a total of 2,093 participants consented and completed visit 0; 1,888 were randomized, with a final study group of 1,815 completing eligible surgery (909 in the nonopioid group, 906 in the opioid group). Although

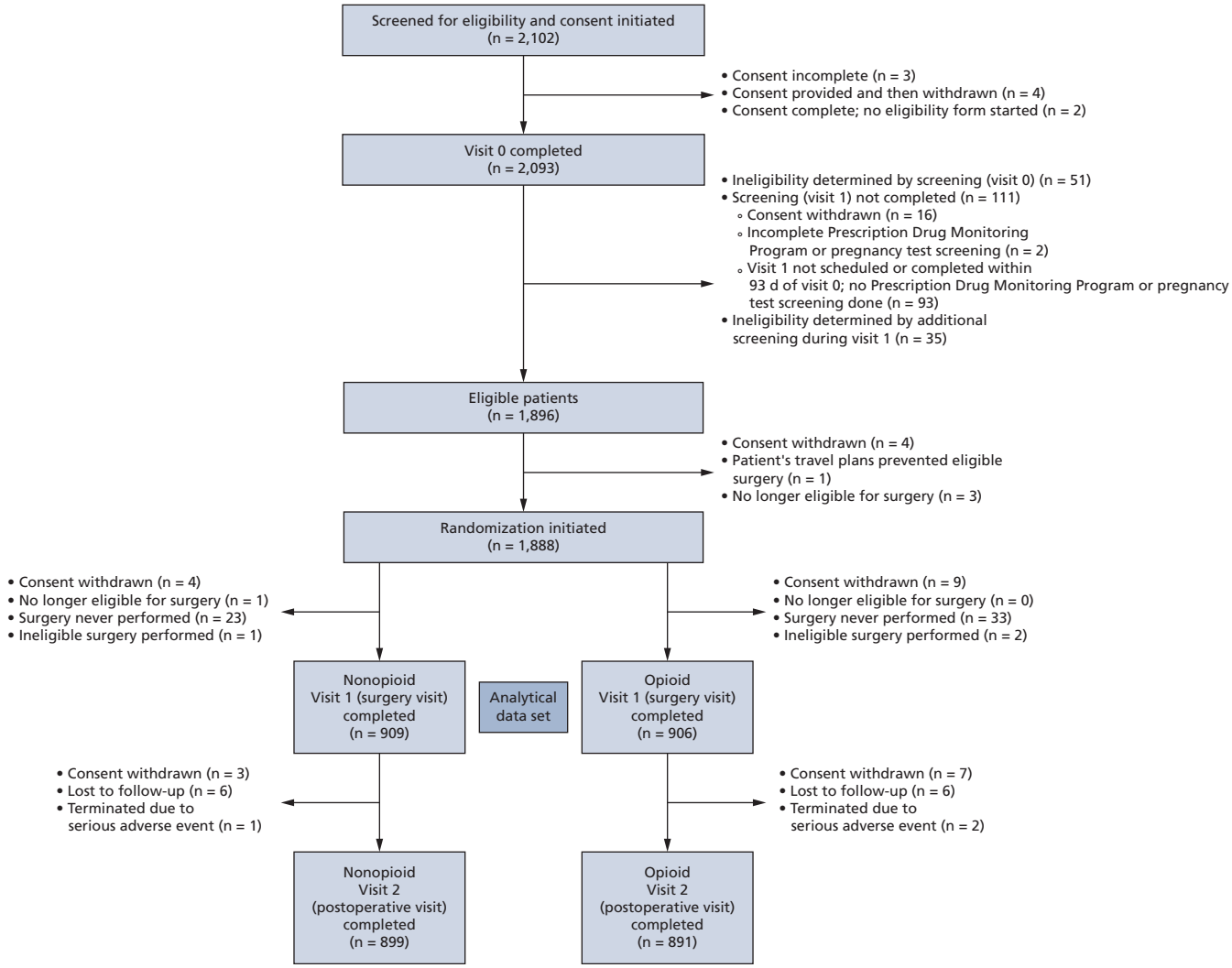

Figure 2. Consolidated Standards of Reporting Trials[70] diagram.

percentage eligible and enrolled varied according to site, eligibility criteria were equally applied across all sites using the same checklist form to determine eligibility (Figure 2 and eTable 4, available online at the end of this article). After surgery, 9 withdrew consent, 13 were lost to follow-up, and 3 were terminated due to noninvestigational product–related hospitalizations, reported as serious AEs, resulting in 1,790 participants completing the protocol (1,790 of 1,815 [98.6%]). After surgery, 898 of 909 (98.8%) participants not taking opioids and 883 of 906 (97.5%) participants taking opioids took their required first dose.

Participants completing eligible surgery (n = 1,815) did not differ in baseline demographic or surgical characteristics (Table 2). Mean (SD) age of participants was 25.7 (6.2) years; 50.1% were female and 68.9% were non-Hispanic (15.0% were Asian, 28.2% were Black, 19.7% were White). Most participants completed high school (94.5%) and were nonsmokers (87.9%). Overall, mean (SD) surgical duration was 39.0 (19.9) minutes, mean (SD) number of third molars extracted was 2.8 (1.2); 36.8% received a general anesthetic, concomitant pharmaceuticals included antibiotics (17.1%), corticosteroids (30.5%), and a long-lasting local anesthetic (7.5%), and 77.6% required osteotomy with sectioning, the most difficult surgical technique.

Primary outcomes

Results (Figure 3) showed nonopioids were superior to opioids in pain on first day and night (mean difference, –0.70; 98.75% CI, –0.94 to –0.45) and second day and night (mean difference, –0.28;

Table 2. Participant baseline demographic and surgical characteristics.*

CHARACTERISTIC	FULL STUDY GROUP (n = 1,815)	NONOPIOID (n = 909)	OPIOID (n = 906)
Demographic			
Age, y, mean (SD)	25.7 (6.2)	25.6 (6.0)	25.8 (6.5)
Sex assigned at birth, female, no. (%)	910 (50.1)	457 (50.3)	453 (50.0)
Race or ethnicity,† no. (%)			
Hispanic	561 (30.9)	279 (30.7)	282 (31.1)
Non-Hispanic Asian	272 (15.0)	141 (15.5)	131 (14.5)
Non-Hispanic Black	512 (28.2)	255 (28.1)	257 (29.4)
Non-Hispanic White	357 (19.7)	179 (19.7)	178 (19.7)
Other	62 (3.4)	32 (3.5)	30 (3.3)
Do not want to report	51 (2.8)	23 (2.5)	28 (3.1)
Education, no. (%)			
Some high school	99 (5.5)	42 (4.6)	57 (6.3)
High school graduate	992 (54.7)	486 (53.5)	506 (55.8)
Associate degree	193 (10.6)	104 (11.4)	89 (9.8)
College graduate	357 (19.7)	185 (20.4)	172 (19.0)
Master's degree	104 (5.7)	57 (6.3)	47 (5.2)
Doctoral degree	44 (2.4)	21 (2.3)	23 (2.5)
Smoking, no. (%)			
Do not smoke	1,596 (87.9)	798 (87.8)	798 (88.1)
Smoke < 1 pack per day	194 (10.7)	96 (10.6)	98 (10.8)
Smoke 1 pack per day	21 (1.2)	13 (1.4)	8 (0.9)
Smoke > 1 pack per day	4 (0.2)	2 (0.2)	2 (0.2)
Preoperative pain level, mean (SD)			
Composite pain experience rating‡	1.10 (2.1)	1.1 (20)	1.1 (2.2)
Worst pain§	1.6 (2.8)	1.6 (2.8)	1.6 (2.9)
Average pain§	1.2 (2.3)	1.1 (2.2)	1.2 (2.3)
Least pain§	0.7 (1.8)	0.6 (1.6)	0.8 (1.9)
Pain now§	0.9 (2.1)	0.9 (2.0)	0.9 (2.1)
Pain tolerance¶	5.9 (2.3)	5.9 (2.3)	5.9 (2.3)
Preoperative swelling, no. (%)			
None	1,520 (83.7)	775 (85.3)	745 (82.2)
Mild	228 (12.6)	103 (11.3)	125 (13.8)
Moderate	51 (2.8)	25 (2.8)	26 (2.9)
Severe	16 (0.9)	6 (0.7)	10 (1.1)
Surgical			
Surgical treatment duration, min, mean (SD)	39.0 (19.9)	38.6 (19.7)	39.3 (20.2)
Teeth extracted, no., mean (SD)			
Maxillary third molars	1.1 (0.9)	1.09 (0.9)	1.1 (0.9)
Mandibular third molars	1.7 (0.5)	1.7 (0.5)	1.7 (0.5)
Third molars, total no.	2.8 (1.2)	2.8 (1.2)	2.8 (1.2)
Full bony impacted third molars	1.0 (1.2)	1.0 (1.2)	1.0 (1.2)
Full bony impacted mandibular third molars	0.7 (0.9)	0.7 (0.9)	0.7 (0.8)
Anesthesia or analgesia used during surgery, no. (%)			
Local	1,729 (95.3)	867 (95.4)	862 (95.1)
Oral or enteral	4 (0.2)	2 (0.2)	2 (0.2)

* There are no statistically significant differences between treatment groups with respect to patient demographic and surgical characteristics. † Race and ethnicity are self-reported by participants. ‡ Mean of participants' worst, average, least, and current pain using an 11-point numeric rating scale (from 0 [no pain] through 10 [worst pain imaginable]). § 11-point numeric rating scale (from 0 [no pain] through 10 [worst pain imaginable]). ¶ 11-point numeric rating scale (from 0 [not tolerant at all] through 10 [extremely tolerant]).

Table 2. Continued

CHARACTERISTIC	FULL STUDY GROUP (n = 1,815)	NONOPIOID (n = 909)	OPIOID (n = 906)
Conscious sedation	165 (9.1)	81 (8.9)	84 (9.3)
Nitrous oxide	105 (5.8)	54 (5.9)	51 (5.6)
General anesthesia	668 (36.8)	339 (37.3)	329 (36.3)
Other pharmaceutical used, no. (%)			
Antibiotics	310 (17.1)	151 (16.6)	159 (17.5)
Anti-inflammatory agents	554 (30.5)	283 (31.1)	271 (29.9)
Marcaine	136 (7.5)	73 (8.0)	63 (7.0)
Most difficult surgical technique used, no. (%)			
Forceps only	104 (5.7)	58 (6.4)	46 (5.1)
Osteotomy	302 (16.6)	155 (17.1)	147 (16.2)
Osteotomy with sectioning	1,409 (77.6)	696 (76.6)	713 (78.7)

98.75% CI, –0.52 to –0.04), and were noninferior for third day and night (mean difference, –0.09; 98.75% CI, –0.34 to 0.15) and postoperative period (mean difference, –0.20; 98.75% CI, –0.45 to 0.05, with noninferiority margin d = 1). The nonopioid group had higher overall satisfaction at the postoperative visit (85.3% extremely satisfied or satisfied vs 78.9%; odds ratio, 1.55; 95% CI, 1.21 to 1.98; $P = .006$).

Secondary outcomes

Participants not taking opioids had less need for rescue analgesic (n = 26 [2.89%] vs n = 54 [6.07%]; odds ratio, 0.45; 95% CI, 0.28 to 0.73; $P = .001$), reported less pain interference (pain interference on first day and night: mean difference, –0.36; 98.75% CI, –0.49 to –0.22; $P < .001$; second day and night: mean difference, –0.23; 98.75% CI, –0.36 to –0.09; third day and night: mean difference, –0.14; 98.75% CI, –0.27 to –0.00; $P = .044$; and postoperative period: mean difference, –0.12; 98.75% CI, –0.23 to –0.01; $P = .019$) (Figure 3). Participants not taking opioids had better sleep quality during the first night (sleep quality: mean difference, –0.34; 98.75% CI, –0.65 to –0.02; $P = .030$) with no subsequent differences noted. On average, participants taking opioids returned 8.5 of the 20 hydrocodone-containing capsules provided. Participants not taking opioids were less likely to fill new opioid prescriptions within 6 months after surgery (nonopioid: 13 [3.22%]; opioid: 23 [5.81%]; odds ratio, 0.54; 95% CI, 0.27 to 1.08; $P = .082$).

Participants not taking opioids also reported lower frequency and severity of AEs (Table 3). Three participants (1 in the nonopioid group and 2 in the opioid group) experienced a serious AE; none were attributed to study analgesics (Table 3). Few participants (76 of 1,815) required emergent clinic visits, with similar prevalence between groups: nonopioid (38 [4.18%]), opioid (38 [4.19%]). Emergent clinic visit reasons can be found in eTable 5 (available online at the end of this article); pain and bleeding were the most common specified causes for interim visits. Participants not taking opioids experienced fewer self-reported AEs (787 [86.8%] vs 825 [91.7%]; $P < .001$), including less fatigue and drowsiness, inability to concentrate, nausea, diarrhea, dizziness, vomiting, headache, and weight gain with lower severity (severity: mean difference, –0.06; 95% CI, –0.10 to –0.03). Severity of AEs reported in the electronic diary can be found in eTable 6 (available online at the end of this article). Participants not taking opioids experienced AEs with lower severity (severity score comparison: mean difference, –0.06; 95% CI, –0.10 to –0.03); fatigue and drowsiness, headache, and inability to concentrate were the most cited events.

Subgroup, missing data, and site analyses

Missing data analyses reached the same conclusions except for pain for the second day and night, which was found to be noninferior (eTable 7, available online at the end of this article). Participants not taking opioids reported less pain in all study sites (eFigure 1, available online at the end of this article). Although there were slight differences in satisfaction between sites, these differences were not statistically significant. The same conclusions regarding treatment effect were reached for male and female participants separately (eFigure 2, available online at the end of this article).

	NONOPIOID (n = 909)	OPIOID (n = 906)	COMPARISON	
Composite pain experienc rating[*] (primary outcome)	**Mean (95% CI)**	**Mean (95% CI)**	**Mean difference (98.75% CI)[†]**	***P* value[†]**
First day and night[‡] (day of surgery)	3.77 (3.58 to 3.96)	4.47 (4.28 to 4.65)	–0.70 (–0.94 to –0.45)[§]	< .001
Second day and night[¶]	3.20 (3.01 to 3.39)	3.48 (3.29 to 3.67)	–0.28 (–0.52 to –0.04)[§]	< .001
Third day and night[#]	2.97 (2.78 to 3.16)	3.06 (2.87 to 3.25)	–0.09 (–0.34 to 0.15)[**]	< .001
Entire postoperative period[††]	2.73 (2.54 to 2.92)	2.94 (2.74 to 3.13)	–0.20 (–0.45 to 0.05)[**]	< .001
Satisfaction with pain medication at postoperative visit[‡‡] (primary outcome)	**No. (%)**	**No. (%)**	**Odds ratio (95% CI)[§§]**	***P* value**
Very satisfied and satisfied	764 (85.3)	703 (78.9)	1.55 (1.21 to 1.98)	.006
Neither satisfied nor dissatisfied, dissatisfied, very dissatisfied	132 (14.7)	188 (21.1)		
Rescue medication	**No. (%)**	**No. (%)**	**Odds ratio (95% CI)[§§]**	***P* value**
Received rescue medication, no. (%)	26 (2.89)	54 (6.07)	–0.45 (0.28 to 0.73)	.001
Composite pain interference rating[¶¶]	**Mean (95% CI)**	**Mean (95% CI)**	**Mean difference (98.75% CI)[##]**	***P* value[##]**
First day (day of surgery)	2.75 (2.65 to 2.85)	3.11 (3.01 to 3.21)	–0.36 (–0.49 to –0.22)	< .001
Second day	2.27 (2.17 to 2.37)	2.50 (2.40 to 2.59)	–0.23 (–0.36 to –0.09)	< .001
Third day	2.20 (2.10 to 2.30)	2.34 (2.24 to 2.44)	–0.14 (–0.27 to –0.00)	.044
Entire postoperative period	2.09 (2.01 to 2.18)	2.21 (2.13 to 2.30)	–0.12 (–0.23 to –0.01)	.019
Overall quality of sleep[***]	**Mean (95% CI)**	**Mean (95% CI)**	**Mean difference (98.75% CI)[##]**	***P* value[##]**
First day (day of surgery)	4.28 (4.02 to 4.54)	4.62 (4.36 to 4.88)	–0.34 (–0.65 to –0.02)	.030
Second day	4.10 (3.84 to 4.35)	4.14 (3.88 to 4.40)	–0.04 (–0.36 to –0.27)	.999
Third day	3.78 (3.52 to 4.04)	3.82 (3.56 to 4.08)	–0.04 (–0.36 to 0.28)	.999
Entire postoperative period	3.69 (3.44 to 3.94)	3.62 (3.37 to 3.87)	0.07 (–0.23 to 0.37)	.999
Capsules returned[†††]	**No. (%)**	**No. (%)**	**Odds ratio (95% CI)[§§]**	***P* value**
Participants with investigational product remaining	680 (75.8)	714 (80.13)	0.78 (0.62 to 0.97)	.030
	Mean (95% CI)	**Mean (95% CI)**	**Mean difference (95% CI)[‡‡‡]**	***P* value[¶¶]**
Brown capsules returned (nonopioid = ibuprofen; opioid = hydrocodone), no.	7.23 (6.18 to 8.28)	8.55 (7.50 to 9.60)	–1.32 (–1.91 to –0.74)	< .001
Future opioid prescription	**No.[§§§] (%)**	**No.[§§§] (%)**	**Odds ratio (95% CI)[§§]**	***P* value**
Participants who had Prescription Drug Monitoring Program check	404 (44.6)	396 (43.9)	Not applicable	Not applicable
Participants with new opioid prescription within 6 mo	13 (3.33)	23 (5.81)	0.54 (0.27 to 1.08)	.082

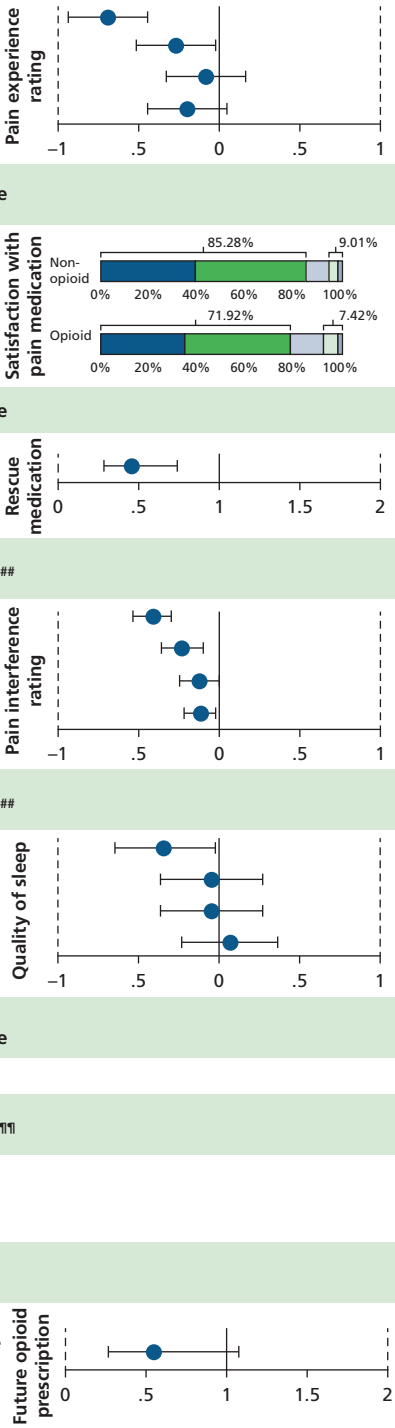

Figure 3. Primary and secondary outcomes. * Mean of participants' worst, average, least, and pain now using an 11-point numeric rating scale (from 0 [no pain]-10 [worst pain imaginable]). † Mixed-model analysis with random effects for site and person. The 98.75% CIs were constructed using the Bonferroni corrections to control the overall α at 5% (2-sided) for making comparisons at 4 different times. *P* values were reported on the basis of testing the 1-sided test: H_0: $(\mu_{NONOPIOID,t} - \mu_{OPIOID,t}) \geq d$ vs H_1: $(\mu_{NONOPIOID,t} - \mu_{OPIOID,t}) < d$, for t = first day and night, second day and night, third day and night, and the entire postoperative period, and d = 1 is the prespecified noninferiority margin, with the Bonferroni adjustment to control the overall α at 2.5% (1-sided). ‡ Mean of first day and night. § Superiority. ¶ Mean of second day and night. # Mean of third day and night. ** Noninferiority. †† Mean ratings from the day of surgery until the postoperative visit or on study day 8, whichever came first. ‡‡ 5-point Likert scale (1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5 = very dissatisfied). §§ Random-effects logistic regression with random effects for site. ¶¶ Mean of pain interference with enjoyment in life, ability to concentrate, recreational activities, day-to-day activities, tasks away from home, and socializing (range, 1-5; lower number is less pain interference, higher number is more pain interference). ## Mixed-model analysis with random effects for the site and

Table 3. Safety outcomes and AEs.*

VARIABLE	ALL (N = 1,815)	NONOPIOID (n = 909)	OPIOID (n = 906)	*P* VALUE†
Serious AEs,‡ No. (%)	3 (0.17)	1 (0.11)	2 (0.22)	NA§
Related to investigational product (possibly, probably, or definitely)	0 (0)	0 (0)	0 (0)	NA
Terminated from study due to serious AE	3 (0.17)	1 (0.11)	2 (0.22)	NA
AEs Resulting in Clinic Visit,¶ No. (%)				
AEs resulting in clinic visit	76 (4.19)	38 (4.18)	38 (4.19)	NA
AEs related to investigational product (possibly, probably, or definitely)	4 (5.26)	0 (0)	4 (10.53)	NA
Patients Ever Reporting an AE in Electronic Diary,# No. (%)	1612 (89.2)	787 (86.8)*	825 (91.7)*	< .001
Severity of all Occurrences for Those Reporting Any AE, ** **Mean (95% CI)**	1.29 (1.27 to 1.31)	1.26 (1.23 to 1.28)	1.32 (1.30 to 1.35)	< .001
AE, No. (%)				
Fatigue or drowsiness	1,210 (67.0)	558 (61.5)	652 (72.4)	< .001
Inability to concentrate	1,102 (61.0)	499 (55.0)	603 (67.0)	< .001
Nausea	732 (40.5)	307 (33.8)	425 (47.2)	< .001
Diarrhea	257 (14.2)	158 (17.4)	99 (11.0)	< .001
Constipation	396 (21.9)	183 (20.2)	213 (23.7)	.072
Dizziness	858 (47.5)	355 (39.1)	503 (55.9)	< .001
Skin rashes	87 (4.81)	44 (4.85)	43 (4.78)	.942
Stomachaches	549 (30.4)	261 (28.8)	288 (32.0)	.132
Heartburn	192 (10.6)††	100 (11.0)††	92 (10.2)††	–††
Vomiting	232 (12.8)	87 (9.59)	145 (16.1)	< .001
Euphoria	409 (22.6)	187 (20.6)	222 (24.7)	.039
Headache	1128 (62.4)	509 (56.1)	619 (68.8)	< .001
Itching	213 (11.8)††	88 (9.70)††	125 (13.9)††	NA††
Urinary retention	109 (6.03)	53 (5.84)	56 (6.22)	.735
Weight gain	59 (3.27)	38 (4.19)	21 (2.33)	.729
Other	180 (9.96)	87 (9.59)	93 (10.3)	.599

* AE: Adverse event. † *P* value is not adjusted for multiple comparisons, as these outcomes are measured at a single time point. ‡ Three participants experienced AEs (1 nonopioid vs 2 opioid); however, none of the AEs were attributed to study analgesics. One patient was hospitalized due to a spider bite, and 2 experienced considerable swelling due to infection. § NA: Not applicable. ¶ Few participants experienced AEs requiring an emergency or extra clinic visit. # AEs were also recorded in participant electronic diaries. Overall, fatigue or drowsiness, headache, and inability to concentrate were the most common AEs noted in the electronic diary entries. ** 4-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe); severity calculations based on AEs that were rated mild, moderate, or severe. †† The random-effects logistic regression model with an adjustment for site failed to converge. The frequencies and percentages are reported from a simple bivariate analysis.

DISCUSSION

Our study results showed that a combination of ibuprofen and acetaminophen is at least as good as the most frequently prescribed opioid for dental pain, with a high level of satisfaction among patients experiencing acute surgical pain after third-molar extraction surgery. When pain was most severe, during the first 48 hours after surgery, patients taking the ibuprofen and acetaminophen combination experienced less pain than patients taking hydrocodone and acetaminophen. Although differences between groups in pain ratings were less than 10% and, therefore, fell short of a meaningful clinical difference, which has been reported as 13%,[67] our finding of nonopioid superiority to opioids at times and noninferior at other times, support limiting the use of opioids after third-molar extraction. Subgroup analysis according to sex revealed

person. Bonferroni adjustment was applied to adjust for comparisons at 4 different times to control the overall α at 5% (2-sided). The 98.75% CI and *P* value reflect this adjustment in α. *** 11-point numeric rating scale (from 0 [excellent]-10 [very poor]). ††† Opioid capsules returned is a proxy for opioid tablets available for potential diversion or misuse if a patient does not destroy unused opioid tablets. ‡‡‡ Mixed-model analysis with random effects for site. *P* value is based on an α of .05. §§§ Number of participants residing in states (ie, Illinois and New Jersey) allowing a 6-month Prescription Drug Monitoring Program check.

no differences in treatment effect. Similarly, participants taking nonopioids reported higher levels of satisfaction, although the difference fell just short of clinical importance. We did not meet our predefined margins for clinical significance, the difference required for patients to notice a difference in pain management or satisfaction; however, our results are more than sufficient to limit the use of opioids, given their societal cost.

Besides better sleep for the first night and less pain interference over the postoperative period, participants taking nonopioids also experienced fewer adverse effects with less severity. Participants taking opioids were twice as likely to need rescue medication.

Analgesic dosage was driven by a number of factors, including overencapsulation size constraints that could compromise patient compliance, FDA daily maximum recommendations, American Dental Association recommendations, and results of analgesic efficacy studies. An ibuprofen dose of 400 mg was selected due to a pain relief profile similar to 600 mg and the ability to take additional doses if needed, while not exceeding FDA maximum recommended daily dosages. A hydrocodone dose of 5 mg with 300 mg of acetaminophen was selected as it is the most commonly prescribed dose and minimizes the potential for AEs in higher doses.

Although the first dose was required, subsequent doses were prescribed as needed for pain. Essentially, all of our participants were compliant with the first dose, eliminating the need for a per-protocol analysis, as is typical in a noninferiority randomized controlled trial. Participants were allowed to replace study analgesic with over-the-counter ibuprofen at any time, potentially reducing the magnitude of the difference between groups. Even so, this bias would only underestimate the difference between groups.

Professional organizations and government agencies have issued recommendations that are based on evidence they rated as low certainty.[71-73] We now provide support for these recommendations. Other than the use of randomization and blinding, our quasi-pragmatic trial is the first, to our knowledge, large-scale comparative effectiveness study in which surgeons were not limited by surgical protocols and participants had the discretion to use analgesics as needed for pain. Given the millions of unnecessary opioids dispensed every year and the associated addictive risk of opioids, we recommend the nonopioid combination as the standard of care for this patient population, thereby minimizing the number of opioids in circulation.

Study strengths

Together, our diverse patient population, quasi-pragmatic design, large sample size (n = 1,815), and multistudy sites with a high completion rate (98.6%) make our findings generalizable to the US population. Results of our subgroup analyses showed that male and female participants had similar findings related to the effect of the study analgesics. Using analgesics and dosages commonly used in practice makes our results practical and easily implemented. Surgical techniques, anesthesia, and concomitant medications were not dictated and varied according to site, providing more robust conclusions. Participants were also able to take their analgesics as needed for pain, providing closer approximation to how patients often take pain management analgesics.

We modeled our primary pain outcome measure after the pain severity domain of the Brief Pain Inventory,[57] which is a validated pain measure used commonly in pain studies. This domain consisted of a composite pain rating, which included worst pain, average pain, least pain, and pain now. As the Opioid Analgesic Reduction Study required participants to report their pain experience over 12-hour periods, we believe that the composite pain measure is a more robust measure that takes into account that pain experience varies over time.

We believe that the noninferiority design was a strength. In superiority studies, if an analgesic does not turn out to be superior, no other conclusions can be drawn. A benefit of the noninferiority design is if noninferiority is established, superiority can also be assessed. In this case, we found superiority early in the postoperative period and noninferiority later in the postoperative period. From a public health perspective, determining at least noninferiority of the nonopioid means that opioids do not provide added benefits and should not be routinely prescribed.

Limitations

Ethical considerations resulted in the exclusion of people with personal or familial history of addiction or substance abuse, potentially reducing generalizability. As the purpose of our study was to examine the comparative effectiveness of the nonopioid combination with opioids, use of long-lasting local

anesthetics would mask the treatment effect. As we did not restrict participants to a prescribed dosing schedule, we observed differences in the number of pills taken; this requires more detailed analyses to address the affect of the treatment effect, which is beyond the scope of this article. Although fixed-interval dosing would have resulted in a more direct comparison, as-needed dosing was used to minimize the potential for future addiction. We required twice daily diary entries at prespecified times to mitigate inaccurate recollection of pain levels and medication use, which may wane over time.

CONCLUSIONS

The opioid crisis, with an estimated 81,000 deaths per year,[74] continues to be fueled by unnecessary use of opioids to manage postsurgical pain. Finding effective analgesic alternatives to opioids is needed to quell the surge in opioid-related addiction and death. The belief that opioid analgesics are more effective than nonopioid alternatives influences patient requests for opioids and surgeon prescribing.[75] Despite evidence to support the use of nonopioid alternatives, opioids are often prescribed by surgeons to preemptively address concerns about uncontrolled pain during the overnight and weekend hours when surgeons or follow-up care may not be readily available. Across all patient outcomes, the Opioid Analgesic Reduction Study provides evidence that the combination of ibuprofen and acetaminophen should be the analgesic of choice for acute pain after impacted third-molar extraction surgery. ■

DISCLOSURE

Dr. Desjardins is the chief executive officer, Desjardins & Associates, and a clinincal consultant for Haleon, Antibe Therapeutics, Senju USA, Bayer Consumer Health, and Taiwan Liposome Corp. None of the other authors reported any disclosures.

SUPPLEMENTAL DATA

Supplemental data related to this article can be found at: https://doi.org/10.1016/j.adaj.2024.10.014

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APPENDIX: SUPPLEMENTAL METHODS

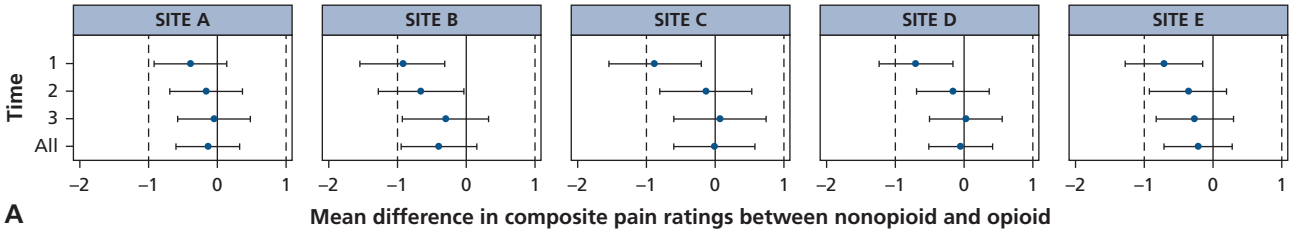
Study halting rules and reasons for participant withdrawal

Halting Rules

Should there be a fatality due to the study analgesic or should there be 2 hospital admissions for the same serious adverse event, the study will be halted for a safety review.

Participant Withdrawal by Study Protocol

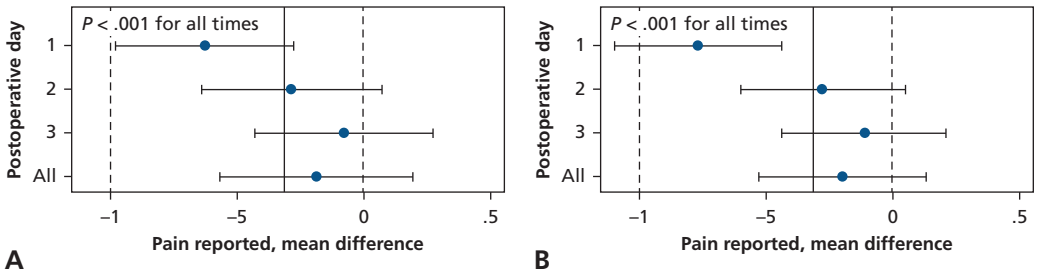
There were no predefined reasons for withdrawal. No participants were withdrawn from the study by the investigators, other than participants experiencing a serious adverse event. They were removed from data analysis.



B

	SITE A		SITE B		SITE C		SITE D		SITE E	
	Nonopioid	Opioid	Nonopioid	Opioid	Nonopioid	Opioid	Nonpioid	Opioid	Nonpioid	Opioid
Overall Satisfaction With Pain Medication at Time of Post Operative Visit	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Very satisfied	67 (31.2)	62 (29.4)	61 (40.1)	54 (35.1)	57 (42.5)	40 (30.8)	88 (42.5)	82 (38.5)	82 (43.4)	70 (38.0)
Satisfied	114 (53.0)	93 (44.1)	70 (46.1)	64 (41.6)	59 (44.0)	61 (46.9)	89 (43.0)	90 (42.3)	78 (41.3)	88 (47.8)
Neither satisfied nor dissatisfied	22 (10.2)	38 (18.0)	18 (11.8)	25 (16.2)	11 (8.2)	24 (18.5)	16 (7.73)	23 (10.8)	20 (10.6)	12 (6.5)
Dissatisfied	9 (4.2)	15 (7.1)	2 (1.32)	8 (5.19)	6 (4.5)	4 (3.1)	9 (4.35)	14 (6.57)	7 (3.7)	13 (7.1)
Very dissatisfied	3 (1.4)	3 (1.4)	1 (0.7)	3 (1.95)	1 (0.8)	1 (0.8)	5 (2.42)	4 (1.9)	2 (1.1)	1 (0.5)

eFigure 1. Study site analysis of composite pain experience rating. **A.** Difference in composite pain experience: nonopioid vs opioid (98.75% CI). Site differences were assessed using mixed-model analysis with treatment, day, and site as well as their 2-way and 3-way interactions as fixed effects and participant as a random effect. Most sites found lower pain in participants not taking opioids on the first day/night (time 1), and the difference in nonopioid vs opioid did not vary much among sites (3-way interaction of treatment by day by site assessment, the type III F test: $F(24, 2.10E+04) = 1.84$ and $P = .065$). **B.** Overall participant satisfaction with pain medication (nonopioid vs opioid). Site differences were assessed using generalized or multinomial logistic regression analysis with site as fixed effect. The model included treatment, site, and treatment by site interaction as independent variables (all fixed effects). Distribution of the participant satisfaction with pain medication was similar across sites (treatment by site interaction in the type III Wald test: $\chi^2_{16} = 15.31$, $P = .50$).



eFigure 2. Subgroup analysis according to sex: female (**A**) and male (**B**). Difference in composition pain experience according to sex: nonopioid vs opioid (98.75% CI). P values were reported on the basis of testing the 1-sided test: H_0: (mean $[\mu]_{NONOPIOID,\ t}$-$\mu_{OPIOID,\ t}$) $\geq$ d vs H_1: ($\mu_{NONOPIOID,\ t}$-$\mu_{OPIOID,\ t}$) $<$ d, for t = first day and night, second day and night, third day and night, and the entire postoperative period, and d = 1 is the prespecified noninferiority margin, after the Bonferroni adjustment to control for the overall α at 1.25% (1-sided) for men and women respectively.

eTable 1. Inclusion and exclusion criteria.

CHARACTERISTIC	INCLUSION	EXCLUSION
Demographic		
Age	≥ 18 y	< 18 y
Health Conditions	Planning to undergo extraction of ≥ 1 partial or fully impacted mandibular third molars In good general health as evidenced by medical history	Patients who self-report the following were excluded: History of gastrointestinal bleeding or peptic ulcer History of kidney disease (excluding kidney stones) History of hepatic disease History of cardiovascular disease (myocardial infarction or stroke with the past 6 mo) History of bleeding disorder History of respiratory depression Any prior respiratory effect of an opioid or other anesthetic drugs that required respiratory support postoperatively Active or untreated asthma History of known allergic reaction to ibuprofen, acetaminophen, hydrocodone, or anesthesia Currently taking any of the following medications: CYP3A4 inhibitor, such as macrolide antibiotics (eg, erythromycin), azole-antifungal agents (eg, ketoconazole), and protease inhibitors (eg, ritonavir), which may increase plasma concentrations of hydrocodone bitartrate and acetaminophen and prolong opioid adverse reactions, and which may cause potentially fatal respiratory depression Central nervous system depressants (including benzodiazepines) Consumes 3 or more alcoholic drinks every day or has a history of alcoholism History of drug or alcohol abuse (excludes marijuana use) Family history of drug or alcohol abuse in a first-degree relative Patients who are currently pregnant or lactating Patients who have had more than 1 opioid prescription filled within the past 12 mo according to Prescription Drug Monitoring Program check
Other Criteria		
Cognitive ability	Able to understand the informed consent Provide signed and dated informed consent form	Inability or refusal to provide informed consent
Language	Able to understand all directions for data gathering instruments in English	Not able to understand directions and data gathering instruments in English
Compliance	Willing and able to comply with all study procedures, including having a smartphone, and available for the duration of the study	Unwilling to comply with all study procedures
If female	Willing to undergo pregnancy test Agree to use contraception while participating in the study	Positive pregnancy test or lactating
Other	NA	Prior participation in this study

eTable 2. Description of Opioid Analgesic Reduction Study data items and timing.*

MEASURE	DESCRIPTION†	POSTOPERATIVE DAY‡														POSTOPERATIVE VISIT	AE§ REPORT
		1		2		3		4		5		6		7			
		Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night		
Pain																	
Average pain	11-point NRS¶ (0-10)	NA#	•	•	•	•	•	•	•	•	•	•	•	•	•	NA	NA
Worst pain	11-point NRS (0-10)	NA	•	•	•	•	•	•	•	•	•	•	•	•	•	NA	NA
Least pain	11-point NRS (0-10)	NA	•	•	•	•	•	•	•	•	•	•	•	•	•	NA	NA
Pain now	11-point NRS (0-10)	NA	•	•	•	•	•	•	•	•	•	•	•	•	•	NA	NA
Composite pain rating	Mean of 4 pain measures above, 11-point NRS (0-10)	NA	√	√	√	√	√	√	•	•	•	•	•	•	•	NA	NA
Satisfaction																	
Overall, how satisfied with pain medication	5-point Likert scale 1-5**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	√	NA
Time for pain medication to work	5-point Likert scale 1-5**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Amount of pain relief by pain medication	5-point Likert scale 1-5**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Duration of pain relief provided by pain medication	5-point Likert scale 1-5**	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Overall, pain relief meet expectations	5-point Likert scale 1-5††	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Could pain medication have been more effective?	5-point Likert scale 1-5‡‡	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Rescue																	
Need for rescue	0 = no, 1 = yes	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	•
Pain Interference																	
Pain interference with enjoyment of life	5-point Likert scale 1-5§§	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA
Pain interference with ability to concentrate	5-point Likert scale 1-5§§	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA
Pain interference with enjoyment with recreational activities	5-point Likert scale 1-5§§	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA
Pain interference with day-to-day activities	5-point Likert scale 1-5§§	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA

* Outcome measures collected as part of the Opioid Analgesic Reduction Study protocol and the timing of data collection are listed. † The description includes the range of valid responses and definition of values, when appropriate. For all variables shown, lower values favor nonopioid. ‡ Each variable has been identified as either primary (√) or secondary (•) outcome, per the data collection time point. § AE: Adverse event. ¶ NRS: Numeric rating scale (0 [no pain] through 10 [worst possible pain]). # NA: Not applicable. ** 1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5 = very dissatisfied. †† 1 = Generally exceeds my expectation, 2 = somewhat exceeds my expectations, 3 = meets my expectations, 4 = does not quite meet my expectations, 5 = does not meet my expectations at all. ‡‡ 1 = Definitely, 2 = probably yes, 3 = I don't know, 4 = probably not, 5 = definitely not. §§ 1 = Not at all, 2 = a little bit, 3 = somewhat, 4 = quite a bit, 5 = very much. ¶¶ 0 = Best possible sleep, 10 = worst possible sleep. ## SAE: Serious adverse event. *** IP: Investigational product.

eTable 2. Continued

MEASURE	DESCRIPTION[†]	POSTOPERATIVE DAY[‡]														POSTOPERATIVE VISIT	AE[§] REPORT
		1		2		3		4		5		6		7			
		Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night		
Pain interference with tasks away from home	5-point Likert scale 1-5[§§]	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA
Pain keeping you from socializing	5-point Likert scale 1-5[§§]	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA
Composite pain interference score	Mean of the 6 pain interference measures above. Ratings 1-5 (lower number indicates less pain interference).	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA
Sleep Quality																	
Overall quality of sleep	11-point NRS 0-10[¶¶]	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	•	NA
Last night trouble falling asleep	0 = no, 1 = yes	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	•	NA
Last night were you awakened by pain during the night?	0 = no, 1 = yes	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	•	NA
Were you awakened by pain this morning?	0 = no, 1 = yes	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	NA	•	•	NA
Investigational Analgesic Use, Drug Diversion Opportunity, and Future Opioid Prescription Filled																	
Brown capsules returned, no.	Brown (nonopioid = ibuprofen, opioid = hydrocodone) capsules remaining, no.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Participants with a new opioid prescription within 6 mo	No. of participants with new opioid prescription within 6 mo	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•	NA
Safety Measures																	
SAEs[,## no.]	Participants hospitalized, no.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•
SAEs related to IP[***]	SAEs possibly, probably, or definitely related to IP, no.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•
Terminated from study due to SAE due to IP, no.	Participants with SAE terminated from study, no.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•
AEs resulting in clinic visit, no.	Participants with unexpected hospital emergency department or oral and maxillofacial surgery clinic visit, no.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•
AEs related to IP	AEs possibly, probably or definitely related to IP, no.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	•

eTable 2. Continued

MEASURE	DESCRIPTION[†]	POSTOPERATIVE DAY[‡]														POSTOP-ERATIVE VISIT	AE[§] REPORT
		1		2		3		4		5		6		7			
		Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night	Day	Night		
Mean rate of AE occurrence across all electronic diaries completed	AEs recorded in electronic diary per participant/total no. of electronic diaries, no.	NA	•	•	•	•	•	•	•	•	•	•	•	•	•	•	NA
Severity of AEs of those reporting any AE (in electronic diary)	Average severity of all AEs in electronic diary 1-3 (1 = mild, 2 = moderate, 3 = severe)	NA	•	•	•	•	•	•	•	•	•	•	•	•	•	•	NA

eTable 3. Cronbach α of pain and pain interference composite scores.

VARIABLE	CRONBACH α	MORNING ELECTRONIC DIARY AFTER SURGERY	CRONBACH α
Composite Pain Experience Rating*			
Evening electronic diary after surgery			
First	0.91	First	0.95
Second	0.95	Second	0.95
Third	0.95	Third	0.95
Fourth	0.95	Fourth	0.95
Fifth	0.95	Fifth	0.96
Sixth	0.96	Sixth	0.96
Seventh	0.96	Seventh	0.96
Composite Pain Interference Rating†			
Evening electronic diary after surgery			
First	0.94	NA‡	NA
Second	0.95	NA	NA
Third	0.96	NA	NA
Fourth	0.96	NA	NA
Fifth	0.97	NA	NA
Sixth	0.97	NA	NA
Seventh	0.97	NA	NA

* Mean of 4 items: pain (worst, average, least, and now), each used the numeric rating scale (0 = no pain, 10 = worst pain imaginable). † Items of pain interference: pain interference with enjoyment of life, ability to concentrate, enjoyment with recreational activities, day to day activities, tasks away from home, and pain keeping you from socializing, each used a 5-point Likert scale (1 = not at all, 2 = a little bit, 3 = somewhat, 4 = quite a bit, 5 = very much). ‡ NA: Not applicable.

eTable 4. Enrollment according to site.

VARIABLE	SITE, NO. (%)					TOTAL, NO. (%)
	A	B	C	D	E	
Screened for Eligibility and Consent Initiated						
Screened and consent initiated	473 (22.5)	324 (15.4)	285 (13.6)	514 (24.5)	506 (24.1)	2,102 (100)
Total Enrollment						
Enrollment	431 (23.7)	310 (17.1)	266 (14.7)	430 (23.7)	378 (20.8)	1,815 (100)
Enrollment According to Sex						
Female	222 (51.1)	162 (52.3)	114 (42.9)	215 (50.0)	197 (52.1)	910 (50.1)
Male	209 (48.9)	148 (47.7)	152 (57.1)	215 (50.0)	181 (47.9)	905 (49.9)
Enrollment According to Treatment Arm						
Nonopioid	217 (50.3)	153 (49.4)	136 (51.1)	212 (49.3)	191 (50.5)	909 (50.1)
Opioid	214 (49.7)	157 (50.6)	130 (48.9)	218 (50.7)	187 (49.5)	906 (49.9)
Enrollment According to Treatment and Sex						
Nonopioid, female	111 (25.8)	81 (26.1)	58 (21.8)	107 (28.3)	100 (23.3)	457 (25.2)
Nonopioid, male	106 (24.6)	72 (23.2)	78 (29.3)	105 (27.8)	91 (21.2)	452 (24.9)
Opioid, female	111 (25.8)	81 (26.1)	56 (21.1)	108 (28.6)	97 (22.6)	453 (25.0)
Opioid, male	103 (23.9)	76 (24.5)	74 (27.8)	110 (29.1)	90 (20.9)	453 (25.0)

eTable 5. Safety outcomes.

VARIABLE	NONOPIOID (n = 909)	OPIOID (n = 906)
Adverse Events Requiring Clinic Visit		
Severity of adverse events,* mean (95% CI)	1.38 (1.11 to 1.66)	1.66 (1.38 to 1.93)
Related to surgical procedure (possible, probable, definite), no. (%)	34 (89.5)	33 (86.8)
Related to investigational product (possible, probable, definite), no. (%)	0 (0)	4 (10.5)
Patients with Specific Adverse Events Requiring Clinic Visit, No. (%)		
Pain	25 (2.8)	27 (3)
Other	20 (2.2)	14 (1.5)
Bleeding	5 (0.6)	5 (0.6)
Headache	3 (0.3)	1 (0.1)
Nausea	1 (0.1)	1 (0.1)
Diarrhea	1 (0.1)	0 (0)
Constipation	1 (0.1)	0 (0)
Dizziness	1 (0.1)	0 (0)
Vomiting	1 (0.1)	1 (0.1)
Fatigue or drowsiness	0 (0)	0 (0)
Inability to concentrate	0 (0)	0 (0)
Skin rashes	0 (0)	2 (0.2)
Stomachaches	0 (0)	0 (0)
Heartburn	0 (0)	0 (0)
Euphoria	0 (0)	0 (0)
Itching	0 (0)	0 (0)
Urinary retention	0 (0)	0 (0)
Weight gain	0 (0)	0 (0)

* 3-point Likert scale (1 = mild, 2 = moderate, 3 = severe).

eTable 6. Severity of AEs* reported by participants indicating an AE.†

AE	NONOPIOID (n = 909)		OPIOID (n = 906)		COMPARISON	
	No.‡	Mean (95% CI)	No.‡	Mean (95% CI)	Mean (95% CI)	*P* Value§
Fatigue or Drowsiness	558	1.33 (1.29 to 1.37)	652	1.41 (1.37 to 1.44)	–0.08 (–0.13 to –0.03)	.003
Headache	509	1.30 (1.26 to 1.33)	619	1.33 (1.30 to 1.37)	–0.04 (–0.09 to 0.01)	.149
Inability to Concentrate	499	1.24 (1.20 to 1.28)	603	1.36 (1.32 to 1.40)	–0.12 (–0.17 to –0.06)	< .001
Dizziness	355	1.22 (1.17 to 1.26)	503	1.29 (1.25 to 1.33)	–0.08 (–0.14 to –0.02)	.011
Nausea	307	1.25 (1.20 to 1.31)	425	1.40 (1.35 to 1.44)	–0.15 (–0.22 to –0.08)	< .001
Stomachaches	261	1.20 (1.15 to 1.25)	288	1.22 (1.18 to 1.27)	–0.03 (–0.10 to 0.04)	.422
Euphoria	187	1.20 (1.12 to 1.27)	222	1.26 (1.19 to 1.34)	–0.07 (–0.15 to 0.02)	.127
Constipation	183	1.23 (1.17 to 1.30)	213	1.29 (1.22 to 1.35)	–0.05 (–0.14 to 0.03)	.217
Diarrhea	158	1.25 (1.17 to 1.32)	99	1.21 (1.11 to 1.30)	0.04 (–0.07 to 0.15)	.449
Heartburn	100	1.14 (1.06 to 1.23)	92	1.23 (1.14 to 1.32)	–0.09 (–0.21 to 0.03)	.137
Itching	88	1.14 (1.06 to 1.23)	125	1.22 (1.15 to 1.29)	–0.08 (–0.19 to 0.03)	.165
Vomiting	87	1.48 (1.33 to 1.64)	145	1.70 (1.58 to 1.82)	–0.22 (–0.41 to –0.03)	.023
Other	87	1.55 (1.39 to 1.70)	93	1.71 (1.55 to 1.86)	–0.16 (–0.36 to 0.04)	.116
Urinary Retention	53	1.22 (1.11 to 1.34)	56	1.23 (1.12 to 1.34)	–0.01 (–0.17 to 0.15)	.917
Skin Rashes	44	1.20 (1.05 to 1.34)	43	1.32 (1.18 to 1.47)	–0.12 (–0.33 to 0.08)	.241
Weight Gain	38	1.23 (1.07 to 1.38)	21	1.21 (1.01 to 1.42)	0.01 (–0.25 to 0.27)	.929
All	787	1.26 (1.23 to 1.28)	825	1.32 (1.30 to 1.35)	–0.06 (–0.10 to –0.03)	< .001

* AE: Adverse event. † 3-point Likert scale (1 = mild, 2 = moderate, 3 = severe) among those reporting an adverse event in their electronic diary. ‡ No. of participants ever reporting specific AEs in the electronic diaries during the postoperative period. § Mixed-model linear regression analysis with random effect for site. *P* value is based on an α of .05.

eTable 7. Missing data analysis.

VARIABLE	NONOPIOID (n = 909)	OPIOID (n = 906)	COMPARISON, NONOPIOID VS OPIOID		
			Mean Difference (98.75% CI)*	Odds Ratio (95% CI)	*P* Value
Multiple Imputation Approach†					
Composite pain experience rating‡					
First day and night (day of surgery)§	3.70 (3.45 to 3.45)	4.42 (4.18 to 4.18)	–0.73 (–1.07 to –0.39)¶	NA#	NA
Second day and night**	3.10 (2.85 to 2.85)	3.37 (3.12 to 3.12)	–0.27 (–0.61 to 0.07)††	NA	NA
Third day and night‡‡	2.90 (2.66 to 2.66)	3.02 (2.78 to 2.78)	–0.12 (–0.46 to 0.22)††	NA	NA
Entire postoperative period§§	2.90 (2.67 to 2.67)	3.05 (2.83 to 2.83)	–0.15 (–0.46 to 0.15)††	NA	NA
Overall satisfaction with pain medication at postoperative visit, no. (%)					
Very satisfied	359.4 (39.5)	312.4 (34.5)	NA	NA	NA
Satisfied	415.8 (45.7)	401.7 (44.3)	NA	NA	NA
Neither satisfied nor dissatisfied	88.4 (9.7)	124.5 (13.7)	NA	NA	NA
Dissatisfied	33.3 (3.7)	54.8 (6.0)	NA	NA	NA
Very dissatisfied	12.1 (1.3)	12.6 (1.4)	NA	NA	NA
Very satisfied or satisfied¶¶	775.2 (85.3)	714.1 (78.8)	NA	1.58 (1.22 to 2.05)	.001
Multiple Imputation With Pattern-Mixture Models: Control-Based Pattern Imputation##					
Composite pain experience rating‡					
First day and night (day of surgery)§	3.74 (3.55 to 3.93)	4.43 (4.24 to 4.62)	–0.69 (–0.92 to –0.46)¶	NA	NA
Second day and night**	3.20 (3.01 to 3.39)	3.43 (3.24 to 3.62)	–0.23 (–0.46 to –0.00)††	NA	NA
Third day and night‡‡	2.96 (2.77 to 3.15)	3.03 (2.84 to 3.22)	–0.07 (–0.30 to 0.16)††	NA	NA
Entire postoperative period§§	3.74 (3.55 to 3.93)	4.43 (4.24 to 4.62)	–0.69 (–0.92 to –0.46)††	NA	NA
Overall satisfaction with pain medication at postoperative visit, no. (%)					
Very satisfied	358.2 (39.4)	311.3 (34.4)	NA	NA	NA
Satisfied	416.4 (45.8)	402.7 (44.4)	NA	NA	NA
Neither satisfied nor dissatisfied	88.6 (9.7)	123.9 (13.7)	NA	NA	NA
Dissatisfied	33.8 (3.7)	55.4 (6.1)	NA	NA	NA
Very dissatisfied	12.0 (1.3)	12.7 (1.4)	NA	NA	NA
Very satisfied or satisfied¶¶	774.6 (85.2)	714.0 (78.8)	NA	1.57 (1.21 to 2.04)	.002

* Bonferroni adjustment was applied to adjust for comparisons at 4 different time points to control the overall α at 5% (2-sided). The 98.75% CI for the mean difference reflects this adjustment. † Ten imputed data sets were generated using IVEware (Survey Research Center, University of Michigan), assuming missing at random. Mixed-model analysis for pain and random-effect logistic regression analysis for satisfaction were performed on each imputed data set and combined using Rubin's rule via MIANALYZE Procedure in SAS, Version 9.4 (SAS Institute). ‡ Mean of ratings for 4 items (ie, worst, average, least, and now) asking participants to rate on an 11-point numeric rating scale (0 = no pain through 10 = worst pain imaginable). § Mean of first day and night. ¶ Superiority. # NA: Not applicable or not calculated. ** Mean of second day and night. †† Noninferiority. ‡‡ Mean of third day and night. §§ Mean ratings from the day of surgery until the postoperative visit or on study day 8, whichever came first. ¶¶ Dichotomous variable when satisfied = very satisfied and satisfied and the alternative is a combination of neither satisfied nor dissatisfied, dissatisfied, and very dissatisfied. ## Ten imputed data sets were generated using the control (opioid group)-based imputation via PROC MI with the specification of MNAR (missing not at random) and full conditional specification options. Mixed-model analysis for pain and random-effect logistic regression analysis for satisfaction were performed on each imputed data set and combined using Rubin's rule via MIANALYZE procedure in SAS, Version 9.4.

eBox. Data sharing statement.

QUESTION	RESPONSE
Will Individual Participant Data Be Available (Including Data Dictionaries)?	Yes
What Data Will Be Shared?	Participant data collected during the trial after deidentification (ie, preoperative survey, surgical procedure, electronic diary entries, postoperative survey, actigraph, and electronic bottle dosing)
What Other Documents Will Be Available?	Study protocol including statistical analysis plan, informed consent form
When Will Data Be Available?	January 1, 2025-December 30, 2030
Who Can Request Data?	Any researcher who provides a research analysis plan
For What Types of Analyses Can Data Be Requested?	Research aims to improve patient care
How Will Data Be Made Available?	Proposals should be directed to Cecile A. Feldman, DMD, at feldman@rutgers.edu. To gain access, data requestors will need to sign a data access agreement with Rutgers University