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Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort

A Randomized Clinical Trial

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Key Points

Question

What is the effect of perioperative gabapentin on remote pain resolution and opioid cessation after surgery?

Findings

In this randomized clinical trial of 422 patients undergoing a variety of operations, no significant difference was found in time to pain cessation between patients receiving 72 hours of perioperative gabapentin compared with placebo. However, perioperative gabapentin had a significant effect on promoting opioid cessation after surgery.

Meaning

Seventy-two hours of perioperative gabapentin use may promote opioid cessation after surgery and decrease the duration of postoperative opioid use.

Abstract

Importance

Guidelines recommend using gabapentin to decrease postoperative pain and opioid use, but significant variation exists in clinical practice.

Objective

To determine the effect of perioperative gabapentin on remote postoperative time to pain resolution and opioid cessation.

Design, Setting, and Participants

A randomized, double-blind, placebo-controlled trial of perioperative gabapentin was conducted at a single-center, tertiary referral teaching hospital. A total of 1805 patients aged 18 to 75 years scheduled for surgery (thoracotomy, video-assisted thoracoscopic surgery, total hip replacement, total knee replacement, mastectomy, breast lumpectomy, hand surgery, carpal tunnel surgery, knee arthroscopy, shoulder arthroplasty, and shoulder arthroscopy) were screened. Participants were enrolled from May 25, 2010, to July 25, 2014, and followed up for 2 years postoperatively. Intention-to-treat analysis was used in evaluation of the findings.

Interventions

Gabapentin, 1200 mg, preoperatively and 600 mg, 3 times a day postoperatively or active placebo (lorazepam, 0.5 mg) preoperatively followed by inactive placebo postoperatively for 72 hours.

Main Outcomes and Measures

Primary outcome was time to pain resolution (5 consecutive reports of 0 of 10 possible levels of average pain at the surgical site on the numeric rating scale of pain). Secondary outcomes were time to opioid cessation (5 consecutive reports of no opioid use) and the proportion of participants with continued pain or opioid use at 6 months and 1 year.

Results

Of 1805 patients screened for enrollment, 1383 were excluded, including 926 who did not meet inclusion criteria and 273 who declined to participate. Overall, 8% of patients randomized were lost to follow-up. A total of 202 patients were randomized to active placebo and 208 patients were randomized to gabapentin in the intention-to-treat analysis (mean [SD] age, 56.7 [11.7] years; 256 (62.4%) women and 154 (37.6%) men). Baseline characteristics of the groups were similar. Perioperative gabapentin did not affect time to pain cessation (hazard ratio [HR], 1.04; 95% CI, 0.82-1.33; $P = .73$) in the intention-to-treat analysis. However, participants receiving gabapentin had a 24% increase in the rate of opioid cessation after surgery (HR, 1.24; 95% CI, 1.00-1.54; $P = .05$). No significant differences were noted in the number of adverse events as well as the rate of medication discontinuation due to sedation or dizziness (placebo, 42 of 202 [20.8%]; gabapentin, 52 of 208 [25.0%]).

Conclusions and Relevance

Perioperative administration of gabapentin had no effect on postoperative pain resolution, but it had a modest effect on promoting opioid cessation after surgery. The routine use of perioperative gabapentin may be warranted to promote opioid cessation and prevent chronic opioid use. Optimal dosing and timing of perioperative gabapentin in the context of specific operations to decrease opioid use should be addressed in further research.

Trial Registration

clinicaltrials.gov Identifier: NCT01067144

Introduction

Over 51 million Americans undergo surgery annually, and the majority are prescribed opioids for pain management. Up to 13% of patients initiate chronic opioid use after surgery. Most patients undergoing surgery require opioids regardless of prior opioid-related adverse events, and patients receiving opioids prior to surgery require higher doses over extended periods, compounding the risks of chronic opioid use, misuse, addiction, and overdose.

Medicine is facing the challenge of adequately managing pain while limiting opioid consumption. One approach is the concomitant use of nonopioid adjuvants for pain relief. Gabapentin is a ligand of the α2δ subunit of voltage-dependent calcium channels attenuating calcium channel influx, thereby decreasing excitatory transmitter release and spinal sensitization. Gabapentin may also activate the descending noradrenergic pain inhibitory system and decrease microglial activation as well as the expression of proinflammatory cytokines.

Perioperative gabapentin may reduce the incidence and intensity of postoperative pain up to 6 months after otolaryngology, orthopedic, mastectomy, and abdominal/pelvic operations. Professional guidelines advocate for perioperative administration of gabapentin as a component of multimodal analgesia, but its efficacy in the context of multimodal analgesia has been mixed, and usual care varies across operations and hospitals nationwide. Conclusions regarding gabapentin's effect on chronic postsurgical pain have been limited by studies with small sample sizes, limited postoperative follow-up, patient attrition, diverse surgical cohorts, and variable dosing regimens.

Given evidence of reduced opioid requirements, professional societies recommend the use of gabapentin for optimal acute pain mangement. However, a recent meta-analysis found a negligible reduction of 24-hour morphine consumption. These findings were limited by low-quality evidence due to small study sizes and inconsistency highlighting the need for fully powered randomized clinical trials.

Our goal was to examine remote postoperative pain and opioid use with extended follow-up accounting for the natural waxing and waning course of pain and opioid use rather than arbitrarily defining end points of acute, subacute, or chronic pain. Furthermore, prior work emphasizes that the determinants of postoperative pain resolution and opioid cessation are distinct, necessitating separate analysis of gabapentin's efficacy on these outcomes. The primary objective of this trial was to investigate, among adults aged 18 to 75 years undergoing surgery, whether 10 doses of perioperative gabapentin over 72 hours compared with placebo increased the rate of pain cessation after surgery in a double-blind randomized clinical trial with up to 2 years of longitudinal follow-up. To determine the effect of perioperative gabapentin on postoperative opioid use, our prespecified secondary outcome was the rate of opioid cessation after surgery.

Methods

Patients

Patients were recruited from a single US academic medical center. All English-speaking patients aged 18 to 75 years scheduled for an eligible surgery (thoracotomy, video-assisted thoracoscopic surgery, primary or revision total hip replacement, primary or revision total knee replacement, unilateral or bilateral mastectomy, and breast lumpectomy with or without sentinel node biopsy or axillary node dissection) were screened. Owing to gradual recruitment, the following operations were added to the protocol mid-study: hand surgery, carpal tunnel surgery, knee arthroscopy, shoulder arthroplasty, and shoulder arthroscopy.

Exclusion criteria were known kidney disease, current gabapentin or pregabalin use, cognitive impairment, history of excessive sedation or adverse reaction to gabapentin, coexisting chronic pain (severity level of

>4 of 10 on a numeric rating scale of pain score anywhere, with 10 the most severe level, excluding the future surgical site), conditions precluding postoperative follow-up, suicidality assessed by the Beck Depression Inventory-II (scale range, 0-63, with 0-13 indicating minimal depression; 14-19, mild depression; 20-28 moderate depression; and 29-63, severe depression), pregnancy, ataxia, dizziness, sedation, narrow-angle glaucoma, severe respiratory insufficiency, history of gastric bypass surgery, and obstructive sleep apnea requiring a continuous positive airway pressure device.

The Stanford Accelerated Recovery Trial (START) was sponsored by the National Institute on Drug Abuse and the Stanford Department of Anesthesiology. The full trial protocol is available in Supplement 1. The study was approved by the Stanford University Institutional Review Board. All patients provided written informed consent; there was no financial compensation.

Study Design and Treatment

Patients were randomized 2 weeks before surgery using blocked, stratified randomization by surgery and surgeon to 1 of 2 treatment groups after study enrollment by research staff. The randomization list was computer-generated with corresponding randomization log sheets provided to the operating room pharmacy. One log sheet was generated per combination of surgeon/surgery. The pharmacist documented the patient's information on a randomization card that was placed in a sealed envelope indicating which medication was prescribed. Participants, clinicians, and researchers were blinded to allocation until completion of statistical analyses.

The placebo group received 1 capsule of active placebo (lorazepam, 0.5 mg) and 3 capsules of inactive placebo preoperatively, followed by 2 capsules of inactive placebo 3 times a day starting on postoperative day 1 and continued for 72 hours (10 total doses). Lorazepam was chosen as the active placebo to match the sedating effects of preoperative gabapentin. Postoperatively, active placebo was considered unnecessary since most patients received other analgesic medications. The treatment group received 4 capsules of gabapentin, 300 mg (1200 mg total), preoperatively and 2 capsules of gabapentin, 300 mg, 3 times a day (600 mg 3 times a day) postoperatively (10 total doses). Physicians not part of the research team were precluded from prescribing gabapentin or pregabalin.

Participants experiencing significant sedation or dizziness (≥7 of 10 adverse effect severity rating) had subsequent doses of study drug reduced by half (1 capsule). If participant dizziness or sedation remained at a severity level of 7 or more of 10 possible levels at the next assessment, medication administration was discontinued.

Assessments

Prior to surgery, participants completed a presurgical questionnaire packet assessing pain and opioid use with the Brief Pain Inventory. Patients completed the Brief Pain Inventory twice, with the first referencing pain at the upcoming surgical site and the second referencing pain elsewhere. Participants reported on author-generated measures of self-reported likelihood of developing chronic pain after surgery, self-perceived sensitivity to pain, and self-perceived likelihood of addiction to pain medication after surgery (eAppendix 1 in Supplement 2). The Opioid Risk Tool was administered to identify patients at risk for opioid-related aberrant behaviors (score range, 0-26, with 0-3 indicating low risk).

Other assessment tools included the Marlow-Crowne Social Desirability Scale (score range, 0-33, with 0-8 indicating low concern for social approval and 20-33 indicating high concern for social approval), Barratt Impulsivity Scale (score range, 30-120, with higher scores representing greater impulsiveness), Posttraumatic Stress Disorder Checklist–Civilian Version (score range, 17-85, with increasing scores representing more self-reported posttraumatic stress disorder symptoms), State Anxiety Inventory (score

range, 20-80, with higher scores representing increasing state anxiety [anxiety in response to a specific situation]), Trait Anxiety Inventory (score range, 20-80, with higher scores representing increasing trait anxiety [propensity to experience anxiety]), Euroqol Visual Analog Scale (score range for self-assessment of health, 0-100, with 0 representing the worst imaginable health state and 100 representing the best imaginable health state), and the Dizziness or Sedation Scale (11-point numeric rating scales: 0 indicates no sedation and 10, worst sedation imaginable; 0 indicates no dizziness and 10, worst dizziness imaginable; subjective ratings by patients).

After surgery, investigators assessed adverse effects daily while patients were receiving study medication. The participants were asked about the presence and severity of listed and additional adverse effects. To assess blinding, the patients were asked whether they believed they had received placebo or gabapentin on each postoperative day that the study drug was administered.

After discharge, a modified Brief Pain Inventory was administered over the telephone to assess pain related to the surgical site, medication use, and pain interference (eAppendix 1 in Supplement 2). Calls continued until patients had 5 consecutive reports of 0 of 10 average pain levels at their surgical site, 5 consecutive reports of no opioid use, and patient-defined full recovery. Call frequency was daily for 3 months, weekly thereafter up to 6 months, and monthly thereafter up to 2 years after surgery.

Study Outcomes

The primary outcome was time to pain resolution (5 consecutive reports of 0 of 10 levels of average pain at the surgical site on the numeric rating scale of pain). Secondary outcomes were time to opioid cessation (5 consecutive reports of no opioid use) and the proportion of participants with continued pain or opioid use at 6 months and 1 year.

Statistical Analysis

The study was designed to have 90% power to detect a favorable hazard ratio (HR) for an increased time to pain cessation of 1.33 in the gabapentin group compared with the placebo group. With a total 2-sided type I error rate of 0.05, 560 patients had to be enrolled, assuming at least 504 pain cessation events (with a 10% censoring rate based on previous data). Interim analysis was planned following every 100 pain cessation events with a partitioned α level to maintain the overall study α at .05.

Statistical analyses were performed with SAS software, version 9.4 (SAS Institute Inc). All statistical tests were 2-tailed. Continuous variables were compared with the *t* test and categorical data were compared with the χ^2 test. Time to pain and opioid cessation were analyzed in the intention-to-treat (ITT) population with the HR and 2-sided 95% CIs based on a Cox proportional hazards model stratified by surgery type as prespecified in our analytic plan. Stratification controlled for the different degrees of tissue healing associated with each type of surgery and the associated multimodal analgesia protocols of specific operations (eg, total hip or knee replacement). Stratification also controlled for the varying risk of persistent postsurgical pain across different operations. A separate prespecified per-protocol analysis of participants who received all study drug doses was conducted in a similar manner. Continued pain and opioid use at 6 and 12 months was analyzed in the ITT population with the odds ratio based on logistic regression accounting for stratification by surgery type. Prespecified subgroup analyses included high-risk subgroups defined by the presence of posttraumatic stress disorder, depression, and high self-report of addiction susceptibility. Additional post hoc subgroup analyses included surgery type, elevated state and trait anxiety inventory scores, and elevated Opioid Risk Tool scores. All analyses were completed before the data were unblinded. Subgroup analyses were conducted for surgery type and at-risk participant groups based on preoperative assessments (eAppendix 2 in Supplement 2). Adverse events were summarized for all patients

who received at least 1 dose of study drug.

Results

Patients

A total of 1805 patients were screened for eligibility between May 25, 2010, and July 25, 2014. Of the 1383 patients who did not meet inclusion criteria, most exceeded the upper age limit or did not speak English (Figure). Four hundred twenty-two patients underwent randomization, with 215 assigned to receive gabapentin and 207 assigned to receive active placebo (Figure). Treatment was initiated in 208 patients randomized to gabapentin and 203 patients randomized to placebo with at least 1 day of follow-up data in 208 patients receiving gabapentin and 202 patients receiving placebo (ITT and safety analysis population). Of patients included in the ITT analysis, mean (SD) age was 56.7 (11.7) years; 256 (62.4%) were women and 154 (37.6%) were men. A total of 139 (66.8%) patients received the complete protocol of perioperative gabapentin and 146 (71.9%) patients received the complete protocol of active placebo (per-protocol population). Overall, 125 of 410 patients (30.5%) did not receive the full protocol of study drug; 56 of 202 patients (27.7%) randomized to placebo and 69 of 208 patients (33.2%) randomized to gabapentin received a partial dose with no significant difference in the proportions between the groups ($P = .23$). Overall, 94 of 410 patients (22.9%) reported increased dizziness or sedation (Table 1).

Baseline sociodemographic characteristics and intraoperative management were comparable (Table 2). Preoperative pain was similar between the groups. The 2 groups were also similar across author-generated measures of self-perceived likelihood of developing chronic pain after surgery, sensitivity to pain, and likelihood of addiction to pain medication after surgery. No differences were noted in preoperative past 30-day opioid use or ever use of opioids. Opioid Risk Tool scores for both groups fell into the low-risk category for opioid misuse (0-3).

Efficacy

Following a preplanned interim analysis, the study was stopped early for meeting a futility stopping boundary with regard to the primary end point: time to pain cessation. Median time to pain resolution was 84 days (interquartile range [IQR], 36-203 days) in patients receiving gabapentin and 73 days (IQR, 36-231 days) in patients receiving active placebo. After accounting for stratification by surgery type, in our Cox multivariable regression analysis, perioperative gabapentin did not affect time to pain cessation.

However, participants receiving gabapentin had a 24% increase in the rate of opioid cessation after surgery (HR, 1.24; 95% CI, 1.00-1.54; $P = .05$) as reported in Table 3. Median time to opioid cessation was 25 days (IQR, 8-53 days) in patients receiving gabapentin and 32 days (IQR, 9-55 days) in patients receiving active placebo. Opioid cessation rates by time intervals are presented in Table 4. Eighty-two percent of participants were still receiving opioids 5 days after surgery. Median times to opioid cessation within each surgery type are reported in Table 4. In the per-protocol analysis, perioperative gabapentin similarly had no effect on pain cessation, but resulted in a 37% increase in the rate of opioid cessation after surgery (HR, 1.37; 95% CI, 1.06-1.88; $P = .02$). None of the additional secondary analyses was significant (Table 3). Preplanned subgroup analyses were completed for time to opioid and pain cessation with no significant heterogeneity of treatment effects demonstrated except for surgery type (eFigure 1 and eFigure 2 in Supplement 2).

Adverse Events

There was no significant difference in the rate of 1 or more reported adverse events between groups (Table 1), which occurred in 191 of 202 (94.6%) patients receiving placebo and 195 of 208 (93.8%)

receiving gabapentin ($P = .70$). No significant difference was noted in the proportion of patients who did not receive the full protocol of gabapentin or placebo owing to significant sedation or dizziness ($P = .23$). Patients receiving gabapentin reported less constipation than those receiving active placebo (61.5% vs 72.8%; $P = .02$) as well as more impaired coordination (42.3% vs 32.7%; $P = .03$) and rash (13.0% vs 6.9%; $P = .04$).

Serious adverse events were rare, occurring in 2 patients in each group. These events involved postoperative hemodynamic instability and a hematoma at the surgical site in patients randomized to placebo, and pulmonary embolism and pneumothorax in those randomized to gabapentin. The likelihood that these events were related to study medication administration was low. Patients were not able to correctly guess randomization status (χ^2 $P = .30$) suggesting that blinding was successful.

Discussion

To our knowledge, we report the results of the first randomized trial of perioperative use of gabapentin with extensive postoperative longitudinal follow-up and patient contact totaling 19 511 telephone calls up to 2 years after surgery. Perioperative gabapentin, 1200 mg, administered preoperatively plus 600 mg every 8 hours continued for 72 hours after surgery did not affect time to pain cessation, the rate of pain resolution, or the proportion of patients with chronic pain at 6 months or 1 year following surgery. However, perioperative gabapentin demonstrated a modest effect in promoting postoperative opioid cessation. Based on these findings, perioperative gabapentin may promote opioid cessation and prevent the development of chronic opioid use after surgery.

Our clinical trial is consistent with research regarding the lack of efficacy of perioperative gabapentin in the context of acute pain and adds to the existing literature by extending these findings to postoperative pain resolution. The extensive longitudinal follow-up of this clinical trial allows us to characterize the continuum of pain and provides support for our null hypothesis that perioperative gabapentin has no effect on remote pain cessation.

Preoperative gabapentin is associated with significantly decreased levels of consciousness in a dose-dependent manner and longer postanesthesia care unit stays. Similarly, respiratory depression has been reported in patients receiving preoperative gabapentin, with greater risk noted in older patients and those receiving multimodal analgesia. In contrast, our study demonstrates a high rate of adverse events in both groups likely reflecting the postoperative state rather than a medication effect. Elderly patients and those with medical comorbidities excluded from this trial may experience more gabapentin-related adverse effects (somnolence, ataxia, sedation, dizziness) and require reduced dosing.

Gabapentin significantly increased the rate of opioid cessation after hospital discharge. This finding resonates with earlier work suggesting that the determinants of the rate of opioid cessation are largely independent of the duration of pain and the determinants of time to pain resolution. Previous trials examining gabapentin's effect on opioid consumption have been limited to immediate postoperative use during hospital admission. Significant dose reductions in the first 24 to 72 hours may not be clinically relevant as most patients continue to require opioids during this time. Our study shows that 3 days of perioperative gabapentin may promote remote opioid cessation long after hospital discharge. Given the more significant and larger clinical effect noted in the per-protocol analysis, it is possible that extended postoperative gabapentin dosing would lead to even greater increases in postoperative opioid cessation. Although the results of the subgroup analyses presented in eAppendix 2 in Supplement 2 should be interpreted with caution, it appears that perioperative gabapentin may be more efficacious in promoting opioid cessation in the context of specific operations. Future studies should examine discrete surgical populations undergoing specific operations and determine the optimal dosing and timing of postoperative

gabapentin to prevent chronic opioid use.

Our findings mirror the opioid-sparing effects of gabapentin reported in other settings, as coadministration of gabapentin reduces opioid requirements. During opioid detoxification for addiction in patients without comorbid pain, concurrent gabapentin administration reduces illicit opioid use and decreases the intensity of withdrawal symptoms. This effect may result from prevention of tolerance and opioid-induced withdrawal hyperalgesia. Similarly, animal studies and human case studies have reported mitigation of opioid-induced hyperalgesia and reduced opioid use, but the absence of standardized clinical trials precludes definitive conclusions.

Given legislation in several states limiting initial opioid prescribing for acute pain to 5 days, our study demonstrates that strict adaptation of this legislation into clinical practice may be detrimental to optimal acute postoperative pain management. A total of 340 of 410 (82.9%) patients in our mixed surgical cohort were still using opioids 5 days postoperatively, and 395 of 410 (96.3%) reported having continued pain at that time. Given the elevated risk of chronic opioid use for patients receiving opioids preoperatively and those initiating use of opioids after surgery, gabapentin may be a valuable adjuvant to prevent the development of postoperative chronic opioid use.

Limitations

Our protocol tested whether adjunctive gabapentin improves current standard postoperative pain management. However, our permissive regimen may have increased between-patient variance as physicians prescribed different medications to different patients, and this may bias our outcomes toward the null.

Awareness of the potential utility of perioperative gabapentin and pregabalin for reducing immediate postoperative pain severity increased over the course of our study. This contributed directly to most of the protocol violations when patients received gabapentin or pregabalin outside of the study protocol. The mixture of active treatment into both treatment groups would be expected to bias our outcomes toward the null. In contrast, the absence of any effect for gabapentin on time to pain resolution was persistent and similar in the ITT and per protocol analyses, increasing confidence that the absence of such an effect is real.

Conclusions

In a mixed surgical cohort, perioperative gabapentin did not affect time to postoperative pain resolution. However, this regimen resulted in a modest increase in the rate of opioid cessation. Identifying gabapentin as an important adjuvant to promote definitive opioid cessation rather than merely reducing immediate postoperative opioid requirements has important and timely clinical implications in the context of the national epidemic of opioid overdose deaths and addiction. Future work examining the effect of extended postoperative gabapentin regimens and concurrent administration during opioid tapering in patients with chronic noncancer pain is warranted to further characterize the effects of gabapentin on opioid analgesic use (independent of effects on pain duration) and the mechanisms by which this medication promotes opioid cessation and prevents chronic opioid use.

Notes

Supplement 1.

Trial Protocol

Supplement 2.

eAppendix 1. Author-Generated Measures

eAppendix 2. Subgroup Analyses

eFigure 1. Subgroup Analyses for Time to Opioid Cessation

eFigure 2. Subgroup Analyses for Time to Pain Cessation

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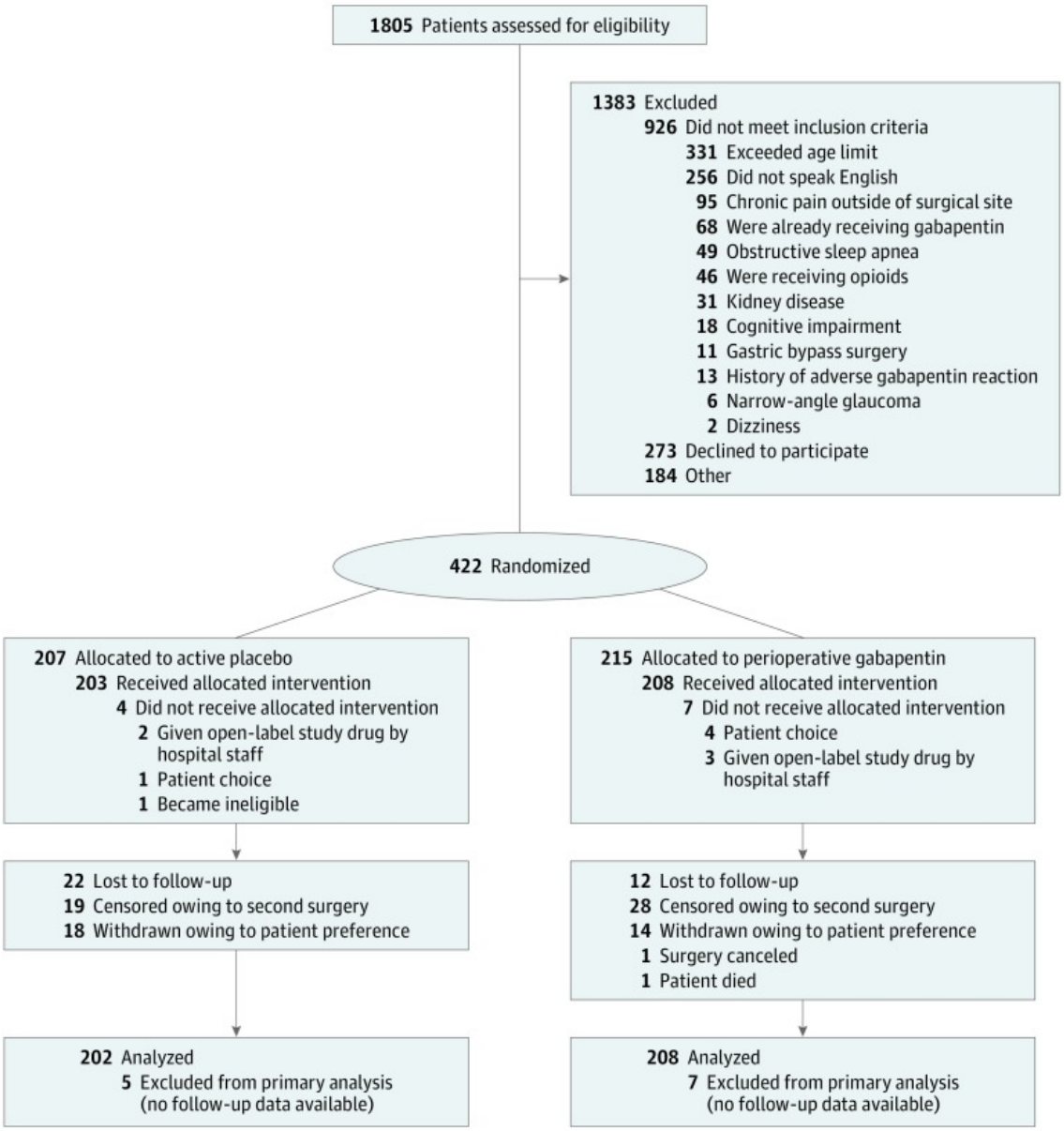
Figures and Tables

Figure.



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Enrollment, Randomization, and Follow-up

A total of 410 patients were analyzed and included in the intention-to-treat analysis.

Table 1.

Frequency of Adverse Events[a]

Type of Event	No. (%) of Patients With Events		*P* Value[b]
	Active Placebo (n = 202)	Gabapentin (n = 208)	
Serious adverse event[c]	2 (0.9)	2 (1.0)	>.99
≥1 Adverse event	191 (94.6)	195 (93.8)	.70
Adverse event leading to discontinuation of trial drug	13 (6.4)	17 (8.2)	.50
Leg swelling	56 (27.7)	49 (23.6)	.40
Generalized weakness	122 (60.4)	119 (57.2)	.60
Headache	68 (33.7)	81 (38.9)	.20
Abdominal pain	44 (21.8)	30 (14.4)	.06
Diarrhea	8 (4.0)	11 (5.3)	.50
Dry mouth	184 (91.1)	192 (92.3)	.40
Constipation	147 (72.8)	128 (61.5)	.02
Nausea	125 (61.9)	117 (56.3)	.30
Vomiting	55 (27.2)	49 (23.6)	.40
Impaired coordination	66 (32.7)	89 (42.8)	.03
Memory	72 (35.6)	75 (36.1)	.90
Sore throat	113 (55.9)	104 (50.0)	.30
Rash	14 (6.9)	27 (13.0)	.04
Visual disturbance	45 (22.3)	63 (30.3)	.06
Eye pain	19 (9.4)	26 (12.5)	.30
Ear pain	3 (1.5)	6 (2.9)	.50
Drug discontinuation	56 (27.7)	69 (33.2)	.23
Reasons for drug discontinuation			
Dizziness or Sedation Scale ≥7[d]	42 (20.8)	52 (25.0)	.96
Nausea, vomiting, or abdominal pain	7 (3.5)	1 (0.5)	.01
Other dose-limiting adverse effects	3 (1.5)	9 (4.3)	.15
Logistical issues	4 (2.0)	7 (3.4)	.56

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[a]Patients could have experienced more than 1 event.
[b]χ^2 Test.
[c]These events involved postoperative hemodynamic instability, and a hematoma at the surgical site in patients randomized to placebo, and pulmonary embolism and pneumothorax in those randomized to gabapentin.

[d]Eleven-point numeric rating scales were used (0, no sedation and 10, worst sedation imaginable; 0, no dizziness and 10, worst dizziness imaginable; subjective rating by patients).

Table 2.

Baseline Preoperative Characteristics of Patients According to Treatment Group[a]

Characteristic[b]	Active Placebo	Gabapentin
Patients, No.	202	208
Age, mean (SD), y	56.4 (11.8)	57.0 (11.7)
Male, No./total No. (%)	78/201 (38.8)	87/207 (41)
Marital status, No./total No. (%)	186	195
Never married	16 (8.6)	17 (8.7)
Married	134 (72.0)	142 (72.8)
Living with someone	8 (4.3)	6 (3.1)
Divorced or separated	21 (11.3)	24 (12.3)
Widowed	7 (3.8)	6 (3.1)
Disability claim pending, No./total No. (%)	25/180 (13.9)	2/191 (11.0)
Family history of chronic pain, No./total No. (%)	61/183 (33.3)	70/188 (37.2)
Employment status, No./total No. (%)	183/202	191/208
Full-time	83 (45.4)	80 (41.9)
Part-time	14 (7.7)	21 (11.0)
Unemployed, not interested in returning to work	8 (4.4)	11 (5.8)
Unemployed, looking for work	9 (4.9)	10 (5.2)
Unemployed, disabled	24 (13.1)	13 (6.8)
Retired due to pain	8 (4.4)	11 (5.8)
Retired not due to pain	37 (20.2)	45 (23.6)
Surgery, No./total No. (%)	202/202	208/208
Thoracotomy	6 (3.0)	9 (4.3)
Total knee replacement	68 (33.7)	83 (39.9)
Total hip replacement	54 (26.7)	43 (20.7)
Mastectomy	23 (11.4)	18 (8.7)
Lumpectomy	14 (6.9)	16 (7.7)
VATS	15 (7.4)	14 (6.7)
Hand surgery	11 (5.4)	13 (6.3)
Carpal tunnel surgery	2 (1.0)	3 (1.4)
Knee arthroscopy	4 (2.0)	4 (1.9)
Shoulder arthroplasty	2 (1.0)	2 (9.6)
Shoulder arthroscopy	3 (1.5)	3 (1.4)
Baseline pain at surgical site, mean (SD)[c]	5.0 (3.0)	5.4 (3.2)
Baseline pain other than surgical site, mean (SD)[c]	2.2 (2.2)	2.5 (2.5)
Self-perceived likelihood of developing chronic pain after surgery, mean (SD)	2.0 (0.7)	2.0 (0.7)
Self-perceived sensitivity to pain, mean (SD)	2.3 (0.6)	2.2 (0.6)
Past 30-d prescription opioid use, No./total No. (%)	18/202 (8.9)	16/208 (7.7)

Characteristic[b]	Active Placebo	Gabapentin
Ever use of prescription opioids, No./total No. (%)	135/164 (82.3)	148/173 (85.5)
Self-perceived likelihood of addiction to pain medication after surgery, mean (SD)	1.5 (0.6)	1.6 (0.6)
Opioid Risk Tool score, mean (SD)[d]	2.4 (3.0)	2.3 (3.3)
Marlow-Crowne Social Desirability Scale score, mean (SD)[e]	20.3 (5.7)	20.4 (5.8)
Barratt Impulsivity Scale score, mean (SD)[f]	68.3 (7.3)	69.0 (6.3)
PCL-C score, mean (SD)[g]	23.8 (7.6)	25.6 (9.8)
State Anxiety Inventory score, mean (SD)[h]	34.5 (11.1)	35.1 (11.1)
Trait Anxiety Inventory score, mean (SD)[i]	32.7 (10.7)	33.0 (10.2)
Beck Depression Inventory-II score, mean (SD)[j]	9.2 (6.3)	10.3 (7.5)
Euroqol VAS, mean (SD)[k]	70.2 (20.3)	72.5 (17.8)
Intraoperative management, No./total No. (%)[l]	188/202	n = 196/208
Intravenous ketamine	13 (6.9)	13 (6.6)
Spinal analgesia	38 (20.2)	43 (21.9)
Epidural analgesia	17 (9.0)	13 (6.6)
Regional anesthetic technique	88 (46.8)	93 (47.4)

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Abbreviations: PCL-C, Posttraumatic Stress Disorder Checklist–Civilian Version; VAS, visual analog scale; VATS, video-assisted thoracoscopic surgery.

[a]There were no significant differences between the treatment groups. $P \leq .002$ was considered to indicate significance in these between-group comparisons.
[b]Percentages do not include patients with missing data.
[c]Scale range, 0 (no pain) to 10 (worst pain imaginable).
[d]Scale range, 0 to 26, with 0 to 3 indicating low risk.
[e]Scale range, 0 to 33, with 0 to 8 indicating low concern for social approval and 20 to 33 indicating high concern for social approval.
[f]Scale range, 30 to 120, with higher scores representing greater impulsiveness.
[g]Scale range, 17 to 85, with increasing scores representing more self-reported posttraumatic stress disorder symptoms.
[h]Scale range, 20 to 80, with higher scores representing increasing state anxiety (anxiety in response to a specific situation).
[i]Scale range, 20 to 80, with higher scores representing increasing trait anxiety (propensity to experience anxiety).
[j]Scale range, 0 to 63, with 0 to 13 indicating minimal depression; 14 to 19, mild depression; 20 to 28 moderate depression; and 29 to 63, severe depression.
[k]Scale range, 0 to 100, with 0 representing the worst imaginable health state and 100 representing the best imaginable health state.
[l]These categories are not mutually exclusive and patients may have received more than 1 intraoperative management technique. Among those randomized to active placebo, 53 of 188 (28.2%) did not receive any of the intraoperative management techniques. Among those randomized to gabapentin, 56 of 196 (28.6%) did not receive any of the intraoperative management techniques.

Table 3.

Primary and Secondary Outcomes

Outcome	No. of Events		HR (95% CI)[a]	OR (95% CI)[a]	*P* Value
	Active Placebo	Gabapentin			
Primary outcome, time to pain cessation[b]	139	142	1.04 (0.82-1.33)		.73
Secondary outcomes					
Time to opioid cessation[b]	176	179	1.24 (1.00-1.54)		.05
Time to pain cessation per-protocol analysis (n = 285)	102	99	1.05 (0.79-1.40)		.74
Time to opioid cessation per-protocol analysis (n = 285)	129	125	1.37 (1.06-1.78)		.02
Patients with continued pain, No. (%)	n = 202	n = 208			
6 mo	37 (18.3)	42 (20.2)		1.07 (0.64-1.78)	.30
12 mo	18 (8.9)	21 (10.1)		1.10 (0.56-2.16)	.80
Patients continuing opioids, No. (%)	n = 202	n = 208			
6 mo	4 (2.0)	5 (2.4)		1.22 (0.32-4.66)	.80
12 mo	3 (1.5)	4 (1.9)		1.28 (0.28-5.87)	.70

Abbreviations: HR, hazard ratio; OR, odds ratio.

[a]Empty cells indicate that test was not conducted.
[b]Intention-to-treat analysis.

Table 4.

Median Days to Pain Resolution or Opioid Cessation

Characteristic	No./Total No. (%)[a]	
	Active Placebo	Gabapentin
Pain resolution overall, median (IQR), d	73 (36-231)	84 (36-203)
Opioid cessation overall, median (IQR), d	32 (9-55)	25 (8-53)
Opioid cessation by day 5	33/197 (16.8)	37/199 (18.6)
Pain cessation by day 5	3/196 (1.5)	12/199 (6.0)
Opioid cessation by day 10	55/196 (28.1)	60/198 (30.3)
Pain cessation by day 10	11/195 (5.6)	19/198 (9.6)
Opioid cessation by day 15	68/192 (35.4)	74/197 (37.6)
Pain cessation by day 15	18/191 (9.4)	24/196 (12.2)
Opioid cessation by day 30	96/194 (52.2)	109/184 (59.2)
Pain cessation by day 30	40/188 (21.3)	41/190 (21.6)
Opioid cessation by day 60	145/184 (78.8)	151/184 (82.1)
Pain cessation by day 60	83/181(45.9)	79/182 (43.4)
Opioid cessation by day 90	163/184 (88.6)	166/184 (90.2)
Pain cessation by day 90	106/178 (59.6)	100/176 (56.8)
Opioid cessation by surgery type, median (IQR), d		
Thoracotomy	49 (25-50)	45 (13-119)
Total knee replacement	49 (30-78)	45 (25-70)
Total hip replacement	33 (16-58)	19 (9-50)
Mastectomy	30 (13-42)	21 (8-37)
Lumpectomy	5 (3-7)	2 (1-4)
VATS	20 (4-38)	11 (7-35)
Hand surgery	32 (5-54)	8 (3-14)
Carpal tunnel surgery	4 (3-4)	3 (2-11)
Knee arthroscopy	7 (5-8)	10.5 (3-68)
Shoulder arthroplasty	3 (1-5)	3 (3-3)
Shoulder arthroscopy	4 (4-5)	73 (7-139)

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Abbreviations: IQR, interquartile range; VATS, video-assisted thoracoscopic surgery.

[a]Participants censored prior to the end of the time interval were not included.