ANESTHESIOLOGY

Prolonged Opioid Use and Pain Outcome and Associated Factors after Surgery under General Anesthesia: A Prospective Cohort Association Multicenter Study

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Opioid exposure at the time of surgery has been identified as a risk factor for persistent opioid use
- Most data examining this association are based on healthcare utilization claims with limited clinical detail, particularly regarding the patient's experience of pain

What This Article Tells Us That Is New

- In these prospectively collected cohort data, preoperative opioid use was identified as the strongest risk factor for opioid use at 3 months postoperatively
- No correlation was found between persistent opioid use at 3 months and surgical site pain at 3 months
- No association was identified between preoperative anxiety, preoperative depression, or surgery type and opioid use at 3 months in multivariable models, although credible intervals were large for some variables

ABSTRACT

Background: There is insufficient prospective evidence regarding the relationship between surgical experience and prolonged opioid use and pain. The authors investigated the association of patient characteristics, surgical procedure, and perioperative anesthetic course with postoperative opioid consumption and pain 3 months postsurgery. The authors hypothesized that patient characteristics and intraoperative factors predict opioid consumption and pain 3 months postsurgery.

Methods: Eleven U.S. and one European institution enrolled patients scheduled for spine, open thoracic, knee, hip, or abdominal surgery, or mastectomy, in this multicenter, prospective observational study. Preoperative and postoperative data were collected using patient surveys and electronic medical records. Intraoperative data were collected from the Multicenter Perioperative Outcomes Group database. The association between postoperative opioid consumption and surgical site pain at 3 months, elicited from a telephone survey conducted at 3 months postoperatively, and demographics, psychosocial scores, pain scores, pain management, and case characteristics, was analyzed.

Results: Between September and October 2017, 3,505 surgical procedures met inclusion criteria. A total of 1,093 cases were included; 413 patients were lost to follow-up, leaving 680 (64%) for outcome analysis. Preoperatively, 135 (20%) patients were taking opioids. Three months postsurgery, 96 (14%) patients were taking opioids, including 23 patients (4%) who had not taken opioids preoperatively. A total of 177 patients (27%) reported surgical site pain, including 45 (13%) patients who had not reported pain preoperatively. The adjusted odds ratio for 3-month opioid use was 18.6 (credible interval, 10.3 to 34.5) for patients who had taken opioids preoperatively. The adjusted odds ratio for 3-month surgical site pain was 2.58 (1.45 to 4.4), 4.1 (1.73 to 8.9), and 2.75 (1.39 to 5.0) for patients who had site pain preoperatively, knee replacement, or spine surgery, respectively.

Conclusions: Preoperative opioid use was the strongest predictor of opioid use 3 months postsurgery. None of the other variables showed clinically significant association with opioid use at 3 months after surgery.

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As the opioid crisis continues in the United States,[1] prospective evidence addressing the role of the surgical experience and associated opioid use for postoperative pain as a contributor to prolonged opioid use is lacking.[2–4] More than 75% of surgical patients do not report preoperative opioid use.[5] The current available data indicate that surgery in patients who do not take opioids preoperatively leads to a higher risk of developing chronic opioid dependence.[6–8] A retrospective cohort study showed a 3.1% incidence of opioid use at more than 90 days postoperatively in 39,140 opioid-naive patients,[7] with the risk of chronic opioid use varying based on the type of surgical procedure.[6–8] For patients not using opioids before surgery, nonsurgical risk factors played

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an important role in chronic opioid use development. Demographics, duration of postsurgical opioid use, anxiety, depression, low household income, comorbidities, preoperative use of benzodiazepines, antidepressants, angiotensin-converting enzyme inhibitors, and drug and alcohol misuse increase the risk of prolonged opioid use in the weeks and months after surgery.[6–8] While most of the postoperative opioid use literature focuses on opioid-naive patients, the literature is much more limited about patients who use opioids preoperatively. Goesling *et al.* followed 574 University of Michigan (Ann Arbor, Michigan) total knee or total hip arthroplasty patients for 6 months postoperatively.[9] Forty-two percent of patients who used opioids preoperatively were still using them at 6 months, compared to 9.8% of patients who did not use opioids preoperatively. More recently, Jivraj *et al.* studied patients who chronically used opioids preoperatively and underwent nonorthopedic surgery.[10] These patients had an increased rate of opioid discontinuation (36%) compared to matched nonsurgical chronic opioid users (29%)—still, a considerable number of patients in both groups continued to take opioids.[10]

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Persistent postoperative pain (postsurgical pain at 3 months[11]) develops in 10 to 56% of surgical patients.[12–14] Reported risk factors include preoperative pain[15] or pain sensitivity,[16] being female or younger,[12,14,17] surgery type and duration,[14,17] preoperative use of opioids,[18,19] and anxiety and depression.[14]

We studied the association of prolonged postoperative opioid consumption and of prolonged surgical site pain with factors including patient characteristics, surgery and surgery type, anesthetic course, and pain management. Patient characteristics included anxiety and depression, pain ratings, physical function, and sleep quality that were elicited through patient survey and combined with intraoperative data in the Multicenter Perioperative Outcomes Group database.[20,21]

The Multicenter Perioperative Outcomes Group is a consortium of hospitals with processes to automatically extract perioperative data, validate the data by clinicians, deidentify the data, and submit it to the group's center. A peer review process evaluates research proposals and governs access to data for research.[20,21]

The primary objective was to model factors associated with opioid use and with surgical site pain at 3 months after surgery. A secondary objective was to explore the proportion of patients who transition from taking opioids preoperatively to discontinuing opioids at 3 months or *vice versa*. We hypothesized that individual patient characteristics and intraoperative factors predict postoperative opioid consumption at 3 months.

Materials and Methods

This was a multicenter, prospective observational study. After approval in the Multicenter Perioperative Outcomes Group consortium peer review forum, all of the consortium's active member institutions were invited to participate. Details about the study's methods have been published previously.[22] The primary outcome variable of this study was opioid consumption at 3 months postoperatively. Study approval was obtained from the University of Utah (Salt Lake City, Utah) Institutional Review Board (IRB), which served as the Single IRB for three of the participating sites. The remaining nine participating institutions obtained approval from their local IRBs. The approved University of Utah Single IRB and individual institutions' IRB protocols used a waiver of documentation of informed consent or full consent.

As described by Stuart *et al.*,[22] we did not formally estimate the sample size, since the effect sizes of perioperative data on the primary outcomes are not established. Similarly, we did not perform a power analysis. We determined an enrollment of 150 patients per week per institution during the 2 weeks of perioperative data collection to be feasible. Ten institutions would allow for a total size of 3,000 patients to be included.

Patient Enrollment

Each institution, using convenience sampling, enrolled patients during a 2- to 4-week period between September

and October 2017, if they were scheduled to undergo spine surgery, open thoracic surgery, knee or hip surgery, mastectomy, or abdominal surgery (including laparoscopic surgery) under general or regional anesthesia. These procedures were chosen because they are known to be associated with a higher incidence of persistent postoperative pain.[9,23–26] Patients were not eligible for inclusion if (1) their surgery was minor without the need for regional or general anesthesia, (2) they participated in a randomized clinical trial, which involved blinding interventions or administered medications that were relevant to this study, or which did not accept patients to be coenrolled in an observational study, (3) they were younger than 18 yr of age, (4) they did not speak English, or (5) they were cognitively impaired.

Using the surgical schedule, patients were pre-creened for eligibility using the above criteria and a list of 415 Current Procedural Terminology codes (see Table S1, Supplemental Digital Content 1, https://links.lww.com/ALN/D22, "Current Procedural Terminology Codes Included and Their Mapping to Surgery Types"), consented, and enrolled during the preoperative period in the preoperative waiting areas or admission suites.

Information Collected

Preoperatively, questionnaires were administered in person to the enrolled patients in order to collect information about their physical characteristics and demographics, and home opioid and nonopioid analgesic use. Patients were asked whether they were currently using pain medication. If they answered yes, follow-up questions elicited more detailed information regarding which particular medications, and for the opioids for how long they were taking the opioids, at which dose, and how often.

In addition, validated questionnaires were used to assess the patients' pain intensity (Brief Pain Inventory severity questions for pain at the site of surgery and overall body pain[24]); comorbid central nervous system symptoms (2011 Fibromyalgia Survey Criteria using the Symptom Severity Index[27]); widespread pain (Michigan Body Map[28]); physical function (Patient Reported Outcome Measurement System Physical Function short form 4a[29]); anxiety (Patient Reported Outcome Measurement System Anxiety short form 4a[29]); depression (Patient Reported Outcome Measurement System Depression short form 4a[29]); catastrophizing, *i.e.*, thoughts about symptoms (Patient Reported Outcome Measurement System Sleep Disturbance short form 5a[29]); and expectations of surgery.

Additional information was collected *via* chart review, namely time until readiness for discharge from the postanesthesia care unit, postoperative intensive care unit length of stay, hospital length of stay, postoperative day 0 and postoperative day 1 pain scores, in-hospital opioid and nonopioid analgesic medications, reintubation, oxygen dependence, new noninvasive ventilation requirements, length of hospital stay, and postoperative myocardial injury.

Enrolled patients were contacted by phone at 3 months postoperatively. If patients could not be reached, three more contact attempts were made at different weekdays and times of day. Patients were asked whether they had taken any opioid or nonopioid analgesic medication since their surgery. If they answered yes, follow-up questions elicited more detailed information regarding which particular medications, and for the opioids for how long they were taking the opioids, at which dose, and how often. Using the same instruments that were used preoperatively, patients were also asked about pain at the site of surgery, overall body pain, symptom severity index, Michigan Body Map, Patient Reported Outcome Measurement System Physical function short form 4a, Patient Reported Outcome Measurement System Anxiety short form 4a, Patient Reported Outcome Measurement System Depression short form 4a, Patient Reported Outcome Measurement System Sleep Disturbance short form 5a, catastrophizing, satisfaction with surgery, and the occurrence of adverse events.

Case report forms to collect these data were fashioned after a study by Brummett *et al.*[26,30] (see Supplemental Digital Content 3, "Case Report Forms," https://links.lww.com/ALN/D24).

Intraoperative data were collected from the Multicenter Perioperative Outcomes Group database.[31] These included the American Society of Anesthesiologists Physical Status, admission diagnosis, comorbidities, type of anesthesia, intraoperative anesthetic technique including all drugs administered, and discharge International Classification of Diseases code. A detailed table with all variables collected, together with the timepoint and the manner in which they were collected, can be found in Supplemental Table S2 (Supplemental Digital Content 2, https://links.lww.com/ALN/D23, "Information Collected").

In the selection of information to collect, we aimed to include variables that were likely relevant to the primary outcomes of prolonged postsurgical opioid use and pain. The selection was guided by experts we had among our authors and previous publications,[6–8,26,32–38] and aided by an internal peer review process within the Multicenter Perioperative Outcomes Group consortium, while—for the manually collected information—attempting to limit the number of variables to a number that would not overwhelm data collectors and participants.

Statistical Analysis

The primary outcomes were opioid consumption and surgical site pain at 3 months as elicited from the telephone survey conducted 3 months postoperatively, described above and detailed in Supplemental Digital Content 3, "Case Report Forms" (https://links.lww.com/ALN/D24). The responses were collated into binary events (opioid use present or absent, surgical site pain present or absent at 3 months).

Patterns in the raw data including missingness were inspected by histograms, density plots, boxplots, x-y plots,

and cross-tabulation. The distributions of covariate values for subjects with and without the primary outcome were compared by standardized mean differences. Standardized mean differences greater than 0.2 were interpreted as showing an imbalance of means.[39,40]

Logistic multivariate, multivariable models were estimated for the primary outcomes; the two outcomes were jointly and simultaneously modeled on the covariates. All covariates considered to putatively influence the outcome were included in the models; these were (1) age, (2) sex, (3) body mass index, (4) race, (5) occupation, (6) relationship status, (7) American Society of Anesthesiologists Physical Status, (8) surgery type, (9) preoperative anxiety score, (10) preoperative depression score, (11) preoperative physical function score, (12) pain at the surgery site preoperatively, (13) preoperative opioid use, (14) preoperative nonopioid analgesic use, (15) anesthesia duration, (16) intraoperative parenteral morphine equivalents, (17) intraoperative nonopioid analgesics, (18) general anesthesia, (19) neuraxial anesthesia, and (20) Multicenter Perioperative Outcomes Group institution (group or random effect). These covariates were chosen by expert opinion and from previous publications.[6–8,26,32–38] The preoperative psycho-social scores used the Patient Reported Outcome Measurement System scores (Physical Function short form 4a, Anxiety short form 4a, and Depression short form 4a).[29] Subjects with missing covariate data were included in outcome models using 20-fold multiple chain imputation techniques to replace missing values; imputation algorithms were predictive mean matching (numeric data), logistic regression (factors with two levels), and polytomous regression (factors with three or more levels). Missing outcomes (opioid consumption and surgical site pain at 3 months) were not imputed.

Model fit was by hierarchical Bayesian regression methods using Markov chain Monte Carlo algorithms, specifically Hamiltonian Monte Carlo with the No-U-Turn Sampler having more rapid convergence for high-dimensional models.[41,42] Bayesian analysis allows direct probability interpretation of intervals bounding the mean values and avoids the frequent misapplication of null hypothesis significance testing.[43] We used a set of increasingly informative prior distributions: noninformative (improper flat prior), weakly informative (Student's *t*), and informative (horseshoe). The weakly informative and informative prior distributions enforced regularization of parameter estimates to prevent overfitting of model coefficients. The model was estimated 20 times, once for each imputed data set; four chains with 4,000 iterations with 50% warmup and a 1-to-1 thinning ratio were used. The posterior distribution was a pooling of the 20 models with a total size of 640,000 draws (2,000 draws times 20 models).

Convergence characteristics of the posterior distribution of parameters were assessed by the $\hat{R}$ statistic, effective sample size, chain mixing, and chain autocorrelation. Model covariates were checked for collinearity. The posterior predictive distribution was used to generate a predictive accuracy metric as measured by leave-one-out cross-validation.[44] A posterior projection of the model was performed and model predictive performance assessed by expected-log-predictive-density and root mean square error, for variable selection.[45,46] Covariate significance was assessed using the region of practical equivalence procedure[47] with a range of –0.1 to 0.1 as suggested by Kruschke,[48] by evaluating the probability of direction, and by inspecting the maximum *a posteriori*-based *P* value.[49]

Institutions were included in the statistical model as group effect. Because of observed differences between institutions in the completion rate of the 3-month surveys, in enrolled patients, and in the mix of surgery types, a variance partition coefficient analysis was performed to assess the contribution of the institutions to the overall observed variance.

Model results are presented as means, medians, SDs, and 95% credible intervals. A 95% credible interval has a 95% probability of containing the true parameter value. By contrast, a 95% CI is interpreted under the assumption that if a large number of analyses are repeated, in 95% of these analyses, the 95% CI will contain the true parameter value. Model coefficients are also presented with density plots to show the probability of direction.[50] Inferences on model coefficients followed methods suggested by Kruschke[48] and Makowski *et al.*[50] Statistical modeling was done in the R software (available at https://www.r-project.org/, accessed February 13, 2023) using the mice, bayestestR, brms, loo, mcmcplot, posterior, tidybayes, and projpred packages. We followed guidelines for reporting Bayesian analysis.[51]

Results

Participating Institutions

Twelve Multicenter Perioperative Outcomes Group member institutions participated in the study (Cleveland Clinic [Cleveland, Ohio], Columbia University [New York, New York], University of Michigan [Ann Arbor, Michigan], Oregon Health & Science University [Portland, Oregon], University of Utah [Salt Lake City, Utah], Utrecht University [Utrecht, the Netherlands], Vanderbilt University [Nashville, Tennessee], University of Vermont [Burlington, Vermont], University of Virginia [Charlottesville, Virginia], University of Washington [Seattle, Washington], Washington University [St. Louis, Missouri], and Yale University [New Haven, Connecticut]). Eleven of the participating institutions were academic hospitals in the United States; one participating institution (Utrecht University) was in the Netherlands.

Enrolled Patients

Between September and October 2017, 3,505 surgical procedures met inclusion criteria. From these patients, a sample of 1,110 cases were enrolled (reasons for not

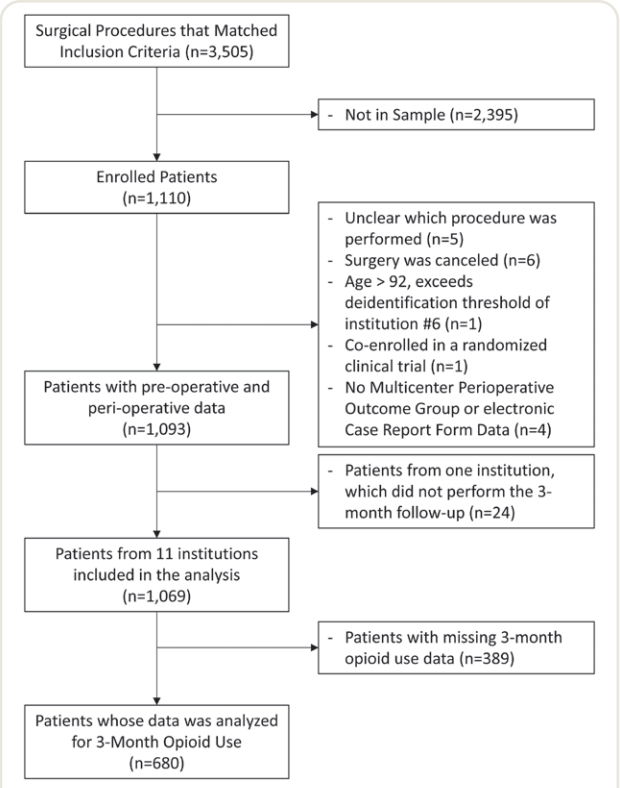

Fig. 1. Flow diagram for study participants.

enrolling included night or weekend cases, availability of study recruitment staff, some institutions focusing their enrollment on certain hospitals within their network). Seventeen cases were excluded (fig. 1), leaving 1,093 patients. One institution did not perform any follow-up on its 24 patients and was dropped from the study. Of the 1,069 remaining patients at 11 institutions, 389 were lost to follow-up at 3 months, leaving 680 (64%) for outcome analyses (fig. 1).

There was considerable imbalance between participating institutions in terms of number of enrolled patients per institution (14 to 190) and type of surgery (see Table S4, Supplemental Digital Content 4, https://links.lww.com/ALN/D25, "Case Numbers by Institution and Type of Surgery"). Additionally, completion rate of the 3-month follow-up varied between institutions: all but four institutions had completion rates of more than 66%, but the remaining four had rates of 34%, 45%, 53%, and 62%, respectively.

Of those variables that were identified as being strong predictors for the outcome variables, the standardized mean difference between participants for whom the 3-month survey was completed and those who were lost to follow-up, preoperative taking of opioids, and preoperative pain at the site of surgery were below the standardized mean difference threshold of 0.2, and surgery type was found to have a standardized mean difference of 0.21, *i.e.*, just slightly above that threshold (table 1).

The vast majority of cases were abdominal surgeries, accounting for 59% of enrolled cases, with none of the other surgery types contributing more than 17% (see Table S4, Supplemental Digital Content 4, https://links.lww.com/ALN/D25, "Case Numbers by Institution and Type of Surgery").

Using a threshold of 0.2 for the standardized mean difference,[39,40] age, institution, race, and surgery type were the modeled variables for which there was a larger than small to medium imbalance between patients who were lost to the 3-month follow-up compared to those who participated in the follow-up (table 1; Table S5, Supplemental Digital Content 5, https://links.lww.com/ALN/D26, "Patient and Case Characteristics and Data Availability").

Outcomes: Descriptive Statistics

Three months after surgery, 96 (14%) patients of the 680 patients in the final dataset were taking opioids. Comparisons of patient and case characteristics between patients taking opioids at 3 months and those not taking opioids at 3 months are shown in table 2 (and in greater detail in Table S6, Supplemental Digital Content 6, https://links.lww.com/ALN/D27, "Patient and Case Characteristics and Outcome 'Taking Opioids at Three Months'"; and Table S7, Supplemental Digital Content 7, https://links.lww.com/ALN/D28, "Patient and Case Characteristics and Outcome 'Taking Opioids at Three Months' (Univariable Testing)"). Patients' preoperative use of opioids, their physical function score, and whether patients preoperatively had pain at their site of surgery were the three variables with the largest standardized mean difference on this primary outcome measure.

The vast majority of the 680 patients in the final analysis (545, 80%) did not take opioids preoperatively (table 3). Four percent (23) of these patients reported taking opioids at 3 months after their surgery. In contrast, more than half (73, 54%) of the 135 patients who did take opioids preoperatively were still taking opioids at 3 months.

Of the 656 patients for whom data were available for surgical site pain preoperatively and at 3 months, a little more than half (341, 52%) reported no pain at the site of their surgery preoperatively (table 4). Thirteen percent (45) of these patients reported surgical site pain 3 months after their surgery. More than half of patients (183, 58%) who did report surgical site pain preoperatively (315, 48%) reported no surgical site pain at 3 months postsurgery. Comparison of patient and case characteristics between patients having surgical site pain at 3 months and those who did not are shown in table 5 (and in greater detail in Table S8, Supplemental Digital Content 8, https://links.lww.com/ALN/D29, "Patient and Case Characteristics and Outcome 'Surgical Site Pain at Three Months'"; and Table S9, Supplemental Digital Content 9, https://links.lww.com/ALN/D30, "Patient and Case Characteristics and Outcome 'Surgical Site Pain at Three Months' (Univariable Testing)").

Table 1. Patient Characteristics and Outcome Data Availability

	3-Month Data		
	Available (n = 680)	Not Available (n = 389)	Standardized Mean Difference
Institution 1	33 (5%)	63 (16%)	0.62*
Institution 2	13 (2%)	1 (0%)	
Institution 3	102 (15%)	51 (13%)	
Institution 4	26 (4%)	23 (6%)	
Institution 5	53 (8%)	18 (5%)	
Institution 6	75 (11%)	32 (8%)	
Institution 7	75 (11%)	30 (8%)	
Institution 8	131 (19%)	59 (15%)	
Institution 9	58 (9%)	72 (19%)	
Institution 10	72 (11%)	14 (4%)	
Institution 11	42 (6%)	26 (7%)	
Age (yr)	59 ± 14 (680)	54 ± 15 (389)	0.33*
Sex female	395 (58%)	242 (62%)	0.08
Race (consolidated): White	527 (78%)	311 (81%)	0.25*
Race (consolidated): not White	66 (10%)	52 (14%)	
Race (consolidated): no response	83 (12%)	23 (6%)	
Body mass index (kg/m^2)	31 ± 8 (673)	31 ± 8 (385)	0.02
ASA Physical Status: III or IV	292 (45%)	167 (45%)	
Relationship: not a couple	199 (29%)	143 (37%)	0.16
Occupation: not employed	431 (64%)	212 (55%)	0.18
Preoperative taking opioids	135 (20%)	109 (28%)	0.19
Preoperative taking nonopioid analgesics	232 (34%)	144 (37%)	0.06
Preoperative Anxiety score	50 ± 9 (658)	51 ± 10 (377)	0.16
Preoperative Depression score	47 ± 8 (661)	47 ± 9 (373)	0.10
Preoperative Physical Function score	32 ± 9 (654)	32 ± 9 (373)	0.02
Preoperative pain last week at surgical site	320 (48%)	212 (55%)	0.14
Surgery type, total hip	54 (8%)	37 (10%)	0.21*
Surgery type, knee replacement	62 (9%)	21 (5%)	
Surgery type, spine surgery	110 (16%)	70 (18%)	
Surgery type, open thoracic	20 (3%)	7 (2%)	
Surgery type, mastectomy	43 (6%)	15 (4%)	
Surgery type, abdominal surgery	391 (58%)	239 (61%)	
General anesthesia	612 (92%)	363 (94%)	0.08
Neuraxial anesthesia	165 (25%)	73 (19%)	0.14
Anesthesia duration (min)	241 ± 140 (668)	244 ± 121 (387)	0.02
Intraoperative parenteral morphine equivalent	27 ± 21 (615)	29 ± 22 (368)	0.09
Intraoperative nonopioid analgesics administered	609 (90%)	359 (92%)	0.10

Values are presented as n (% of reported) or mean ± SD (n). Anxiety, Depression, and Physical Function scores are Patient-Reported Outcomes Measurement Information System Scores (Physical Function short form 4a, Anxiety short form 4a, and Depression short form 4a).[29]

*|Standardized mean difference| > 0.2.

ASA, American Society of Anesthesiologists.

Of the 675 patients for whom pain data were available at 3 months postsurgery, 51 patients (8%) reported both that they took opioids and that they had pain at the site of surgery at 3 months postsurgery. This rate is about half of that observed preoperatively, when 110 patients (17%) of the 661 patients, for whom data on preoperative pain were available, reported both surgical site pain and use of opioids.

Statistical Modeling

Overall, 1.5% of the covariates had to be imputed; in 130 patients, one or more of the covariates' values were missing, while complete data sets were collected from 550 patients.

The Bayesian statistical model had good estimation properties with good chain mixing, absence of chain autocorrelation by lag 2, $\hat{R}$ close to 1.01, and more than adequate effective sample size (see Table S10, Supplemental Digital Content 10, https://links.lww.com/ALN/D31, "Summary of Posterior Distribution for Taking Opioid at Three Months," and Table S11, Supplemental Digital Content 11, https://links.lww.com/ALN/D32, "Summary of Posterior Distribution for Surgical Site Pain at Three Months"). All Pareto k estimates were smaller than 0.7, indicating a good model fit. In addition, the covariates did not show collinearity. The posterior predictive distribution had a good fit with the observations.

Table 2. Patient and Case Characteristics, Outcome "Taking Opioids at 3 Months"

	Not Taking Opioids at 3 Months	Taking Opioids at 3 Months	Standardized Mean Difference	Adjusted Odds Ratio (Credible Interval)
n	584	96		
Institution 1	24 (4%)	9 (9%)	0.529*	(Group Effect)
Institution 2	11 (2%)	2 (2%)		
Institution 3	82 (14%)	20 (21%)		
Institution 4	25 (4%)	1 (1%)		
Institution 5	41 (7%)	12 (13%)		
Institution 6	69 (12%)	6 (6%)		
Institution 7	70 (12%)	5 (5%)		
Institution 8	111 (19%)	20 (21%)		
Institution 9	52 (9%)	6 (6%)		
Institution 10	65 (11%)	7 (7%)		
Institution 11	34 (6%)	8 (8%)		
Age (yr)	59 ± 14	60 ± 12	0.048	0.98 (0.82–1.08)
Sex female	337 (58%)	58 (60%)	0.055	1.00 (0.81–1.27)
Race (consolidated): White	451 (78%)	76 (79%)	0.070	(Reference)
Race (consolidated): not White	56 (10%)	10 (10%)	0.070	1.00 (0.76–1.36)
Race (consolidated): no response	73 (13%)	10 (10%)		0.97 (0.60–1.24)
Body mass index (kg/m^2)	31 ± 8	31 ± 7	0.102	0.99 (0.80–1.14)
ASA Physical Status: III or IV	242 (43%)	50 (53%)	0.199	0.99 (0.76–1.21)
Relationship: not a couple (n = 677)	165 (28%)	34 (35%)	0.152	1.01 (0.81–1.28)
Occupation: not employed	347 (60%)	84 (88%)	0.657*	1.57 (0.96–4.4)
Preoperative taking opioids	62 (11%)	73 (76%)	1.758*	18.6 (10.3–34.5)†
Preoperative taking nonopioid analgesics (n = 679)	189 (32%)	43 (45%)	0.257*	1.00 (0.80–1.24)
Preoperative Anxiety score	49 ± 9	53 ± 10	0.357*	1.01 (0.93–1.14)
Preoperative Depression score	46 ± 8	51 ± 11	0.497*	1.03 (0.95–1.20)
Preoperative Physical Function score	30 ± 8	39 ± 9	1.043*	1.26 (1.01–1.53)†
Preoperative pain last week at surgical site (n = 662)	247 (44%)	73 (77%)	0.721*	1.01 (0.81–1.37)
Surgery type, total hip	42 (7%)	12 (13%)	0.718*	0.99 (0.71–1.29)
Surgery type, knee replacement	47 (8%)	15 (16%)		1.15 (0.89–2.94)
Surgery type, spine surgery	78 (13%)	32 (33%)		1.03 (0.84–1.46)
Surgery type, open thoracic	19 (3%)	1 (1%)		0.99 (0.62–1.45)
Surgery type, mastectomy	38 (7%)	5 (5%)		1.11 (0.84–2.86)
Surgery type, abdominal surgery	360 (62%)	31 (32%)		(Reference)
General anesthesia (n = 668)	529 (92%)	83 (87%)	0.165	0.99 (0.72–1.32)
Neuraxial anesthesia (n = 668)	137 (24%)	28 (30%)	0.126	1.05 (0.87–1.66)
Anesthesia duration (min) (n = 668)	237 ± 139	266 ± 140	0.212*	1.08 (0.99–1.23)
Intraoperative parenteral morphine equivalent (n = 615)	26 ± 20	31 ± 26	0.210*	1.04 (0.96–1.20)
Intraoperative nonopioid analgesics administered	523 (90%)	86 (90%)	0.001	0.97 (0.63–1.22)

Values are presented as n (%) or mean ± SD. Anxiety, Depression, and Physical Function scores are Patient-Reported Outcomes Measurement Information System Scores (Physical Function short form 4a, Anxiety short form 4a, and Depression short form 4a).[29]

*Standardized mean difference > 0.2. †Credible interval > 0; n = 680 unless noted.

ASA, American Society of Anesthesiologists.

The preoperative taking of opioids showed a very strong probability of direction (greater than 99.99%) and the largest mean parameter values for taking opioids at 3 months after surgery (fig. 2). This variable is associated with an adjusted odds ratio of 18.6 (credible interval, 10.3 to 34.5). This variable's probability of significance is so large (greater than 99.9%) and the probability of it being inside the region of practical equivalence is so low (0%) that the hypothesis that its parameter density includes zero (*i.e.*, that coefficient would have no effect on the model's performance) must be rejected. At the same time the Bayesian maximum *a priori*–based *P* value for this variable is low—and the lowest among all variables (less than 0.001), and the probability of direction is high (100%), indicating that its observed positive direction of effect is not due to random sampling (see Table S10, Supplemental Digital Content S10, https://links.lww.com/ALN/D31, "Summary of Posterior Distribution"). Preoperative physical function is the only other variable that seems to have an effect, albeit a weak one (table 2). These results are consistent with the projected prediction analysis (Supplemental Digital Content S12, https://links.lww.com/ALN/D33, "Projected Prediction Analysis for Taking Opioid at Three Months"), which indicates that including preoperative taking of opioids into the submodel yields the largest model prediction performance improvement. Additionally including preoperative physical

Table 3. Patients' Changes in Opioid Taking from before to 3 Months after Surgery (Based on 680 Patients for Whom 3-month Follow-ups were Completed)

	584 Patients Not Taking Opioids at 3 Months (86% of All Patients)	96 Patients Taking Opioids at 3 Months (14% of All Patients)
545 patients not taking opioids before surgery (80% of all patients)	522 (96% of patients not taking opioids before surgery)	23 (4% of patients not taking opioids before surgery)
135 patients taking opioids before surgery (20% of all patients)	62 (46% of patients taking opioids before surgery)	73 (54% of patients taking opioids before surgery)

Table 4. Patients' Changes in Surgical Site Pain from before to 3 Months after Surgery (Based on 656 Patients for Whom 3-month Follow-ups were Completed)

	479 Patients without Site Pain at 3 Months (73% of All Patients)	177 Patients with Site Pain at 3 Months (27% of All Patients)
341 patients with no site pain before surgery (52% of all patients)	296 (87% of patients with no site pain before surgery)	45 (13% of patients with no site pain before surgery)
315 patients with site pain before surgery (48% of all patients)	183 (58% of patients with site pain before surgery)	132 (42% of patients with site pain before surgery)

function into the model provides little incremental performance gain. However, including any additional predictor variables beyond those two changes model performance only very little if at all.

For surgical site pain at 3 months, the presence of preoperative surgical site pain, surgery type knee replacement, and surgery type spine surgery showed very strong probability of direction (greater than 99.99%) and low probability of being inside the region of practical equivalence (0%), such that the hypothesis that their parameter densities include zero (*i.e.*, that coefficient would have no effect on the model's performance) must be rejected. The adjusted odds ratios (credible interval) for these predictors were 2.58 (1.45 to 4.4), 4.1 (1.73 to 8.9), and 2.75 (1.39 to 5.0), respectively. Surgery type mastectomy also has a very strong probability of direction (97%), but in contrast to the other variables, its credible interval is not completely above zero, so the null hypothesis for it cannot be rejected. In contrast, the intraoperative parenteral morphine equivalent has greater than 99.99% probability of being inside of the region of practical equivalence, indicating the null hypothesis (no effect on model performance) should be accepted (see Table S11, Supplemental Digital Content S11, https://links.lww.com/ALN/D32, "Summary of Posterior Distribution, Outcome Surgical Site Pain"). These results are consistent with the projected prediction analysis (Supplemental Digital Content S13, https://links.lww.com/ALN/D34, "Projected Prediction Analysis for Surgical Site Pain at Three Months"), which indicates that including surgery type into the submodel yields the largest model prediction performance improvement. Additionally including preoperative surgical site pain into the model provides some incremental performance improvement. However, including any additional predictor variables beyond those two changes model performance only very little if at all.

No observable correlation was found between the two outcome variables, opioid taking at 3 months and surgical site pain at 3 months. The contribution of the institutions to the observed variance in the outcome variables was found to be less than 2% for either outcome variable.

Discussion

In this multicenter, prospective observational study, we identified one variable as the strongest predictor of opioid use at 3 months postoperatively: preoperative use of opioids. Other factors showed statistical significance in univariable analysis: institution, not being employed, preoperative taking of nonopioid analgesics, anxiety, depression, physical function, preoperative pain at the surgical site, surgery type, and intraoperatively administered morphine equivalent. However, in multivariable statistical modeling analysis (table 2), preoperative use of opioids was the only predictor of opioid use at 3 months postoperatively. Its adjusted odds ratio (18.6; credible interval, 10.3 to 34.5) was large in comparison to other variables and in absolute terms.

In the univariate analysis, a number of predictors achieved statistical significance in their association with the presence of surgical site pain 3 months postsurgery: institution, female sex, not being employed, preoperative taking of opioids or nonopioid analgesics, anxiety, depression, physical function, preoperative surgical site pain, surgery type, general anesthesia, and neuraxial anesthesia. However, in the multivariate model, only three strong predictors were found: preoperative surgical site pain, knee replacement surgery, and spine surgery. Mastectomy showed an elevated signal but did not reach statistical significance.

Notably, no correlation was found between the two outcome variables. This study was not a controlled study, which might have contributed to no correlation being observed.

Table 5. Patient and Case Characteristics, Outcome "Site Pain at 3 Months"

	No Site Pain at 3 Months	Site Pain at 3 Months	Standardized Mean Difference	Adjusted Odds Ratio (Credible Interval)
n	495	180		
Institution 1	22 (4%)	10 (6%)	0.439*	(Group effect)
Institution 2	12 (2%)	1 (1%)		
Institution 3	66 (13%)	34 (19%)		
Institution 4	17 (3%)	9 (5%)		
Institution 5	33 (7%)	20 (11%)		
Institution 6	65 (13%)	10 (6%)		
Institution 7	50 (10%)	25 (14%)		
Institution 8	99 (20%)	31 (17%)		
Institution 9	49 (10%)	9 (5%)		
Institution 10	51 (10%)	20 (11%)		
Institution 11	31 (6%)	11 (6%)		
Age (yr)	59 ± 14	59 ± 13	0.001	0.94 (0.80–1.05)
Sex female	273 (55%)	120 (67%)	0.238*	1.22 (0.93–1.99)
Race (consolidated): White	387 (79%)	136 (76%)	0.089	(Reference)
Race (consolidated): not White	45 (9%)	21 (12%)	0.089	1.15 (0.86–2.14)
Race (consolidated): no response	59 (12%)	23 (13%)		1.10 (0.81–1.98)
Body mass index (kg/m^2)	31 ± 8	30 ± 7	0.077	0.94 (0.73–1.10)
ASA Physical Status: III or IV	224 (47%)	67 (38%)	0.182	0.87 (0.56–1.10)
Relationship: not a couple (n = 673)	144 (29%)	52 (29%)	0.007	0.94 (0.66–1.16)
Occupation: not employed	301 (62%)	127 (71%)	0.191	1.11 (0.89–1.72)
Preoperative taking opioids	71 (14%)	62 (34%)	0.481*	1.49 (0.97–2.68)
Preoperative taking nonopioid analgesics	154 (31%)	76 (42%)	0.232*	1.03 (0.84–1.39)
Preoperative Anxiety score	49 ± 9	51 ± 10	0.219*	1.03 (0.94–1.15)
Preoperative Depression score	46 ± 8	48 ± 10	0.271*	1.02 (0.93–1.15)
Preoperative Physical Function score	30 ± 8	35 ± 9	0.519*	1.03 (0.94–1.17)
Preoperative pain last week at Surgical site (n = 656)	183 (38%)	132 (75%)	0.788*	2.58 (1.45–4.4)†
Surgery type, total hip	38 (8%)	15 (8%)	0.913*	0.97 (0.59–1.40)
Surgery type, knee replacement	23 (5%)	39 (22%)		4.1 (1.73–8.9)†
Surgery type, spine surgery	56 (11%)	51 (28%)		2.75 (1.39–5.0)†
Surgery type, open thoracic	14 (3%)	6 (3%)		1.44 (0.84–5.4)
Surgery type, mastectomy	27 (6%)	16 (9%)		2.69 (1.00–6.5)
Surgery type, abdominal surgery	337 (68%)	53 (29%)		(Reference)
General anesthesia (n = 663)	463 (95%)	145 (83%)	0.389*	0.76 (0.315–1.13)
Neuraxial anesthesia (n = 664)	108 (22%)	57 (33%)	0.236*	1.14 (0.88–1.88)
Anesthesia duration (min) (n = 668)	242 ± 138	238 ± 146	0.028	1.02 (0.96–1.11)
Intraoperative parenteral morphine equivalent	27 ± 20	26 ± 23	0.059	1.01 (0.92–1.10)

Values are presented as n (%) or mean ± SD. Anxiety, Depression, and Physical Function scores are Patient-Reported Outcomes Measurement Information System Scores (Physical Function short form 4a, Anxiety short form 4a, and Depression short form 4a).[29]

*Standardized mean difference > 0.2. †Credible interval > 0; n = 675 unless noted.

ASA, American Society of Anesthesiologists.

However, this finding was similar to that of Goesling *et al.*,[9] who did not find an association between persistent opioid use and a change in joint pain in knee and hip arthroplasty patients, and the suggestion by Brummett *et al.* from nationwide insurance claims data that prolonged opioid use after surgery may not be associated with pain.[26]

The findings about long-term opioid use are similar to findings of mostly retrospective or database-based studies.[52–55] For example, in a retrospective analysis in 490 shoulder arthroplasty patients, patients who had used opioids preoperatively were seven times more likely to still use them 1 yr after discharge.[56] Gil *et al.*, analyzing insurance claims data of 104,154 shoulder arthroscopy patients, found that filling an opioid prescription in the month before the procedure, was one of the factors associated with the highest odds ratios for prolonged opioid use after the procedure.[52] Others found that preoperative opioid use is associated with less improvement or more difficult surgical recovery.[8,53,57] For example, a retrospective analysis of claims data from more than 34,000 adult orthopedic surgery patients found that patients who used opioids preoperatively had worse outcomes in terms of length of stay and revision rates and a 64% smaller rate of opioid use discontinuation in the 18 months after their procedure.[53]

In contrast to the current study, most reports of factors associated with prolonged use of opioids after surgeries were from retrospective studies.[58] Findings in those studies included an association of prolonged postoperative

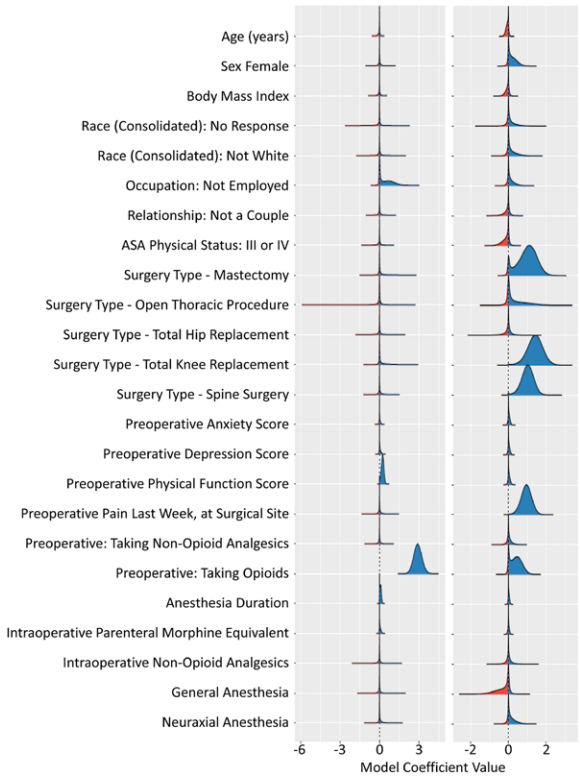

Fig. 2. Posterior values distribution of model coefficients of the relationship with the patient taking opioids at 3 months or not (*left*) and the patient having surgical site pain at 3 months or not (*right*). For each coefficient, the area under the part of the curve that is to the right of the 0.0 line represents the probability that an increase in that variable is associated with an increased chance of the patient taking opioids or having surgical site pain at 3 months. Anxiety, Depression, and Physical Function scores are Patient-Reported Outcomes Measurement Information System Scores (Physical Function short form 4a, Anxiety short form 4a, and Depression short form 4a).[29] ASA, American Society of Anesthesiologists.

opioid use with preoperative depression, anxiety, or mood disorders,[6,26,32] age and lower household income,[7] type of surgery,[6–8] preoperative pain,[23,32] preoperative use of opioids,[32,33,59] and discharge prescription of opioids.[59–61] No association was found between prolonged opioid use and nerve blocks[62,63] or minor *versus* major surgery.[26] Our prospective study included most of these factors, and did not confirm most findings of these retrospective studies, other than preoperative opioid use. However, our study findings were consistent with a prospective study of 574 patients undergoing total knee or total hip arthroplasty that found that patients who reported opioid use on the day of surgery had a much higher rate (41.7%) of still using opioids 6 months after surgery than patients who were opioid-naive on the day of surgery (9.8%).[9]

The incidence of prolonged postsurgical pain in our study is within the range found in previously reported studies.[12–14] While our study's findings about the association of preoperative pain and surgical type are consistent with previous studies,[15,16] they did not confirm other risk factors found in previous studies, including female sex, surgery duration, preoperative use of opioids, and anxiety and depression.[12,14,17–19]

Our multicenter study may not have detected previously identified associations with prolonged postoperative opioid use or prolonged postsurgical pain due to larger variability of care in multicenter *versus* single-center studies. Thus, our study may have been underpowered to detect these previously identified associations,[32,64] which might also have played a role in the relatively large credible intervals of the odds ratios (*e.g.*, table 2, table 5). The addressing of imperfect data by using Bayesian analysis techniques and imputation is a strength of our study. The probability of direction, an inherent output from Bayesian analysis, showed a very strong indication of the emerging predictor variables' effect.

Our study had the following limitations. Outcomes, including the primary outcomes, were patient-reported, which is known to be associated with inherent shortcomings and might have introduced bias.[65] The 3-month completion rate of 64% potentially introduced nonresponse bias. Of those variables that were identified as being strong predictors, the standardized mean differences between participants for whom the 3-month survey was completed and those who were lost to follow-up were below the threshold, except for surgery type, which was slightly above the threshold—indicating that the impact of nonresponse bias on those variables was small. Institution was one of the variables that were not identified as strong predictors but showed an above-threshold standardized mean difference. The contribution of less than 2% by institutions to the observed variance on either outcome variable indicates a limited impact of completion rate differences between institutions. Age also had an above-threshold standardized mean difference: patients lost to follow-up were a few years younger than those who responded at 3 months. The difference in age, however, was not clinically significant. Finally, consolidated race showed a standardized mean difference larger than 0.2, with nonwhite respondents having a somewhat larger loss to follow-up than white respondents. Considering the overall small portion of nonwhite participants, the strength of the signals of the variables that were identified as impactful predictors, and the very small signals of those that were not, the bias introduced by this difference is limited.

This study's completion rate was comparable to other postoperative follow-up studies, especially considering the duration of the follow-up period. In a single-site study of opioid use after cesarean delivery, Bateman *et al.*[66] lost 252 of 975 patients (25.9%) to follow-up by phone, but in a much shorter time after discharge than in this study. A study of 330 general surgery patients yielded a 38% response rate *via* phone after 12 months.[67] Given these comparisons and the lack of evidence for nonresponse bias in our enrolled

sample, we suggest that nonresponse bias is not a major concern for interpretation of our study results.

There were limitations related to the information we were able to collect. For example, while the inclusion of variables in the questionnaires was guided by experts, literature, and a consortium-internal peer review process, we had to limit the number of variables so as not to overwhelm data collectors and participants, lest the data quality would suffer. As another example, while we can confidently detect opioid use, the data quality of patient-reported opioid dosage did not allow us to draw reliable quantitative conclusions about the opioid amounts taken. In addition, not all potential covariates could be included in the models, and we studied only a limited set of type of surgeries, selected for their propensity to cause postoperative pain and prolonged opioid use.

The numbers for the different race categories the participants identified as were imbalanced. Most patients identified as "White," and for many patients (10%), "no response" was recorded in place of their race. The two largest self-reported racial groups were "White" and "Black or African American." The number of participants who identified as "White" was 10 times larger than the number of participants who identified as "Black or African American," the next largest category. None of the nonwhite categories rose above single-digit percentages.

The statistical modeling included all patients for whom data about their 3-month opioid use was available. Some of these patients had missing data in other variables, which we addressed by using imputations. Another limitation is that the statistical model did not consider interactions between variables because of estimation difficulties. Relying on a convenience sample (*e.g.*, no night or weekend cases, availability of study recruitment staff, some institutions focusing their enrollment on certain hospitals within their network) might have introduced bias and did not ensure that recruitment was representative of the general population. There is a wide variation of postsurgical opioid prescribing patterns between individual prescribers[67]; however, both single-institution reports (*e.g.*, Nobel *et al.*[68]) and reports about national trends[69] indicate that postsurgical opioid prescribing is changing over time. With that, another limitation of this report is the age of the data, which were collected toward the end of 2017. Finally, both preoperative and prolonged opioid use might be affected by factors that are challenging to determine in a patient phone survey, including cultural norms and expectations, physician prescribing behaviors, and risk factors for addiction. The use of opioids preoperatively was found to be a predictor of opioid use at 3 months after surgery with a very strong statistical indication of effect.

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Competing Interests

Dr. Brummett reports being a consultant for Heron Therapeutics (San Diego, California), Vertex Pharmaceuticals (Boston, Massachusetts), Benter Foundation (Pittsburgh, Pennsylvania), and Alosa Health (Boston, Massachusetts), and providing expert medical malpractice testimony. Dr. Domino declares no competing interests. She reports research funding to the institution provided by Mathematica (Princeton, New Jersey) and Edwards Lifesciences (Irvine, California), unrelated to this project. Dr. Johnson declares no competing interests. He reports research funding unrelated to this work from Medtronic (Dublin, Ireland) and the National Institute of Neurologic Disorders and Strokes (Bethesda, Maryland). He also reports being an equity partner in Applied Medical Visualizations,

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Supplemental Digital Content

Supplemental Digital Content 1. Table: Table S1, Current Procedural Terminology Codes, https://links.lww.com/ALN/D22
Supplemental Digital Content 2. Table: Table S2, Information Collected, https://links.lww.com/ALN/D23
Supplemental Digital Content 3. Forms: Case Report Forms, https://links.lww.com/ALN/D24
Supplemental Digital Content 4. Table: Table S4, Case Numbers by Institution, https://links.lww.com/ALN/D25
Supplemental Digital Content 5. Table: Table S5, Patient and Case Characteristics and Data Availability, https://links.lww.com/ALN/D26
Supplemental Digital Content 6. Table: Table S6, Patient and Case Characteristics, Outcome "Taking Opioids at Three Months," https://links.lww.com/ALN/D27
Supplemental Digital Content 7. Table: Table S7, Patient and Case Characteristics, Outcome "Taking Opioids at Three Months" (Univariable Testing), https://links.lww.com/ALN/D28
Supplemental Digital Content 8. Table: Table S8, Patient and Case Characteristics, Outcome "Site Pain at Three Months," https://links.lww.com/ALN/D29
Supplemental Digital Content 9. Table: Table S9, Patient and Case Characteristics, Outcome "Site Pain at Three Months" (Univariable Testing), https://links.lww.com/ALN/D30
Supplemental Digital Content 10. Table: Table S10, Summary of Posterior Distribution (Taking Opioids at Three Months), https://links.lww.com/ALN/D31
Supplemental Digital Content 11. Table: Table S11, Summary of Posterior Distribution (Site Pain at Three Months), https://links.lww.com/ALN/D32
Supplemental Digital Content 12. Table: Table S12, Projected Prediction Analysis for Taking Opioid at Three Months, https://links.lww.com/ALN/D33
Supplemental Digital Content 13. Table: Table S13, Projected Prediction Analysis for Surgical Site Pain at Three Months, https://links.lww.com/ALN/D34

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Appendix 1

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Multicenter Perioperative Outcomes Group Enhanced Observation Study Investigator Group

Mitchell F. Berman, M.D., M.P.H., Anesthesiology, Columbia University, New York, New York. Professor of Anesthesiology at the Columbia University Medical Center. Coordinated the performance of the study at the local site, recruited study subjects at the local site, collected and entered data at the local site, created software and database infrastructure for the project, consulted/commented on the manuscript.

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Appendix 2

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Multicenter Perioperative Outcomes Group Enhanced Observation Study Collaborator Group

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