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Day-of-Surgery Gabapentinoids and Prolonged Opioid Use: A Retrospective Cohort Study of Medicare Patients using Electronic Health Records

Jessica C. Young, PhD[1,2], **Nabarun Dasgupta, PhD**[3], **Brooke A. Chidgey, MD**[4], **Til Stürmer, MD, PhD**[1], **Virginia Pate, MS**[1], **Michael Hudgens, PhD**[5], **Michele Jonsson Funk, PhD**[1]

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 135 Dauer Drive, Chapel Hill, NC, 27599-7400, U.S.A.

[2]Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, 725 Martin Luther King Jr. Blvd, Chapel Hill, NC 27599

[3]Injury Prevention Research Center, University of North Carolina at Chapel Hill, 725 Martin Luther King Jr. Blvd., Chapel Hill, NC 27599

[4]Department of Anesthesiology and Pain Management, University of North Carolina School of Medicine, Chapel Hill, NC 27599

[5]Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 135 Dauer Drive, Chapel Hill, NC, 27599-7400, U.S.A.

STRUCTURED ABSTRACT

Background: While preoperative gabapentinoids are commonly used in surgical multimodal analgesia protocols, little is known regarding the effects this therapy has on prolonged postsurgical opioid use. In this observational study, we used data from a large integrated healthcare system to estimate the association between preoperative day-of-surgery gabapentinoids and the risk of prolonged postsurgical opioid use.

Corresponding Author & Request for Reprints: Jessica C. Young, PhD, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 135 Dauer Drive, Chapel Hill, 27599-7400, jessica.young@unc.edu, Phone: (919) 966-7430.

Author Contributions:

Jessica Young: This author led the project planning, analyses, presentation of results, and wrote the manuscript.

Nabarun Dasgupta: This author contributed expertise in pain management research and consulted on the study question, study design, and interpretation of the results, and provided comments and edits to the manuscript.

Brooke Chidgey: This author helped provide dates and specific policy recommendations at the clinical level, contributed knowledge on the mechanisms of action and use of the drugs under study, refined the research question, and provided comments and edits to the manuscript.

Virginia Pate: This author helped with dataset management and infrastructure, statistical coding, and general programming and analytic support.

Til Stürmer: This author helped guide the study design and methodology of this research and provided comments and edits to the manuscript.

Michael Hudgens: This author helped guide study design and statistical methods, provided guidance on interpretation, and provided substantial comments and edits to the manuscript.

Michele Jonsson Funk: This author helped provide oversight over this research, and helped with the study conception, design, analysis, and interpretation, and provided comments and edits to the manuscript.

Conflicts-of-interest: TS owns stock in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk. MJF received consulting fees via UNC from GlaxoSmithKline.

Methods: We identified adults ≥65 years undergoing major therapeutic surgical procedures from a large integrated healthcare system from 2016–2019. Exposure to preoperative gabapentinoids on the day of surgery was measured using inpatient medication administration records and the outcome of prolonged opioid use was measured using outpatient medication orders. We used stabilized inverse probability of treatment weighted log-binomial regression to estimate risk ratios and 95% confidence intervals (CI) of prolonged opioid use comparing patients who received preoperative gabapentinoids to those who did not, adjusting for relevant clinical factors. The main analysis was conducted in the overall surgical population and a secondary analysis was conducted among procedures where at least 30% of all patients received a preoperative gabapentinoid.

Results: Overall, 13,958 surgical patients met inclusion criteria, of whom 21.0% received preoperative gabapentinoids. The observed 90-day risk of prolonged opioid use following surgery was 0.91% (95% CI: 0.77%, 1.08%). Preoperative gabapentinoid administration was not associated with a reduced risk of prolonged opioid use in the main analysis including a broad surgical population (adjRR=1.19 [0.67, 2.12]) or in the secondary analysis conducted in patients undergoing colorectal resection, hip arthroplasty, knee arthroplasty, or hysterectomy (adjRR=1.01 [0.30,3.33]).

Conclusions: In a large integrated health system, we did not find evidence that preoperative gabapentinoids was associated with reduced risk of prolonged opioid use in patients undergoing a broad range of surgeries.

INTRODUCTION

As multimodal analgesic techniques increase in response to the opioid crisis, it is important to investigate the role and appropriateness of gabapentinoids in surgical pain management. Between 2006 and 2007, three systematic reviews evaluating perioperative gabapentinoids and postoperative pain were published, contributing to widespread acceptance that gabapentinoids could help reduce pain and opioid consumption in the immediate post-operative period.[1–3]

More recently, a meta-analysis by Verret et al found that perioperative use of gabapentinoids were not associated with a meaningful reduction in acute, subacute, or chronic pain.[4] In December 2019, the FDA issued a safety communication warning of respiratory depression when gabapentinoids are used concurrently with central nervous system depressants, such as opioids. This communication also discussed growing rates of gabapentinoid misuse and abuse.[5] Despite the fact that gabapentinoid use for preoperative pain is not approved by the FDA, clinical guidelines increasingly recommend use of preoperative gabapentinoids as a component of multimodal analgesia at surgery.[6–8] Likewise, as opioid-sparing techniques gained in popularity,[9,10] hospital protocols increasingly added off-label gabapentinoid use to surgical protocols.[11–13]

It remains unknown to what extent off-label use of gabapentinoids in perioperative pain management can safely reduce opioid consumption and long-term risks of opioid use in different surgical settings and patient populations.[14] To address this knowledge gap, this study uses a large surgical cohort of Medicare patients from an integrated health system

to test the hypothesis that preoperative day-of-surgery gabapentinoid administration is associated with reduced prolonged opioid use following major surgical procedures.

METHODS

This study was approved under UNC IRB 18–1248, and the requirement for written informed consent of these retrospective data was waived by the IRB. This manuscript adheres to the applicable STROBE guidelines.

Data source

Electronic health records (EHR) dating from April 4, 2014 – December 16, 2019 from a large integrated healthcare system in the United States were used. The EHR contains detailed clinical and administrative data for patient care provided across 11 hospitals and over 700 clinics. These data provide an in-depth view of medical encounters, including longitudinal data on diagnosis and procedure codes from any encounter. Relevant to the current study, these data include date and timestamp for start of surgery, surgical procedure code, preoperative pain scores, outpatient medication orders, and inpatient medication administrations. The EHR also include demographic data including height, weight, race, and ethnicity, in addition to self-reported alcohol and tobacco use.

Study Population

Patients undergoing major therapeutic surgical procedures (non-ocular) between January 1, 2016 and September 16, 2019 within the two main surgical facilities in the integrated healthcare system were identified.[15] Both inpatient and outpatient surgeries were included. For patients undergoing multiple surgeries, only the index surgery was examined. Inpatient surgeries were limited to those with a total length of stay of four nights or less, with patients discharged home for self-care.

Patients with any outpatient medication orders for gabapentinoids or diagnoses of epilepsy or postherpetic neuralgia prior to surgery were excluded. Patients with a documented history of opioid abuse, addiction, or dependence, or who had evidence of prolonged opioid use (opioid orders in 3 consecutive months) at any time in the 12 months prior to surgery were excluded. To assess prolonged opioid use, patients were required to have at least 90 days of follow-up after discharge from surgery. Patients who underwent additional surgical procedures, died, or disenrolled from the database during the 90-day follow-up were excluded. The impact of this exclusion on each cohort is reported.

Exposure

The primary exposure was preoperative gabapentinoids, defined using inpatient medication administration records. Administration records for oral gabapentinoids must have been on the day of surgery with an administration start time stamp prior to the start of the surgery, with a description of “GIVEN”. We identified whether pregabalin or gabapentin was administered and the dosage in milligrams.

Outcome

We examined the proportion with prolonged opioid use following surgery. Prolonged opioid use was defined as at least one outpatient opioid order in each of 3 consecutive 30-day windows immediately following surgical discharge.[16]

Potential Confounding Variables

We reported and adjusted for demographic factors that have been found to be associated with healthcare delivery and opioid prescribing practices including patient gender, age, and patient reported race (black, white, other). Because use of preoperative gabapentinoids and rates of opioid prescribing have changed over calendar time and by institution, we controlled for calendar time using 6-month increments and for medical facility of surgery. To address baseline health imbalances, we adjusted for maximum recorded preoperative pain (0, 1–3, 4–6,7+), number of outpatient prescriptions in the prior 6 months (0, 1–6, 7+), patient-reported smoking history (current smoker, former smoker, never smoker, other), patient-reported alcohol use (yes vs no), and body mass index (BMI) categorized according to the US Centers for Disease Control and Prevention. We also adjusted for pain-related medications and diagnoses using binary variables indicating the presence of prescriptions for opioids, benzodiazepines, and pain-related diagnoses (arthritis, cancer, depression, chronic back pain, fibromyalgia, neuralgia, headache/migraine, abdominal pain) during baseline.

Our main analyses controlled for calendar time in 6-month intervals. Because calendar time may be an important confounding variable, we conducted two additional analyses using different specifications to account for calendar time. The first modeled surgery date as a continuous variable (number of days from the start of the study period) using a quadratic term, and the second used a cubic spline with 3 knots at the 10^{th}, 50^{th}, and 90^{th} percentile.[17] Because the healthcare system in this study first implemented Enhanced Recovery After Surgery (ERAS) protocols including preoperative gabapentinoid recommendations on March 1, 2018, we additionally conducted analyses examining whether the association between preoperative gabapentinoids and prolonged opioid use differed in the period before any ERAS protocols (surgery between January 1, 2016 and February 28, 2018) and after the implementation of ERAS protocols (surgery between March 1, 2018 – September 16, 2019). We assessed the interaction between the exposure and period and conducted stratified analyses by period.

Statistical Analyses

Because of the rapidly evolving landscape surrounding opioid prescribing and pain management, we report the percent of patients receiving preoperative gabapentinoids and having prolonged opioid use following surgery by 6-month intervals based on the date of surgery.

Crude and adjusted risk and risk ratios with 95% confidence intervals (CI) of prolonged opioid use in the exposed (received gabapentinoids on the day of surgery) and unexposed (no gabapentinoids on day of surgery) were calculated using log-binomial regression.

Logistic regression adjusting for the potential confounders detailed above was used to calculate propensity scores predicting administration of preoperative gabapentinoids. Adjusted estimates were calculated using stabilized inverse probability of treatment weights (IPTW) to reduce bias due to measured confounders.[18] Exposed subjects received a weight of *(1/ps)*p*, where *ps* represents the predicted probability of exposure to gabapentinoids, and *p* represents the proportion of patients observed as treated with gabapentinoids. Unexposed patients received a weight of *(1-p)/(1-ps)*.[19] Asymmetric trimming at the 1st and 99th percentile of the propensity score was used to define a study population with greater treatment equipoise resulting in more clinically relevant estimates.[20,21] IPTW weights were recalculated among the trimmed population, and balance between the weighted groups were assessed using absolute standardized mean differences (ASMD), with ASMD <0.1 indicating balance.[22] Separate propensity score models were fit for the main, secondary, and sensitivity analyses described below, and asymmetric trimming with stabilized IPTW were repeated within each analysis. Due to extreme weights, 1.5% asymmetric trimming was used in the calendar time stratified analyses.

Main Analysis

The main analysis was conducted in the total population of surgeries meeting the inclusion criteria.

Secondary Analysis

A secondary analysis was conducted on a subset of four surgical procedures (colorectal resection, hip arthroplasty, knee arthroplasty, and hysterectomy) where at least 30% of all patients received a preoperative gabapentinoid, in effort to focus on a clinical population with higher equipoise where preoperative gabapentinoids appeared to be a more common part of care. Results in the population undergoing surgical procedures where less than 30% of patients received preoperative gabapentinoid are also presented in the supplemental materials. Due to small sample size, the secondary analysis controlled for calendar time in 1-year increments instead of 6-month increments.

Sensitivity Analysis

Because we only observe healthcare and medications received within the healthcare system from which the EHR were extracted, we conducted a sensitivity analysis restricting the population to patients with at least one outpatient visit and one outpatient medication order in the healthcare system in the 182 days prior to surgery. This subset of patients represents a group that has a more regular history of interaction with this healthcare system in which we have higher confidence that baseline and follow-up care will be captured in the data. Results in the population who did not meet these criteria are also presented in the supplemental materials. Due to small sample size, the sensitivity analysis controlled for calendar time in 1-year increments instead of 6-month increments.

Quantitative Bias Analyses

Quantitative bias analyses estimate the impact systematic error (such as outcome misclassification) may have on effect estimates. To examine the potential bias due to

imperfect capture of opioid prescriptions during follow-up, we linked a subset of the patients to insurance claims data and conducted two sets of quantitative bias analyses. The first analysis addressed the potential of underestimating prolonged opioid use and assumed that any patients with prolonged opioid use in either EHR or Medicare claims data were correctly classified as having prolonged opioid use ("gold-standard" was the combined EHR and claims data). The second analysis addressed the potential of overestimating prolonged opioid use in the EHR and treated the Medicare claims data as the "gold-standard".[23,24]

For both bias analyses we estimated the positive predictive value (PPV) and negative predictive value (NPV) of prolonged opioid use measured by the EHR data. Using these estimates and corresponding estimated standard errors (SE), we conducted a probabilistic bias analysis which reclassifies the data to present bias-adjusted risk ratios incorporating uncertainty in the measurement of the outcome as well as random error. We resampled the population with replacement creating 1,000 pseudo-populations. For each iteration, the NPV and PPV were randomly drawn from normal distributions with mean and standard deviation equal to the estimated NPV and PPV and the corresponding SEs. The mean risk ratio over the 1,000 iterations is reported as the bias-adjusted risk ratio, and the 2.5th and 97.5th percentile of the 1,000 iterations were reported as the 95% confidence interval.[23]

All analyses were conducted using SAS 9.4 (Cary, North Carolina).

RESULTS

We identified 13,958 Medicare patients undergoing major therapeutic surgical procedures between January 1, 2016 and September 16, 2019 who met study inclusion criteria and had 90 days of follow-up (Figure 1, Supplemental Table 1). Overall, 4.2% (exposed) and 6.0% (unexposed) of patients were excluded for having less than 90 days of follow-up. The vast majority, 94.6% (exposed) and 93.0% (unexposed) of patients were excluded because they had surgery during the 90-day follow-up. In both cohorts, less than 0.4% of patients died during the 90-day follow-up (Supplemental Table 2).

The mean age of eligible patients was 72.7 years (SD=6.0), 57.7% were female, 82.2% reported White race, and 12.4% had opioid orders in the prior 182 days (Table 1). Overall, 21.0% had had preoperative gabapentinoid administration on the day-of-surgery (84.5% of which was pregabalin). The median dose for pregabalin was 100mg (IQR: 50mg, 100mg) while the median dose for gabapentin was 300mg (IQR: 300mg, 600mg).

Calendar Trends

The proportion of patients who received preoperative gabapentinoid administration on the day-of-surgery increased from 7.4% in the first half of 2016 to 28.3% in the first half of 2019 (Table 2).

The observed risk of prolonged opioid use decreased throughout the study period from 1.4 (95% CI: 0.9%, 2.0%) in the first half of 2016, to 0.6% (95% CI: 0.3%, 0.9%) in the first half of 2019. This decreasing trend in prolonged opioid use was larger in patients who

received preoperative gabapentinoids, decreasing from 3.7% (95% CI: 0.5%, 6.8%) to 0.3% (95% CI: 0.0%, 0.8%).

Main Analysis

The observed 90-day risk of prolonged opioid use across the study period was 0.91% (95% CI: 0.77%, 1.08%) (Table 3).

Following IPTW adjustment, the estimated risk of prolonged opioid use after receiving preoperative gabapentinoids was 1.00% (95% CI:0.59,1.68). In contrast, in the absence of receipt of preoperative gabapentinoids, the estimated risk of prolonged opioid use was 0.84% (95% CI: 0.66,1.06). Patients receiving preoperative gabapentinoids were not found to be at higher risk of prolonged opioid use compared to those who did not receive gabapentinoids, with an estimated risk ratio (95% CI) of 1.19 (95% CI: 0.67, 2.12) (Figure 2, Table 3).

Models adjusting for calendar time as a continuous variable using a quadratic term and cubic splines had similar results and are presented in the supplemental materials (Supplemental Table 3). Analysis of interaction between exposure and period (pre-ERAS vs post-ERAS) was not significant (p=0.20), and results from stratified analyses are presented in the supplemental materials (Supplemental Table 4).

Secondary Analysis

There were four distinct procedures in which over 30% of patients received preoperative gabapentinoids: colorectal resection, hip arthroplasty, knee arthroplasty, and hysterectomy. The analysis subset to patients undergoing one of these procedures included 2,626 patients. After adjustment via IPTW, patients receiving preoperative gabapentinoids were at 1.01 (95% CI: 0.30,3.33) times the risk of prolonged use compared to those who did not (Figure 2, Table 3). Among those undergoing surgical procedures where less than 30% of patients received perioperative gabapentinoids, exposed patients were at higher risk of prolonged opioid use, with an estimated risk ratio (95% CI) of 2.34 (1.02,5.41) (Supplemental Table 4).

Sensitivity Analyses

Overall, 5,084 patients had at least one outpatient visit and one outpatient medication order in the 182 days prior to surgery and 22.2% received preoperative gabapentinoids. After adjustment patients receiving preoperative gabapentinoids were at 1.06 (95% CI: 0.57,1.99) times the risk of prolonged use compared to those who did not receive preoperative gabapentinoids (Figure 2, Table 3). Among those without at least one outpatient visit and one outpatient medication order in the 182 days prior to surgery, patients receiving preoperative gabapentinoids were at 1.73 (0.57, 5.30) times the risk of prolonged opioid use compared to those who did not (Supplemental Table 4).

Bias Analyses

A subset of the population (N=3,446) was linked to Medicare insurance claims. The first quantitative bias analysis adjusted for potential underestimation of prolonged opioid use in the EHR (combined EHR and Medicare data used as the gold-standard). The

bias-adjusted risk ratio for the risk of prolonged use comparing patients who received preoperative gabapentinoids to those who did not was 1.45 (95% CI: 0.78, 2.17). A second quantitative bias analysis using Medicare insurance claims as the gold standard resulted in a bias-adjusted risk ratio of 1.48 (95% CI: 0.78, 2.27) (Supplemental Table 5).

DISCUSSION

Our analysis of preoperative gabapentinoid exposure in a cohort of Medicare patients undergoing major therapeutic surgical procedures at a large integrated healthcare delivery system found that 21.0% of patients were administered preoperative gabapentinoids. The observed risk of prolonged opioid use during the 90 days after surgery was relatively low, at 0.91%. The surgeries with the highest proportion of patients receiving preoperative gabapentinoids were colorectal resection, hip arthroplasty, knee arthroplasty, and hysterectomy.

Use of preoperative gabapentinoids increased throughout the study period while the observed risk of prolonged opioid use decreased, suggesting that prescribing behaviors for perioperative pain management changed throughout the study period. The decreasing trend of prolonged opioid use was more dramatic in the gabapentinoid exposed group compared to those who did not receive preoperative gabapentinoids. However, following IPTW adjustment, we did not find that gabapentinoids were associated with a reduced the risk of prolonged opioid use. Given the wide confidence interval (adjRR=1.19 [0.67,2.12]) neither a protective nor harmful effect can be ruled out.

While many past studies have found a reduction in opioid consumption in the first 24–48 hours following surgery among patients who receive preoperative gabapentinoids, a recent systematic review found no clinically significant analgesic effect for perioperative gabapentinoid use.[4] Our study also did not find that preoperative gabapentinoids were associated with a reduction in the risk of postsurgical prolonged opioid use. A randomized controlled trial conducted among patients undergoing a similar mix of surgeries found that perioperative gabapentin promoted opioid cessation (HR=1.24 [1.00, 1.54]). While we focused on gabapentinoids administered on the day of surgery, the RCT continued gabapentin administration for 72 hours following surgery. The mean age of patients in the RCT was also 16 years younger than the current study (56.7 vs 72.7), and opioid cessation was based on self-report instead of prescription data. Further research understanding the potential impact of postsurgical gabapentinoids on the safety and efficacy of gabapentinoid use on opioid consumption following surgery are warranted.

Making causal inference in non-randomized settings requires the assumption of no uncontrolled founding, an assumption which is impossible to verify and difficult to obtain in practice. While we controlled for potential confounding variables using propensity score methods, it is likely there remains unmeasured confounding that was not accounted for in these analyses. We were unable to measure the dosage of opioids administered perioperatively due to limitations in data availability for intravenously administered medications during surgery. Preoperative opioid use could be a proxy for preoperative pain and may also play a role in the amount of opioids prescribed postoperatively. We were

unable to assess and account for potential differences in preoperative opioid administration. Unmeasured confounding may also be present due to changes in practice and increased caution with opioid prescribing during this study periods. We controlled for time trends using 6-month increments as well as additional dates where ERAS protocols were put into place, however it is possible that there remains residual confounding by elements associated with calendar time. While we conducted a stratified analysis splitting the surgeries into two time periods, a larger sample size allowing for more granular stratifications of calendar time and other factors for which the association may differ, such as surgical procedure, would be informative in future work.

This study used EHR from a large integrated healthcare system. These data provide clinical details including inpatient medication orders, preoperative pain scores, patient status upon admission, and patient details including body mass index, smoking, and alcohol history, which are often unavailable in large population based epidemiologic studies. However, the current data include only information for care provided and medication orders from a single healthcare system (could contribute to underestimation of opioid use), and do not include pharmacy fulfillment information (could result to overestimation of opioid use). To address this, we linked a subset of the cohort to Medicare claims data, and conducted probabilistic bias analyses addressing potential misclassification of prolonged opioid use in the EHR data, and found that estimates remained above the null.

We also required that patients had 90 days of follow-up after surgery. Overall, 0.3% of patients died within 90 days after surgery, and examination of medical records found no evidence that any of the deaths were opioid-related fatalities. This study was limited to patients aged 65 or older undergoing surgery in a single health system in the Southeastern United States. Results may not be generalizable to younger populations or other systems and regions with differing surgical and prescribing practices. However, older patients represent an understudied and vulnerable population of interest and these findings add to the limited evidence evaluating the association of preoperative gabapentinoids on downstream opioid use.

Currently, the use of presurgical gabapentinoids has been recommended by diverse professional societies. However gabapentinoid use for surgical pain is considered off-label, and in 2019 the FDA issued a warning and labeling updates to address risks of breathing difficulties in patients who use gabapentinoids, particularly in combination with opioids.[5] Overall, we did not find that presurgical gabapentinoids were associated with a reduction in risk of prolonged opioid use. Given the limited clinical evidence supporting off-label effectiveness, caution is needed when prescribing these medications.[25,26] Attempts to reduce opioid abuse by shifting prescribing towards different drugs for pain management has the potential of unintentionally creating new avenues of abuse.[27,28] The off-label use of these medications to manage surgical pain should be carefully balanced against known harm, and more research is needed to understand the efficacy and safety of preoperative gabapentinoid use.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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GLOSSARY OF TERMS

ASMD	Absolute standardized mean difference
CI	Confidence intervals
BMI	Body Mass Index
EHR	Electronic health records
ERAS	Enhanced Recovery After Surgery
FDA	Food and Drug Administration
IPTW	Inverse probability of treatment weights

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KEY POINTS

Question:

Is preoperative gabapentinoid administration associated with a reduction in prolonged opioid use following surgery?

Findings:

In a cohort study of 13,958 patients, preoperative gabapentinoid administration was not associated with a reduced risk of prolonged opioid use (adjRR=1.19 [0.67, 2.12]); given the limited sample size, the estimate was imprecise with a wide confidence interval ranging from a 33% reduction to 212% increase in risk, suggesting potential for a substantial increase in risk of prolonged opioid use.

Meaning:

The off-label use of preoperative gabapentinoids for surgical pain should be carefully evaluated, as this study did not find an association between prolonged opioid use and preoperative gabapentin.

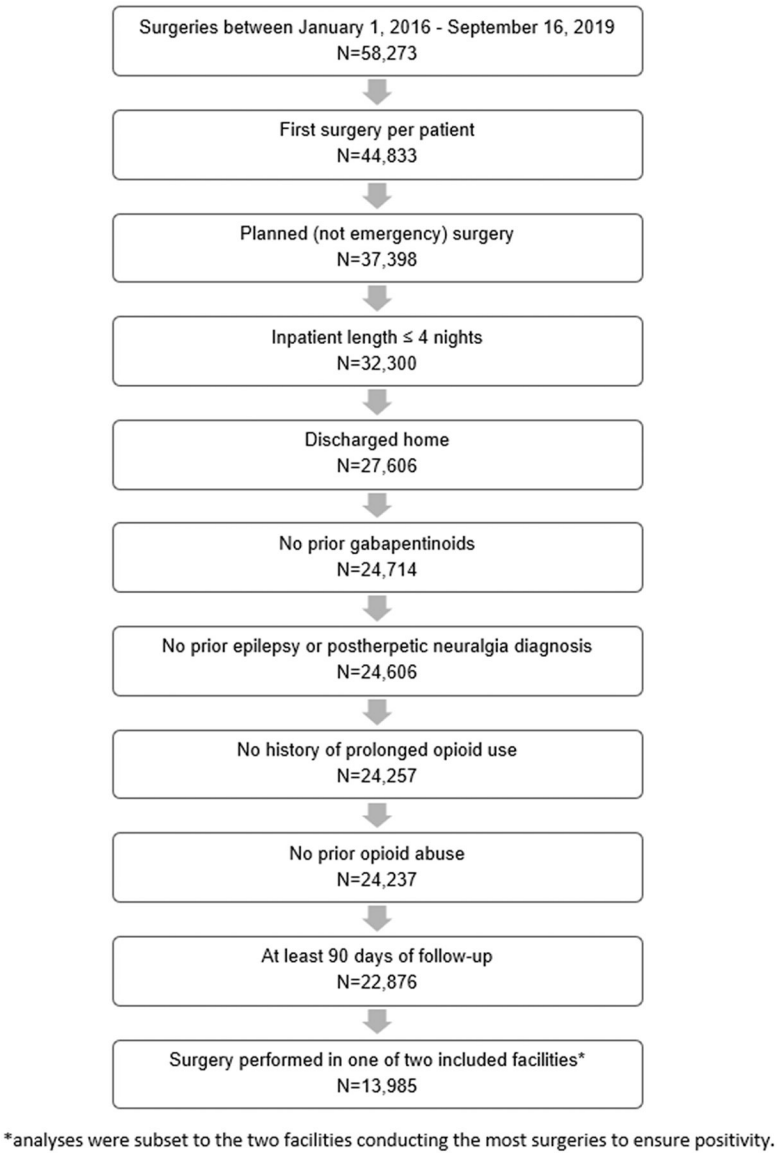

Figure 1.
Flow diagram describing cohort inclusion criteria.

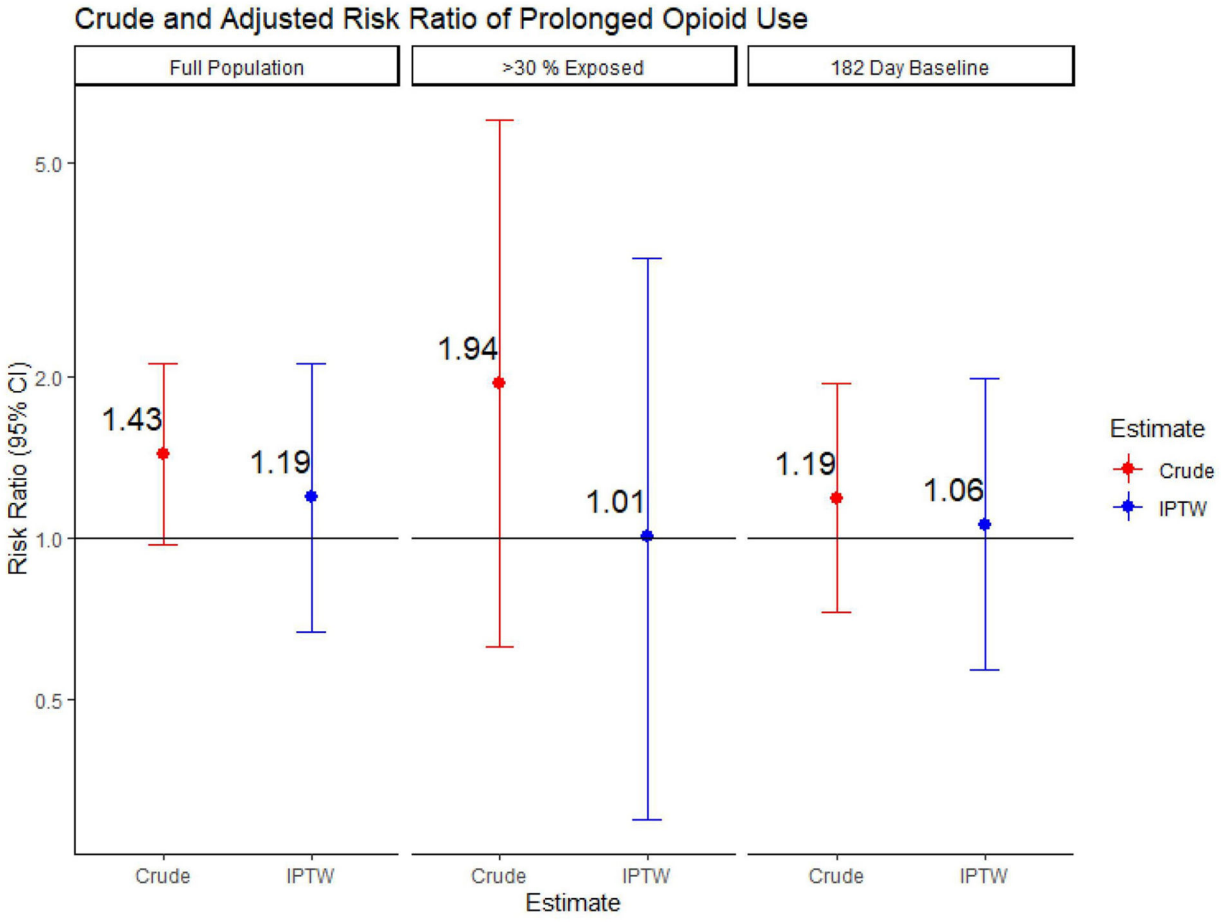

Figure 2.

Crude and adjusted risk ratios of prolonged opioid use comparing patients who received preoperative gabapentinoids to those who did not receive preoperative gabapentinoids.

Table 1.

Baseline Characteristics for Patients undergoing surgery, stratified by receipt of preoperative gabapentinoids.

Characteristic	Observed Patients Before IPTW			After IPTW with 1% Asymmetric Trimming		
	No Preoperative Gabapentinoid	Preoperative Gabapentinoid	ASMD	No Preoperative Gabapentinoid	Preoperative Gabapentinoid	ASMD
	N=11,027	N=2,931		N=8,812	N=2,491	
Female	6,216 (56.4%)	1,844 (62.9%)	0.13	5,278 (59.9%)	1,384 (55.5%)	0.09
Age at admission, mean (SD)	72.9(6.16)	71.7(5.40)	0.22	72.4(5.85)	72.6(5.82)	0.03
Patient Race			0.06			0.06
White	9,021 (81.8%)	2,455 (83.8%)		7,280 (82.6%)	2,074 (83.3%)	
Black	1,419 (12.9%)	324 (11.1%)		1,044 (11.9%)	282 (11.3%)	
Other	587 (5.3%)	152 (5.2%)		488 (5.5%)	136 (5.4%)	
Date of Surgery			0.51			0.08
Jan 2016 - Jun 2016	1,695 (15.4%)	136 (4.6%)		638 (7.2%)	157 (6.3%)	
Jul 2016 - Dec 2016	1,530 (13.9%)	201 (6.9%)		901 (10.2%)	267 (10.7%)	
Jan 2017 - Jun 2017	1,545 (14.0%)	321 (11.0%)		1,209 (13.7%)	348 (14.0%)	
Jul 2017 - Dec 2017	1,395 (12.7%)	374 (12.8%)		1,261 (14.3%)	322 (12.9%)	
Jan 2018 - Jun 2018	1,407 (12.8%)	416 (14.2%)		1,329 (15.1%)	369 (14.8%)	
Jul 2018 - Dec 2018	1,367 (12.4%)	617 (21.1%)		1,365 (15.5%)	372 (14.9%)	
Jan 2019 - Jun 2019	1,517 (13.8%)	600 (20.5%)		1,545 (17.5%)	498 (20.0%)	
Jul 2019 - Sep 2019	571 (5.2%)	266 (9.1%)		563 (6.4%)	159 (6.4%)	
Location			0.32			0.04
Facility 1	7,818 (70.9%)	1,632 (55.7%)		5,476 (62.1%)	1,562 (62.7%)	
Facility 2	3,209 (29.1%)	1,299 (44.3%)		3,336 (37.9%)	929 (37.3%)	
Patient BMI			0.10			0.05
Missing	69 (0.6%)	21 (0.7%)		60 (0.7%)	17 (0.7%)	
Low	128 (1.2%)	24 (0.8%)		100 (1.1%)	33 (1.3%)	
Optimal	2,872 (26.0%)	649 (22.1%)		2,170 (24.6%)	579 (23.2%)	
Overweight	3,975 (36.0%)	1,078 (36.8%)		3,197 (36.3%)	891 (35.8%)	
Obese	3,983 (36.1%)	1,159 (39.5%)		3,284 (37.3%)	972 (39.0%)	
Maximum Presurgical Pain Recorded			0.18			0.04
Missing	34 (0.3%)	4 (0.1%)		20 (0.2%)	7 (0.2%)	
0	8,373 (75.9%)	1,712 (58.4%)		6,287 (71.3%)	1,773 (71.1%)	
1–3	996 (9.0%)	388 (13.2%)		930 (10.6%)	281 (11.3%)	
4–6	1,075 (9.7%)	628 (21.4%)		1,088 (12.3%)	303 (12.2%)	
7+	549 (5.0%)	199 (6.8%)		487 (5.5%)	128 (5.1%)	
Alcohol Use	4,053 (36.8%)	1,195 (40.8%)	0.08	3,247 (36.8%)	942 (37.8%)	0.02
Smoking Status			0.21			0.09
Current	614 (5.6%)	102 (3.5%)		429 (4.9%)	144 (5.8%)	

Characteristic	Observed Patients Before IPTW			After IPTW with 1% Asymmetric Trimming		
	No Preoperative Gabapentinoid	Preoperative Gabapentinoid	ASMD	No Preoperative Gabapentinoid	Preoperative Gabapentinoid	ASMD
	N=11,027	N=2,931		N=8,812	N=2,491	
Former	4,256 (38.6%)	1,036 (35.3%)		3,240 (36.8%)	1,001 (40.2%)	
Other	1,329 (12.1%)	541 (18.5%)		1,403 (15.9%)	404 (16.2%)	
Never	4,828 (43.8%)	1,252 (42.7%)		3,740 (42.4%)	943 (37.8%)	
Baseline Outpatient Medication Orders						
# unique orders			0.06			0.05
0	3,797 (34.4%)	1,072 (36.6%)		3,002 (34.1%)	790 (31.7%)	
1–6	4,511 (40.9%)	1,142 (39.0%)		3,618 (41.1%)	1,022 (41.0%)	
7+	2,719 (24.7%)	717 (24.5%)		2,192 (24.9%)	680 (27.3%)	
Opioids	1,370 (12.4%)	358 (12.2%)	0.01	1,171 (13.3%)	413 (16.6%)	0.09
Benzodiazepines	1,268 (11.5%)	301 (10.3%)	0.04	1,028 (11.7%)	271 (10.9%)	0.03
Baseline Health Conditions						
Recent outpatient visit and outpatient medication order	3,956 (35.9%)	1,128 (38.5%)	0.05	3,399 (38.6%)	970 (39.0%)	0.01
Arthritis	2,003 (18.2%)	731 (24.9%)	0.17	1,781 (20.2%)	574 (23.0%)	0.07
Cancer	2,166 (19.6%)	659 (22.5%)	0.07	1,883 (21.4%)	541 (21.7%)	0.01
Depression	456 (4.1%)	164 (5.6%)	0.07	413 (4.7%)	116 (4.7%)	0.00
Chronic Back Pain	1,980 (18.0%)	484 (16.5%)	0.04	1,612 (18.3%)	491 (19.7%)	0.04
Fibromyalgia	176 (1.6%)	47 (1.6%)	0.00	144 (1.6%)	42 (1.7%)	0.00
Neuralgia	403 (3.7%)	94 (3.2%)	0.03	325 (3.7%)	88 (3.5%)	0.01
Headache/Migraine	454 (4.1%)	141 (4.8%)	0.03	387 (4.4%)	113 (4.5%)	0.01
Abdominal Pain	1,195 (10.8%)	299 (10.2%)	0.02	914 (10.4%)	284 (11.4%)	0.03
Surgical Procedure						
Knee Arthroplasty	505 (4.6%)	875 (29.9%)	0.71	925 (10.5%)	268 (10.8%)	0.01
Lumpectomy	954 (8.7%)	113 (3.9%)	0.20	672 (7.6%)	92 (3.7%)	0.17
Inguinal / Femoral Hernia Repair	769 (7.0%)	39 (1.3%)	0.29	347 (3.9%)	71 (2.9%)	0.06
Laminectomy	679 (6.2%)	49 (1.7%)	0.23	480 (5.4%)	158 (6.3%)	0.04
Hip Arthroplasty	194 (1.8%)	393 (13.4%)	0.45	351 (4.0%)	101 (4.1%)	0.01
Laparoscopic Cholecystectomy	504 (4.6%)	19 (0.6%)	0.25	195 (2.2%)	53 (2.1%)	0.01
Prostate Surgery	395 (3.6%)	8 (0.3%)	0.24	74 (0.8%)	18 (0.7%)	0.01
Colorectal Resection	172 (1.6%)	227 (7.7%)	0.30	244 (2.8%)	71 (2.8%)	0.00
Hysterectomy	146 (1.3%)	75 (2.6%)	0.09	179 (2.0%)	49 (2.0%)	0.00
Other Procedure[a]	6,709 (60.8%)	1,133 (38.7%)	0.46	5,346 (60.7%)	1,610 (64.6%)	0.08

ASMD-absolute standardized mean difference; BMI-body mass index; IPTW-inverse probability of treatment weights; SD-standard deviation

[a]Other procedures include other hernia repair, thyroidectomy, endocrine procedures, shoulder arthroplasty, muscle tendon procedures, heart valve procedures, endarterectomy, spinal fusion, rotator cuff repair, mastectomy, and other procedures occurring in less than 1.5% of patients.

Table 2.

Percent of patients exposed to preoperative day-of-surgery gabapentinoids and observed to have prolonged opioid use by time period.

Time Period	Total Number of Patients	Percent Exposed (95% CI)	Percent with Prolonged Opioid Use (95% CI)		
			Overall	Unexposed	Exposed
January 2016-June 2016	1,878	7.4% (6.2,8.6)	1.4% (0.9,2.0)	1.2% (0.7,1.8)	3.7% (0.5,6.8)
July 2016 - December 2016	2,310	11.6% (10.1,13.1)	0.9% (0.4,1.3)	0.5% (0.2,0.9)	3.5% (0.9,6.0)
January 2017 - June 2017	2,390	17.2% (15.5,18.9)	0.9% (0.5,1.3)	0.9% (0.4,1.4)	0.9% (0.0,2.0)
July 2017 - December 2017	2,248	21.1% (19.2,23.0)	1.0% (0.5,1.4)	0.7% (0.3,1.2)	1.9% (0.5,3.2)
January 2018 - June 2018	2,300	22.8% (20.9,24.7)	1.0% (0.6,1.5)	1.1% (0.5,1.6)	1.0% (0.0,1.9)
July 2018 - December 2018	2,484	31.1% (29.1,33.1)	0.9% (0.5,1.3)	0.8% (0.3,1.3)	1.1% (0.3,2.0)
January 2019 - June 2019	2,735	28.3% (26.4,30.3)	0.6% (0.3,0.9)	0.7% (0.3,1.2)	0.3% (0.0,0.8)
July 2019 - September 2019	1,090	31.8% (28.6,34.9)	0.2% (0.0,0.6)	0.4% (0.0,0.8)	0.0% (0.0,1.1)
Cochran-Armitage Test for Trend		p<.0001	p=.0072	p=.2167	p<.0001

Table 3.

Crude and adjusted risk and risk ratios of prolonged opioid use comparing patients who received preoperative gabapentinoids to those who did not (referent).

Population	Exposure Status	Number of Patients	Observed Risk (95% CI)	Number of Patients after Trimming	Adjusted[a] Risk (95% CI)	Adjusted[a] Risk Ratio (95% CI)
Full Population	Overall	13,958	0.91% (0.77,1.08)	11,303	0.87% (0.70,1.09)	1.19 (0.67,2.12)
	Gabapentinoid=1	2,931	1.19% (0.86,1.66)	2,491	1.00% (0.59,1.68)	
	Gabapentinoid=0	11,027	0.83% (0.68,1.02)	8,812	0.84% (0.66,1.06)	
Surgeries with >30% Exposed	Overall	2,626	0.62% (0.38,1.01)	2,410	0.70% (0.41,1.21)	1.01 (0.30,3.33)
	Gabapentinoid=1	1,587	0.76% (0.44,1.34)	1,481	0.70% (0.39,1.28)	
	Gabapentinoid=0	1,039	0.39% (0.15,1.05)	929	0.70% (0.25,1.98)	
Outpatient Visit and Rx in Prior 182 Days	Overall	5,084	1.63% (1.32,2.02)	4,192	1.85% (1.42,2.40)	1.06 (0.57,1.99)
	Gabapentinoid=1	1,128	1.86% (1.22,2.84)	927	1.94% (1.11,3.36)	
	Gabapentinoid=0	3,956	1.57% (1.22,2.01)	3,264	1.82% (1.35,2.45)	

[a]Stabilized Inverse probability of treatment weights (IPTW) were calculated within each population after conducting 1% asymmetric trimming to adjust for baseline confounding.