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Safety implications of concomitant administration of antidepressants and opioid analgesics in surgical patients

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Abstract

Background: Commonly prescribed antidepressants (paroxetine, fluoxetine, duloxetine, bupropion) inhibit bioconversion of several prodrug opioid medications to their active metabolite, potentially decreasing analgesic effect. There is a paucity of studies assessing the risk-benefit of concomitant administration of antidepressants and opioids.

Research design and methods: Observational study of adult patients taking antidepressants prior to scheduled surgery using 2017–2019 electronic medical record data to assess perioperative use of opioids and to determine the incidence and risk factors for developing postoperative delirium. We conducted a generalized linear regression with the Gamma log-link to assess the association between use of antidepressants and opioids and a logistic regression to assess the association between antidepressants use and the likelihood of developing postoperative delirium.

Results: After controlling for patient demographic and clinical characteristics, and postoperative pain, use of inhibiting antidepressants was associated with 1.67 times greater use of opioids per hospitalization day ($p = 0.00154$), a two-fold increase in the risk for developing postoperative delirium ($p = 0.0224$), and an estimated average of four additional days of hospitalization ($p < 0.00001$) compared to use of non-inhibiting antidepressants.

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Conclusions: Careful consideration to drug-drug interactions and risk of related adverse events remains critical in the safe and optimal management of postoperative pain in patients taking concomitantly antidepressants.

Keywords

Adverse events; antidepressants; drug safety; drug-drug interactions; opioid analgesics; postoperative complications; delirium

1. Introduction

In the United States (US), approximately one in five adults will suffer from a mental health disorder in any given year [1] with nearly a third of adults experiencing a mental health disorder, including a major depressive disorder, during their lifetime [2]. In 2020, 8.4% of adults in the US had a major depressive episode in the past 12 months and 66.0% of those who suffered a major depressive episode received treatment for depression [1].

Antidepressants are one of the most prescribed medications in the US [3]. In the period 2015–2018, 13.2% of adults reported using antidepressants in the past 30 days for major depressive disorders, anxiety disorders, and mood disorders [4]. Overall, use of antidepressants increased from 10.6% to 13.8% during the decade between 2009–2010 and 2017–2018 [4]. Use of antidepressants is also common in patients undergoing surgery. Approximately, 13–15% of adults undergoing surgery were taking selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) during the perioperative period [5]. Perioperative use of antidepressants has been identified as a risk factor for developing postoperative delirium [6], one of the most prevalent postoperative complications in the US [7].

Immediate-acting oral opioids are the drugs of choice to achieve postoperative analgesia [8]. Several oral opioids, including hydrocodone, tramadol, and codeine, require conversion to their active metabolite by the enzyme cytochrome P450 (CYP) 2D6 [9]. Some commonly prescribed antidepressants strongly inhibit CYP2D6 metabolism (paroxetine, fluoxetine, duloxetine, and bupropion) limiting the bioconversion of an opioid prodrug (a drug that is administered in a biologically inactive form and is enzymatically activated into an active metabolite) to its active analgesic metabolite [10]. When used concomitantly with an opioid prodrug, CYP2D6-inhibiting agents may decrease prodrug conversion and analgesia, potentially leading to greater opioid requirements.

Adverse events due to drug-drug interactions may be of clinical significance and are preventable. A literature review suggested that moderate-to-strong inhibiting antidepressants should be avoided in patients taking codeine [11]. Another study found an increased risk of opioid overdose-related hospitalizations and emergency department visits in older adults taking inhibiting antidepressants fluoxetine or paroxetine who were initiated on oxycodone [12]. Conversely, others have recommended to prescribe direct acting opioids such as oxycodone in patients taking inhibiting antidepressants [13]. Hence, further research is needed to elucidate the risk of adverse events in patients taking antidepressants and opioid analgesics concomitantly [11].

Furthermore, achieving a balance between patient safety and optimal pain management requires a better understanding of drug-drug interactions in surgical patients [5]. A study assessing the difference between preoperative and postoperative pain found that surgical patients taking inhibiting antidepressants and hydrocodone, codeine, or tramadol had significantly worse postoperative pain control compared to patients taking non-inhibiting antidepressants [13]. Authors used prescription orders to assess use of opioids but lack data on daily morphine milligram equivalents (MME) administered to patients and did not evaluate how antidepressant-opioid drug interactions may affect clinical outcomes. This study strives to fill this knowledge gap by assessing perioperative use of opioid analgesics in MME per hospitalization day by type of antidepressants and by examining how concomitant use of antidepressants and opioids may impact postoperative delirium.

2. Patients and Methods

2.1. Study Data and Design

This was a retrospective observational study to assess perioperative use of opioid analgesics, incidence of postoperative delirium, and risk factors for developing postoperative delirium in non-cancer adult surgical patients taking CYP2D6-inhibiting antidepressants prior to hospital admission compared to their counterparts taking non-CYP2D6-inhibiting antidepressants. Study data were extracted from the University of California San Francisco (UCSF) Medical Center electronic medical record data (EMR) software (Epic Systems, Verona, Wisconsin, USA). The UCSF Institutional Review Board (IRB) approved this study and waived the written informed consent for all study subjects (IRB #19–29449).

2.2. Patient Population

The patient population consisted of non-cancer adult patients who underwent scheduled elective surgery in the period January 2017 through December 2019 with a hospital stay of at least 24 hours. In the instance a patient underwent multiple procedures during the study period (n= 132) only the first procedure was included. We included patients who were taking antidepressants prior to hospitalization and received at least one inpatient administration of an antidepressant and a prodrug opioid (hydrocodone, codeine, or tramadol) to manage postsurgical pain. We excluded patients who were taking both inhibiting and non-inhibiting antidepressants prior to hospital admission (n= 44) and patients who received both antidepressant types during the hospitalization (n = 160). To determine the patient's clinical complexity at hospital admission, we used the American Society of Anesthesiologists (ASA) physical status classification system. We excluded patients who had an ASA score of IV and V (Incapacitating Disease/Moribund/Brain dead) at hospital admission (n= 14) or who had no documented ASA score (n=3). Lastly, we excluded patients who had a documented diagnosis of substance use disorder or methadone use prior to hospital admission (n= 11) and patients with confidential medical records (i.e., break-the-glass) (n=3). Patients undergoing oncology related procedures during hospitalization of interest (n= 3) were also excluded in the final analytical sample.

Use of antidepressants and opioid analgesics, prior to hospital admission and during hospitalization, was ascertained by EMR drug administration data. Patients were stratified

by prior to hospital admission use of antidepressants that strongly inhibit CYP2D6 (paroxetine, fluoxetine, duloxetine, and bupropion) and patients taking antidepressants that do not strongly inhibit CYP2D6 (citalopram, desvenlafaxine, escitalopram, fluvoxamine, sertraline, and venlafaxine). Patients who did not have an opioid prescription on their EMR medication history list were deemed as opioid naïve.

2.3. Measures

Study data included patients' sociodemographic characteristics (age, sex and race, and health insurance type) and clinical characteristics (surgery type and duration, ASA score). Diagnoses for opioid-related disorders (ICD-10-CM F11), depression (ICD-10-CM F32 & F33), anxiety disorders (ICD-10-CM F41), and liver (ICD-10-CM K70-K77) and kidney (ICD-10-CM N17-N19 & N28) co-morbidities were ascertained using the International Classification of Diseases, Tenth Revision (ICD-10-CM) codes.

The primary outcome of interest was perioperative use of opioids per day of hospitalization stratified by antidepressant type. Secondary outcomes were incidence of postoperative delirium and risk factors for developing postoperative delirium. We also assessed length of stay (LOS) as a process outcome. Total opioid usage was summed across the hospital day and divided by the LOS. All opioid doses administered were converted into MME using the 2018 UCSF Pain Management Committee's opioid equivalent algorithm [14]. Patient self-reported postoperative pain scores throughout the hospital stay were derived from the clinical documentation using the Numeric Rating Scale (0 = no pain, 10 = worst pain imaginable). The time-weighted average pain score was calculated by trapezoidal method from first to last recorded patient's pain score in the EMR.

Postoperative delirium data were ascertained using diagnoses codes (ICD-10-CM F05 and R41.82) documentation in the patient's problem list on Epic. In addition, we used the global search function within the clinical notes/discharge summary to search for the keyword of "delirium". Then, we manually confirmed that the clinical notes referred to the patient experiencing delirium. Delirium documentation was also ascertained using the reliable and validated Nursing Delirium Screening Scale (Nu-DESC) score routinely recorded in the EMR at our institution [15]. We defined postoperative delirium as a Nu-DESC score ≥2 after surgical procedure. Duration of delirium was calculated as the number of days in which a patient had a Nu-DESC score ≥2 through the LOS. In patients admitted into the intensive care unit (ICU), delirium was ascertained using the validated Confusion Assessment Method (CAM-ICU) recommended by the Society of Critical Care Medicine [16]. Postoperative delirium data and co-morbidities documentation were collected in REDCap [17]. Data accuracy was confirmed by chart review, comparison with data extracted in prior studies, and assessment of inconsistencies, missingness, and extreme values. Two study investigators independently extracted data from the EMR and checked for concordance. Data discrepancies were discussed with the study principal investigator and resolved by consensus.

2.4. Statistical Analysis

We conducted descriptive statistics to characterize the study sample. We used Chi-square test and Fisher's exact test to assess statistically significant differences in the patient's demographic and clinical characteristics between patients who used inhibiting and non-inhibiting antidepressants. We used Mann-Whitney U test to assess statistically significant differences between MME, length of surgical procedure, and hospital stay and study groups. We computed the bias-corrected and accelerated (BCa) bootstrap 95% confidence interval (CI) for length of surgical procedure and hospitalization.

We conducted bivariate generalized linear regression to identify predictors of perioperative use of opioids and hospital LOS. Statistically significant variables ($p < 0.05$) from bivariate analysis were included in the multivariable linear regression model. We conducted generalized linear model (GLM) with the Gamma log-link to assess the association between perioperative use of opioid analgesics per day of hospitalization and type of antidepressants while addressing the skewed distribution of perioperative use of opioids and hospital LOS.

In addition, we conducted bivariate logistic regression analysis to identify predictors of risk of developing postoperative delirium. We included statistically significant covariates in the adjusted logistic regression model to assess the association between perioperative use of opioids and the likelihood of developing postoperative delirium and assessed adjusted odds ratios (AORs) to determine the magnitude of the association. We set statistical significance at two-tailed p-value less than 0.05. Analyses were performed using R software (version 4.0.5, R Foundation).

3. Results

In the study period, 662 patients met inclusion criteria. Of them, 442 (63.75%) were female (Table 1). Patients had a mean age of 57.67 (standard deviation [SD], 14.49) years at hospital admission. At hospital admission, most patients were classified as having mild (47.89%) and severe systemic disease (49.09%). Almost half of patients (43.96%) were enrolled in Medicare. Most patients (52.57%) underwent neurological surgery, followed by orthopedic (16.77%) and general surgery (12.37%). There were no statistically significant differences in the demographic or clinical characteristics at hospital admission between patients using inhibiting (50.45%) and non-inhibiting (49.55%) antidepressants except for the proportion of opioid naïve patients (Table 1). A significantly lower proportion of opioid naïve patients used inhibiting antidepressants (36.83%) than patients who used non-inhibiting antidepressants (46.65%; $p = 0.02$).

After adjusting for patient demographic characteristics age and sex, prior to hospitalization use of opioid analgesics and ASA score, surgical procedure type, and patient's reported postoperative pain, and the interaction effect between sex and antidepressant type, we found a statistically significant difference in the adjusted mean;95%CI MME per day of hospitalization between patients taking non-inhibiting antidepressants (99.48; 83.10–119.10) and patients taking inhibiting antidepressants (123.97; 104.59–148.41 p=0.0132) (Figure 1). Furthermore, use of inhibiting antidepressants was significantly associated with 1.67 times greater use of MME per day of hospitalization compared to use of non-inhibiting

antidepressants (p=0.00154) (Table 2). The interaction effect between sex and use of inhibiting antidepressants was also a significant predictor of use of opioid analgesics (p = 0.00375) such that the combination of female sex and use of inhibiting antidepressants was associated with less opioid use perioperatively than would be used by male patients using non-inhibiting antidepressants (Table 2).

The overall incidence of postoperative delirium was 14.35% (n=95). Of the 334 patients who used inhibiting antidepressants, 57(17.0%) developed postoperative delirium. Whereas, of the 328 patients who used non-inhibiting antidepressants, 38(11.59%) developed postoperative delirium (p =0.05742). The incidence of delirium in patients admitted in the ICU was 16.62% (n=110). Furthermore, 75 (11.33%) patients had at least one instance of NuDesc score ≥ 2 documented in the EMR. A greater proportion of patients using inhibiting antidepressants experienced at least one instance of NuDesc score ≥ 2 than patients using non-inhibiting antidepressants. Of the 334 patients who used inhibiting antidepressants, 41(12.28%) patients had at least one instance of NuDesc score ≥ 2. Whereas, of the 328 patients who used non-inhibiting antidepressants, 34(10.37%) patients had at least one instance of NuDesc score ≥ 2 (p=0.5405). The mean±SD number of days patients had a NuDesc score ≥ 2 was 3.64 ± 4.33 days.

Bivariate analysis showed that unadjusted odds ratios for age (p=0.00036), ASA physical status score (p <0.00001), and neurological surgery (p= 0.02670) and use of inhibiting antidepressants (p= 0.00455) were significant predictors of the risk for developing postoperative delirium (Table 3). We also found an inverse association between perioperative use of opioids and the unadjusted risk of developing postoperative delirium (p =0.0470). After controlling for patient's demographic and clinical characteristics, use of opioid analgesics prior to hospitalization, and surgical procedure type, use of inhibiting antidepressants was associated with a 1.96 times greater risk of developing postoperative delirium compared to use of non-inhibiting antidepressants (p =0.0224) (Table 3).

Lastly, after controlling for patient's demographic and clinical characteristics prior to hospitalization, ICU admission, and perioperative use of opioids, developing postoperative delirium was associated with a significantly longer hospital length of stay (p <0.00001) (Table 4). Postoperative delirium was associated with an estimated average of four additional days of hospitalization (p <0.00001).

4. Discussion

To our knowledge, this is the first study to assess safety implications of concomitant administration of opioid analgesics and antidepressants, stratified by the antidepressant's degree of CYP2D6 inhibition, in surgical patients. Our findings suggest that, compared to use of non-inhibiting antidepressants, use of inhibiting antidepressants was significantly associated with greater perioperative use of opioids per day of hospitalization and a greater risk of developing postoperative delirium. We also found that developing postoperative delirium was significantly associated with longer hospitalizations.

Our findings on the decreased analgesic effect of opioids in patients concomitantly taking inhibiting antidepressants contribute to a growing body of evidence that supports the consideration of pharmacokinetic drug-drug-interactions, such as CYP2D6 inhibition, when addressing pain management. A recent study found that patients undergoing total knee replacement or total hip surgery taking CYP2D6 inhibitors used a higher total dose of hydrocodone during hospitalization and after discharge [18]. Other retrospective studies found that paroxetine inhibited the bioconversion of tramadol [19] and hydrocodone [20,21] to active metabolites subsequently attenuating the agent's analgesic properties. Lastly, a randomized controlled study, including a small sample of healthy volunteers, found that paroxetine diminished the oxycodone analgesic effect [22]. The 2022 updated Clinical Pharmacogenomics Implementation Consortium guidelines recommend against the use of codeine and tramadol in poor and ultrarapid metabolizers and acknowledge that there is insufficient evidence to make conclusive recommendations for hydrocodone and oxycodone [23].

Furthermore, our findings on the statistically significant differences in the interaction effect between antidepressant type and sex and amount of morphine needed to achieve same level of analgesia, add to the emerging evidence on the pharmacogenomic differences in the response to pain medications suggesting that a patient's CYP2D6 genotype may be clinically important to consider since it may affect the metabolism of some opioids. Previous studies explored the genetic variation in CYP2D6 phenotypes and response to opioids [24]. A study assessing the interaction between sex and CYP2D6 phenotypes found a statistically significant difference in the opioid response among female (but not male) in patients taking codeine and tramadol [25]. Authors recommended sex differences to be considered in the interactions between pharmacogenomics and response to pain medications [25].

In line with previous studies, we found a 14.35% incidence rate of postoperative delirium. Previous studies estimated the incidence of postoperative delirium between 11% and 27% [26]. We also found that the incidence of postoperative delirium was greater in patients using inhibiting antidepressants than in their counterparts using non-inhibiting antidepressants and use of inhibiting antidepressants was a significant predictor of the likelihood of developing postoperative delirium. While the root causes of delirium are often multifactorial, predisposing risk factors for postoperative delirium include old age and comorbidity of depression and dementia [26,27]. Some studies found that use of opioid analgesics is a major contributing factor for developing delirium [28,29]. Whereas other studies found that preoperative [30,31] and postoperative pain [32] were independently associated with a greater risk for delirium. The complex interplay of pain, use of pain medications, and delirium may be bi-directional as both inadequate management of acute postoperative pain and over-treatment of pain can precipitate postoperative delirium. Furthermore, the lack of perioperative guidelines for the management of co-administration of central nervous system medications in the inpatient setting, where opioids are heavily relied upon for analgesia, may lead to variations in pain management and to greater risk of postoperative complications [33]. Hence, pain management interventions and opioid stewardship initiatives need to carefully consider the risk-benefit of concurrent use of opioids and antidepressants in designing effective and safe opioid regimens [29].

Lastly, we found that postoperative delirium was significantly associated with excess hospitalization days. Patients who develop delirium after surgery use significantly more healthcare resources and cost more to health care systems. The annual per patient healthcare costs attributable to postoperative delirium in older Medicare patients undergoing surgery have been estimated at $44,291 (95% CI $34,554-$56,673) and $56,474 (95% CI, $40,927-$77,440) for severe delirium [34].

Our study has some limitations. Due to the retrospective nature of this study, we cannot conclude that identified associations with study outcomes represent causal effects. As in any retrospective study, there is a possibility of underestimating the incidence of adverse events including postoperative delirium. To overcome this limitation, we used diagnosis codes, applied validated and commonly used metrics for delirium ascertainment, and thoroughly reviewed clinicians' narrative documentation. While regression analyses accounted for known potential confounders, there is a potential risk that unknown confounders may impact observed associations with study outcomes. Data on prior to hospital admission use of antidepressant medications were derived from the admission medication history lists which may be incomplete or contain errors. In addition, it is possible that patients who were not taking their antidepressant medications at home as prescribed and were restarted on antidepressants during the hospitalization may not have been taking their antidepressants long enough to observe the pharmacokinetic interaction with opioids of interest. Lastly, study findings may not be generalizable to non-surgical patients or to other healthcare settings. Our findings warrant further investigation to determine the clinical significance and overall economic impact of perioperative use of antidepressants and CYP2D6-metabolized opioids in a larger patient population.

5. Conclusions

In this observational study on the drug-drug interactions and risk factors for postoperative complications in non-cancer adult patients undergoing elective surgery, we found that, after controlling for patient's demographic and clinical characteristics and postoperative pain, patients taking inhibiting antidepressants used more opioids per day of hospitalization and had a greater likelihood of experiencing postoperative delirium than patients taking non-inhibiting antidepressants. We also found that postoperative delirium was significantly associated with an estimated average of four additional days of hospitalization. This study provides evidence of the patient safety implications of drug-drug interactions between antidepressants and opioid analgesics. This work highlights the importance of routine monitoring of patients undergoing surgery who may be at risk of post-operative complications.

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Ethical approval:

The UCSF Institutional Review Board (IRB) approved this study and waived the written informed consent for all study subjects (IRB #19-29449).

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interest or of considerable interest to readers (• and •• (single and double bullet marks), respectively) with a short note below t

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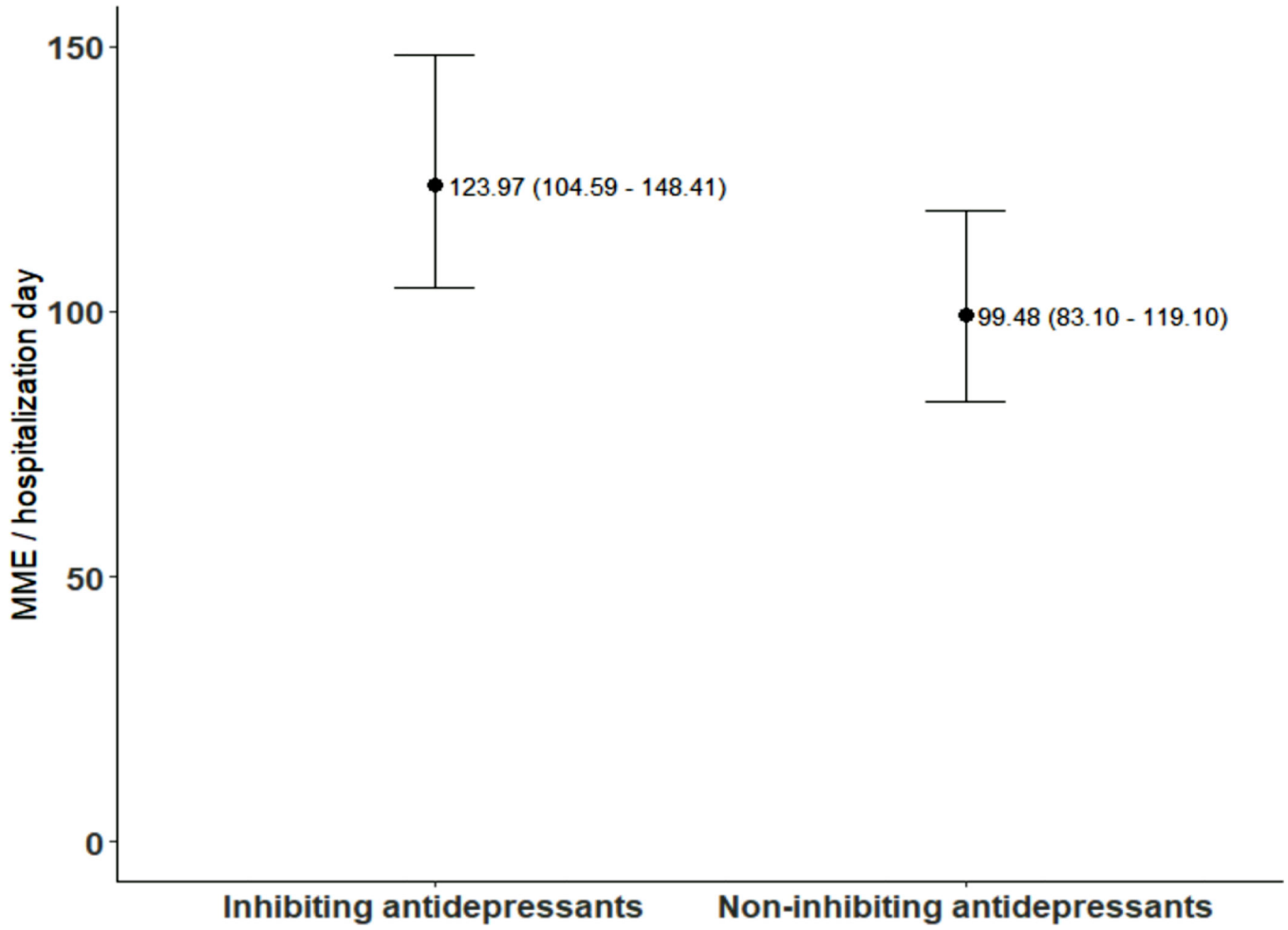

Figure 1.
Adjusted mean (95% CI) morphine milligram equivalents per day of hospitalization

Table 1.

Patients' Characteristics at Hospital Admission, 2017– 2019

	All patients	%	Inhibiting Antidepressants		Non-inhibiting Antidepressants		p-value
N	**662**		**334**	**50.45%**	**328**	**49.55%**	
Female	422	63.75%	225	67.37%	197	60.06%	0.0610
Age (mean(sd))	57.67(14.49)		58.10(14.82)		57.24 (14.15)		0.1652
Age							
18–34	59	8.91%	29	8.68%	30	9.15%	0.4430
35–44	71	10.73%	34	10.18%	37	11.28%	
45–54	101	15.26%	50	14.97%	51	15.55%	
55–64	192	29.00%	89	26.65%	103	31.40%	
65+	239	36.10%	132	39.52%	107	32.62%	
Health Insurance Type							
Commercial	198	29.91%	90	26.95%	108	32.93%	0.1995
Medicare	291	43.96%	159	47.60%	132	40.24%	
Medi-Cal	144	21.75%	69	20.66%	75	22.87%	
Other	29	4.38%	16	4.79%	13	3.96%	
ASA physical status class							0.3613
ASA 1- Healthy	20	3.02%	9	2.69%	11	3.35%	
ASA 2- Mild Systemic Disease	317	47.89%	152	45.51%	165	50.30%	
ASA 3- Severe Systemic Disease	325	49.09%	173	51.80%	152	46.34%	
Comorbidities							
Liver disease (ICD-10 codes K70-K77)	37	5.59%	21	6.29%	16	4.88%	0.5352
Kidney disease (ICD-10 code N17-N19, N28)	133	20.09%	75	22.46%	58	17.68%	0.1512
Depression (ICD-10 F32 & F33)	528	79.76%	265	79.34%	263	80.18%	0.8629
Anxiety disorder (ICD-10 F41)	368	55.59%	189	56.59%	179	54.57%	0.6577
Analgesic opioids use prior to hospitalization							0.0232
Opioid naïve patients	276	41.69%	123	36.83%	153	46.65%	
IR opioids	323	48.79%	173	51.80%	150	45.73%	
ER/LA opioids	63	9.52%	38	11.38%	25	7.62%	
Preoperative Self-Reported Pain	86	12.99%	48	14.37%	38	11.59%	0.7862
Procedure Type							0.5676
General Surgery	82	12.39%	36	10.78%	46	14.02%	
Neurological Surgery	348	52.57%	175	52.40%	173	52.74%	
Orthopedic Surgery	111	16.77%	59	17.66%	52	15.85%	
Other	121	18.28%	64	19.16%	57	17.38%	
ICU Admission	110	16.62%	59	17.66%	51	15.55%	0.5308

	All patients	%	Inhibiting Antidepressants	Non-inhibiting Antidepressants	p-value
Length of Surgery in Hours mean (95%CI Bias-corrected)	4.67 (4.49– 4.85)		4.80 (4.55–5.10)	4.53 (4.30–4.78)	0.2055
Hospital Length of Stay in Days mean (95%CI Bias-corrected)	7.37 (6.73–8.21)		7.22(6.47–8.18)	7.5287 (6.50–9.06)	0.0917

ASA: American Society of Anesthesiologists physical status classification system. PTA: Prior to Admission. ER/LA opioids: Extended release/ Long-Acting opioids. IR opioids: Immediate release opioids

Table 2:

Multivariable linear regression for perioperative use of opioids per day of hospitalization

	Ratio of means	(95% CI)	P-value
Inhibiting antidepressants (ref. non-inhibiting antidepressants)	1.6765	(1.2204– 2.3118)	0.00154
Female (ref. Male)	1.4862	(1.1250– 1.9543)	0.00508
≥ 65 years (ref. < 65 years)	0.9393	(0.7607– 1.1632)	0.55655
Severe ASA physical status (ref. healthy-mild physical status)	1.0173	(0.8337– 1.2425)	0.86434
PTA ER/LA opioid users (ref. opioid naïve)	1.2481	(0.8754– 1.8186)	0.23222
PTA IR opioid users (ref. opioid naïve)	1.1715	(0.9464– 1.4492)	0.14697
Neurological surgery (ref. general surgery)	1.0629	(0.7756– 1.4342)	0.69113
Orthopedic surgery (ref. general surgery)	1.0807	(0.7497– 1.5492)	0.67084
Other (ref. general surgery)	0.7253	(0.5089– 1.0275)	0.07127
Postoperative pain	1.3019	(1.2259– 1.3823)	<0.00001
Inhibiting antidepressants & female (ref. non-inhibiting antidepressants & male)	0.5535	(0.3708– 0.8237)	0.00375

Null deviance: 743.08; Residual deviance: 544.39; AIC: 7086.7; pseudo R-squared: 0.2673813

ASA: American Society of Anesthesiologists physical status classification system. PTA: Prior to admission. ER/LA opioids: Extended release/Long-acting opioids. IR opioids: Immediate release opioids. Use of opioids in morphine milligram equivalents (MME)

Table 3:

Unadjusted and Adjusted Odds Ratios for Risk of Developing Delirium

	Unadjusted OR	(95% CI)	P-value	Adjusted OR	(95% CI)	P-value
Inhibiting antidepressants (ref. non-inhibiting antidepressants)	1.5704	(1.0128, 2.4588)	0.0455	1.9627	(1.1062, 3.5344)	0.0224
Daily MME > 90 (ref. MME ≤ 90)	0.6275	(0.3919, 0.9862)	0.0470	0.8469	(0.3859, 1.7913)	0.6694
Female (ref. Male)	0.7886	(0.5075, 1.2351)	0.2940	0.8620	(0.5371, 1.3933)	0.5405
≥ 65 years (ref. < 65 years)	2.2222	(1.4332, 3.4556)	0.0003	1.6395	(1.0295, 2.6114)	0.0369
Severe ASA physical status (ref. Healthy/Mild)	3.2240	(2.0180, 5.2936)	<0.00001	3.0014	(1.8378, 5.0242)	<0.0001
PTA ER/LA opioid users (ref. opioid naïve)	1.2579	(0.5612, 2.6102)	0.5550	1.0525	(0.4410, 2.3577)	0.9041
PTA IR opioid users (ref. opioid naïve)	1.1922	(0.7517, 1.9060)	0.4580	1.2269	(0.7398, 2.0512)	0.4308
Neurological Surgery (ref. General Surgery)	2.6922	(1.2078, 7.1764)	0.0267	2.7797	(1.2007, 7.6093)	0.0274
Orthopedic Surgery (ref. General Surgery)	2.2908	(0.9027, 6.6076)	0.0969	2.4846	(0.9313, 7.4626)	0.0819
Other surgery (ref. General Surgery)	1.2667	(0.4612, 3.8126)	0.6550	1.1063	(0.3896, 3.4209)	0.8530
Inhibiting antidepressants & daily MME > 90 (ref. non-inhibiting antidepressants & MME ≤ 90)	N/A			0.5147	(0.1952, 1.3700)	0.1798

Hosmer and Lemeshow goodness of fit (GOF) test, p-value = 0.734. Null deviance: 544.53; Residual deviance: 491.24; AIC: 515.24. Area under the curve: 0.7277. Odds ratios: OR

Table 4:

Multivariable linear regression for hospital length of stay (in days)

	Ratio of means	(95% CI)	Relative Increment	P-value
Postoperative delirium	2.0296	(1.6725– 2.4809)	4.02018	<0.00001
Female (ref. Male)	0.9332	(0.8099– 1.0736)	−0.26064	0.32806
≥ 65 years (ref. < 65 years)	0.9746	(0.8475– 1.1224)	−0.09904	0.72109
Severe ASA physical status (ref. Healthy-Mild)	1.3485	(1.1713– 1.5528)	1.36051	0.00002
PTA ER/LA opioid users (ref. Opioid naïve)	0.9605	(0.7515– 1.2397)	−0.15429	0.75013
PTA IR opioid users (ref. Opioid naïve)	1.1297	(0.9744– 1.3089)	0.50631	0.10336
Neurological surgery (ref. General surgery)	0.9048	(0.7300– 1.1122)	−0.37167	0.35769
Orthopedic surgery (ref. General surgery)	0.9801	(0.7619– 1.2572)	−0.07749	0.87635
Other (ref. General surgery)	1.4621	(1.1428– 1.8638)	1.80413	0.00219
ICU admission	2.4950	(2.0845– 3.0048)	5.83700	<0.00001
Daily MME > 90 (ref. ≤ 90)	1.2223	(1.0554– 1.4166)	0.86787	0.00670
Inhibiting antidepressants (ref. non-inhibiting antidepressants)	0.9172	(0.8022– 1.0487)	−0.32310	0.20205

Null deviance: 563.38; Residual deviance: 326.34; AIC: 3574.3. pseudo R-squared: 0.4207391