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Predictors of In-Hospital Postoperative Opioid Overdose After Major Elective Operations: A Nationally Representative Cohort Study

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Abstract

Objective: To describe national trends and outcomes of in-hospital postoperative opioid overdose (OD) and identify predictors of postoperative OD.

Summary Background Data: In 2000 the Joint Commission recommended making pain the 5th vital sign, increasing the focus on postoperative pain control. However, the benefits of pain management must be weighed against the potentially lethal risk of opioid OD.

Methods: This is a retrospective multi-institutional cohort study of patients undergoing one of six major elective inpatient operation from 2002 to 2011 using the Nationwide Inpatient Sample, an approximately 20% representative sample of all United States hospital admissions. Patients with postoperative OD were identified using ICD-9 codes for poisoning from opioids or adverse effects from opioids. Multivariate logistic regression was used to identify independent predictors.

Results: Among 11,317,958 patients, 9,458 (0.1%) had a postoperative OD; this frequency doubled over the study period from 0.6 to 1.1 overdoses per 1,000 cases. Patients with postoperative OD died more frequently during their hospitalization (1.7% vs. 0.4%, p-value < 0.001). Substance abuse history was the strongest predictor of OD (OR=14.8; 95% CI: 12.7–17.2). Gender, age, income, geographic location, operation type, and certain comorbid diseases also predicted OD (p<0.05). Hospital variables including teaching status, size, and urban/rural location did not predict postoperative OD.

Conclusions: Postoperative OD is a rare, but potentially lethal complication, with increasing incidence. Postoperative monitoring and treatment safety interventions should be thoughtfully employed to target high risk patients and avoid this potentially fatal complication.

Introduction:

Adequate pain control is an important component of perioperative care. When the Joint Commission recommended making pain the 5th vital sign in 2000, effective postoperative pain management became an important focus for both the medical community and the public and is now a patient reported outcome that is tracked by many hospitals ¹. In addition to improved quality of life and patient satisfaction, adequate pain control has been linked to better clinical outcomes including improved wound healing and improved immune function ². Opioid medications are currently the standard therapy used in the treatment of postoperative pain; however, the benefits of opioid-based pain control must be considered against its potential risks.

Current data from the CDC suggests that there is an epidemic of overdoses (ODs) from prescribed medications, most importantly opioids ³. While many efforts have focused on limiting outpatient access to prescribed opioids, there has been less research evaluating in-hospital ODs due to opioid use. A recent alert issued by the Joint Commission called attention to safe practices for opioid use in the inpatient hospital setting due to high rates of adverse drug events ⁴. Indeed, opioids are one of the medications most frequently associated with in-hospital adverse drug events⁵ and incidents involving opioid ODs can lead to significant patient injury due to respiratory depression, hypoxic brain injury and even death. A study of anesthesia-related closed claims for postoperative opioid-induced respiratory depression found that 97% of the adverse events involving opioids were preventable with better monitoring and more timely and effective response by providers ⁶.

No large cohort study has evaluated the rate of postoperative opioid OD or the outcomes of patients who suffer these adverse events. In addition, no studies have evaluated patient or hospital factors associated with in-hospital postoperative OD in patients undergoing major elective operations. In order to anticipate and prevent postoperative OD, perioperative healthcare providers need to be aware of risk factors associated with this potentially fatal complication to ensure that appropriate safeguards and monitoring are used. Therefore, the purpose of this study is to 1) describe the national trends and outcomes of in-hospital postoperative opioid OD after elective major operations and 2) identify predictors of postoperative OD in this patient population. We hypothesize that postoperative opioid OD is more common in patients with greater comorbid disease burden and those undergoing thoracic operations due to their susceptibility to respiratory compromise. In addition, we hypothesize that outcomes including mortality and hospital length of stay will be worse in patients who suffer from postoperative OD.

Methods:

Data Source and Study Cohort

This is a multi-institution cohort study of patients undergoing one of six major elective inpatient operations from 2002 to 2011. De-identified data were obtained from the Nationwide Inpatient Sample (NIS) database. NIS was created as part of the Agency for Healthcare Research and Quality's Healthcare Research Cost and Utilization Project, and is the largest, all-payer nationwide inpatient administrative database. It contains hospital

records from approximately 1000 hospitals across the United States and represents a 20% sample of hospitals across the country. The data set contains hospital and patient-specific information in a representative sample.

Patients included in this study cohort had an elective hospital admission during which a major operation was performed on the day of admission or the following day. Major operation was defined by the NIS procedure code (category 3 and 4) with the international classification of diseases, 9th edition (ICD-9) code in the first two procedure coding locations. We then selected a set of common operations across surgical subspecialties: pneumonectomy, lobectomy, colectomy, spinal fusion, coronary artery bypass grafting, hysterectomy, and hip arthroplasty. This operative case mix was selected to sample from a wide range of surgical disciplines and include operations affecting different parts of the body. Patients were excluded from the study if they were less than 18 years old.

Variables and outcomes:

We evaluated information on patient, clinical and hospital characteristics as well as calendar year and geographic location. Patient demographic factors included gender, age (in categories: 18–39, 40–59, 60–79, and 80+ years old), race (white, black, Hispanic, and other), and median household income based on zip code (in quartiles: \$1–24,999, \$25,000–34,999, \$35,000–44,999, \$45,000+). Clinical factors included the type of operation [thoracic (pneumonectomy/lobectomy), colectomy, spinal fusion, coronary artery bypass graft, hysterectomy, or hip arthroplasty], Charlson comorbidity index (in categories: 0, 1, 2, or 3+) ⁷, and specific comorbid diseases [chronic obstructive pulmonary disease, asthma, history of smoking, coronary artery disease, cerebrovascular disease, liver disease, renal disease, diabetes, obesity, history of cancer (solid tumor, hematologic, or metastatic cancer), rheumatoid arthritis, osteoarthritis, history of substance abuse, history of chronic pain, or mood disorder]. Hospital characteristics included urban/rural location, teaching status and hospital size based on bed size (in categories: small, medium, and large). Hospitals are considered as having teaching status if they have an American Medical Association-approved residency program, are a member of the Council of Teaching Hospitals, or have a ratio of full-time equivalent interns and residents to beds of ≥ 0.25 . Geographic location was categorized as Northeast, Midwest, South, or West.

The primary outcome of interest was postoperative OD. Postoperative OD was defined using ICD-9 codes for poisoning or accidental poisoning by opioids and related medications (E850.1, E850.2, 965.00, 965.02 and 965.09) or patients with an E-code for an adverse effect of opioids in therapeutic use (E935.1, E935.2). Patients with an E-code for an adverse effect of opioids were also required to have a concurrent ICD-9 code for apnea, hypoxia or respiratory failure (518.81 518.82 786.03 786.05 786.09 799.0* 799.1*) to be included in the OD group. To evaluate the impact of postoperative OD on patient outcomes, we also examined the unadjusted association between postoperative OD and in-hospital mortality, length of stay and total charges. The total charges reported here are the charges that the hospital billed for services rendered during the patient's episode of care; they do not reflect the actual cost of services or the amount the hospital received as payment.

Statistical Analysis

Descriptive statistics were reported as percentages for categorical variables; mean and standard deviation were used to describe continuous variables. Univariate analysis using chi square and t-tests were performed to determine differences between patients who had a postoperative OD and those who did not. Outcomes including length of stay, total hospital charges, and mortality are also described and compared between the two groups.

After performing the univariate analysis, multivariate logistic regression was used to determine predictors of the primary outcome, postoperative OD. Potential predictors of opioid OD were identified by a group of physicians trained in anesthesia, surgery and epidemiology. All variables that were deemed important through clinical judgment and available in the NIS database were included in the regression model without further selection. In the end, Charlson comorbidity was excluded from the model due to co-linearity with individual comorbidities. The area under the curve was assessed and the Archer-Lemeshow test was performed⁸. A sensitivity analysis excluding patients with a history of substance abuse was performed post-hoc to ensure that this strong predictor did not influence the other predictors in our model. In addition, we performed subgroup analyses by age (greater than 65 vs less than 65) and operation type to see if the predictors changed in our model.

Missing data was evaluated and found to be present in <2.1% of the cohort for every variable with the exception of race. Because the race variable was missing at a rate of 20%, race was coded with an independent category of missing race for this analysis to control for its effect. Other observations with missing values were excluded from the analysis. To ensure accuracy of this sample for the country's population, weights representative of national inpatient use are provided by the NIS for adjustment, which were used in this analysis. All analyses were performed using STATA version 14 (College Station, TX: StataCorp LP). $\alpha < 0.05$.

Results:

There were 11,327,416 patients who underwent one of the selected operations between 2002 and 2011. Figure 1 shows the cohort description based on the primary outcome. Fifty-eight percent of patients were under 60 years old, 67.6% were female, and the majority of the patients were of white race (67.7%). The most common operation type in this study was hysterectomy (33.3%) and the least common was a thoracic operation (4.5%). Few patients had history of substance abuse (1.4%), and 2.7% had a history of renal disease. The overall in-hospital postoperative mortality rate was 0.4% (n=40,066) and a total of 9,458 (0.1%) patients had a postoperative OD during the study period. A full description of patient characteristics of this cohort are shown in Table 1.

Figure 2 depicts the frequency of postoperative OD over the study period, which increased from 0.6 to 1.1 per 1,000 cases per year ($p < 0.001$). Results of univariate analysis comparing characteristics of patients who had a postoperative OD to those who did not are also shown in Table 1. Patients who had a postoperative OD were significantly more likely to be of older age and higher income quartile. Figure 3 shows the frequency of postoperative OD by operation type. The highest rate of postoperative OD was seen in the thoracic

(pneumonectomy/lobectomy) and spinal fusion operation groups at 1.8 and 1.2 postoperative OD per 1,000 cases, respectively. Those who had a postoperative OD had higher frequency of every type of comorbid disease, except for cerebrovascular diseases ($p=0.32$). Patients undergoing operations in more recent years and geographically located in the Midwest or West had significantly higher frequency of postoperative OD. Hospital characteristics, including urban/rural location and teaching status, were not significantly different between the two groups. The in-hospital mortality rate was 1.7% and 0.4% for patients who did and did not have a postoperative OD, respectively ($p<0.001$). The hospital stay was significantly longer (6.7 vs. 3.9 days) and more charges were incurred (\$83,655 vs. \$46,255) for patients who had a postoperative OD compared to those who did not ($p<0.001$).

Unadjusted odds ratios are shown in Table 2. Patients who were older, white race, and higher income quartile were found to have higher odds of postoperative OD. Patients undergoing elective pneumonectomy or lobectomy had greater odds of postoperative OD than all other selected operations. History of substance abuse (OR 18.4, 95% CI: 16.1–21.0), renal disease (OR 4.2, 95% CI: 3.6–5.0), and history of chronic pain (OR 3.5, 95% CI: 2.7–4.5) were the comorbidities with the greatest odds of postoperative OD on unadjusted comparison.

In multivariable logistic regression analysis, significant predictors of postoperative OD were female gender, older age (60 years or older), white race, higher income quartile (\$35,000 or higher), thoracic operation (pneumonectomy or lobectomy), and geographic locations of the midwest or west, as seen in Table 2. Several individual comorbidities were predictive of postoperative OD. Specifically, history of substance abuse was the greatest predictor of postoperative OD (OR 14.8, 95% CI: 12.7–17.2) and renal disease was the second greatest predictor (OR 2.9, 95% CI: 2.5–3.4). Hospital factors, including urban/rural status, teaching status, and hospital size, did not predict postoperative OD. The area under the curve of our model was 0.75 and passed the Archer-Lemeshow test ($p=0.59$). A sensitivity analysis excluding history of substance abuse from the model revealed similar results to the inclusive regression model, see Appendix 1. In addition, subgroup analysis of patients based on age and operation type revealed similar results.

Discussion

This study shows that postoperative OD is a rare complication after major elective operations; however, the prevalence is increasing. Outcomes of patients with postoperative OD are worse than for those who do not suffer from this complication, including a four-fold higher mortality rate and longer length of hospital stay. In addition, total hospital charges were almost double in patients who had a postoperative OD compared to those without this complication. While the odds of postoperative OD are higher in patients undergoing thoracic and spinal fusion operations, the greatest predictors of this complication were patient specific comorbidities. The single greatest predictor of postoperative OD was history of substance abuse; other predictors of postoperative OD included gender, age, race, income status, operation type, comorbid diseases, and geographic location. Interestingly, hospital characteristics, including urban/rural location, teaching status, and hospital size, were not predictive of postoperative OD.

The annual incidence of postoperative OD doubled from 0.6 to 1.1 per 1,000 operative cases in this cohort over the study period. This increase in in-hospital opioid ODs echoes the CDC's concern of ODs from prescribed medications overall, which has led to a nation-wide epidemic³. No previous studies have described the prevalence of in-hospital postoperative OD on a national scale. Previous cohort studies describing complications due to respiratory failure potentially associated with opioid use report a wide range of incidence, between 0.04% to 17%^{6, 9–13}. The definition of postoperative OD used in this study allowed us to identify patients who had an adverse event specifically involving opioids. Due to the stringency of our definition and the potential underreporting of these codes in administrative data, our findings are likely an underestimate of the true incidence of this postoperative event. It is important to note that our study was unable to determine why the frequency of postoperative OD is increasing. The most common causes of in-hospital opioid adverse events have previously been reported to be due to medication dosing errors (47%) and improper monitoring (29%)⁴. Future analysis of adverse event root causes over time could shed light on changing trends and explain why postoperative OD is increasing.

Our study identified predictors of postoperative OD with history of substance abuse as the greatest predictor. History of substance abuse could lead to inpatient OD due to an increased tolerance to opioids among these patients leading to a dangerously narrow therapeutic to toxicity index, worse pain tolerance in these individuals, or abuse of the medication in the inpatient setting. However, it is important to note that there might be a bias for hospital coders to identify patients as having a history of substance abuse if the patient suffered an overdose during their hospital stay. Our sensitivity analysis reveals that excluding patients with codes for substance abuse does not impact our findings. Renal impairment also predicted postoperative OD, which is likely related to decreased clearance of these medications from the patients' blood. In addition, we found that female gender, age greater than 60 years, white race, higher socioeconomic status (measured in income), and mood disorders had an increased odds of postoperative OD. These findings agree with previous studies evaluating outpatient opioid OD risk factors. Specifically, a study by Wichmann and colleagues found that patients who present to the emergency room with an opioid OD are more likely to die from the OD if they are older¹⁴. Other studies have found that patients with higher socioeconomic status (measured in education level), female gender, mood disorders and those taking sedating medications have an increased risk of opioid OD outside the hospital^{15, 16}. Interestingly, Periasamy et al found that male gender was associated with significantly higher consumption of morphine after abdominal operations¹⁷, which contrasts our findings that men are at lower risk of postoperative OD. Perhaps the risk of postoperative OD in these subgroups is due to use of standard dosing for all patients, not considering medication interactions or difference in weight that might be present. While hospital level variables were not predictive of postoperative OD, geographic location was predictive of OD. This finding could be due to regional variation in medical culture and the need to balance patient symptom management with patient safety.

Postoperative OD can have severe consequences including hypoxic brain injury and death. Our study found that postoperative OD patients have a four-fold higher mortality rate and longer length of stay than those who do not have this complication after an elective major operation. A previous study of anesthesia malpractice claims found that 97% of adverse

events leading to injury to the patient due to opioids are potentially avoidable with safety interventions⁶. Importantly, this study found that hospital characteristics are not predictive of postoperative OD; therefore, it is essential that safety interventions are implemented in all hospitals across the country to avoid these devastating outcomes.

Multiple interventions have been proposed to decrease opioid ODs at the systems, provider, and patient level. The information from this study should be used to raise awareness of this problem and target interventions to patients at greatest risk. The predictors of postoperative OD can be used to implement systems level changes by notifying providers if they are caring for high risk patients through the electronic medical record. Systems level interventions utilizing this information might include standardization of policies and procedures for appropriate use of monitoring in high risk patients using continuous pulse oximetry or capnography^{18,19} or creating alerts identifying unusually high doses of opioids prescribed or consumed. In addition, future work evaluating the effect of a hospital's Magnet status or the nurse/bed ratio may provide further information about the resources needed to safely monitor patients in the perioperative period. Provider level interventions might include education on the increasing incidence of postoperative opioid OD, as well as use of opioid alternatives and safer opioid delivery systems (such as patient controlled analgesia)^{20–22}. A recently published study found that patients reported significantly lower pain scores after colorectal surgery if the patient had received local anesthesia, non-steroidal anti-inflammatory drugs, or patient controlled analgesia²³. Finally, informing patients of the negative outcomes associated with postoperative OD and discussing the need to weigh risks and benefits of postoperative pain control might allow for more realistic expectations of postoperative pain control, improving safety and satisfaction among patients.

The findings of this study must be interpreted with respect to important strengths and limitations. This study of the NIS database is a large, nationally representative sample of hospital data, and is the largest study describing postoperative OD to date. However, the NIS is an administrative database, and administrative databases have been found to have coding errors due to non-physician ICD-9 coding techniques used in their creation²⁴. These adverse event codes are most likely underreported in administrative databases. In addition, our definition of postoperative OD is relatively strict because an adverse respiratory event must be concurrently coded for patients who are identified as having an adverse event from opioids to be included as an OD; therefore, this study likely captures the most severe cases of postoperative OD. The prevalence of this complication may be much higher if a more liberal definition of postoperative OD is used. In addition, coding practices may vary between hospitals or in different geographic locations. We have tried to account for this by including hospital level variables (such as bed size, urban/rural location, and teaching status) and geographic region in our model, but this adjustment might be insufficient. Finally, the timing and location (i.e. post-anesthesia care unit versus surgical floor) of the OD and types of opioids and anesthetics used were not available in this database. Future studies exploring these factors may provide further insight into this problem and aide perioperative care providers in improving the safety of these patients.

Postoperative opioid OD in patients undergoing major elective surgery is rare, but the rate of this potentially fatal complication is increasing. The risks of postoperative OD must be

weighed against the benefits afforded by adequate pain control in the postoperative setting. Identifying patients at highest risk for postoperative OD is imperative to ensure appropriate monitoring is provided. Because almost all devastating injuries from postoperative OD are avoidable, early identification of this complication is crucial to allow providers time to intervene. Findings from this study should be used by all perioperative care providers to ensure that patient's discomfort is treated in an appropriate and safe manner.

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Appendix 1:: Adjusted Analysis (Excluding Patients with History of Substance Abuse)

	Adjusted Odds Ratio	p-value
	(95% Confidence Interval)	
Gender, Female	1.55 (1.37–1.76)	<0.001
Age Category (years)		
18–39	Reference	
40–59	0.85 (0.70–1.01)	0.070
60–79	1.23 (1.02–1.48)	0.028
80+	1.20 (0.93–1.55)	0.150
Race		
White	Reference	
Black	0.79 (0.62–1.01)	0.057
Hispanic	0.73 (0.56–0.94)	0.017
Other	0.79 (0.58–1.06)	0.114
Missing	0.88 (0.71–1.10)	0.266
Income Quartile by Zip Code		
\$1–24,999	Reference	
\$25,000–34,999	1.06 (0.89–1.26)	0.504
\$35,000–44,999	1.22 (1.00–1.48)	0.046
\$45,000+	1.24 (1.04–1.49)	0.018
Surgery Type		
Pneumectomy/Lobectomy	Reference	
Colectomy	0.75 (0.59–0.95)	0.019
Spinal Fusion	0.91 (0.70–1.18)	0.463
CABG	0.26 (0.17–0.38)	<0.001
Hysterectomy	0.45 (0.35–0.60)	<0.001
Hip Arthroplasty	0.58 (0.43–0.77)	<0.001
Comorbid Diseases:		
Chronic Obstructive Pulmonary Disease	1.53 (1.28–1.83)	<0.001

	Adjusted Odds Ratio	p-value
	(95% Confidence Interval)	
Asthma	1.43 (1.21–1.69)	<0.001
History of Smoking	1.04 (0.91–1.18)	0.60
Coronary Artery Disease	1.01 (0.84–1.21)	0.94
Cerebrovascular Disease	1.08 (0.56–2.09)	0.81
Liver Disease	1.49 (1.08–2.04)	0.01
Renal Disease	3.36 (2.77–4.09)	<0.001
Diabetes	1.14 (0.98–1.31)	0.08
Obese	1.37 (1.17–1.61)	<0.001
Solid Tumor	1.02 (0.86–1.21)	0.81
Hematologic Malignancy	1.01 (0.62–1.64)	0.97
Metastatic Cancer	1.33 (1.05–1.67)	0.02
Rheumatoid Arthritis	1.04 (0.74–1.46)	0.83
Osteoarthritis	1.21 (0.96–1.52)	0.11
History of Substance Abuse	14.81 (12.74–17.21)	<0.001
History of Chronic Pain	2.09 (1.57–2.80)	<0.001
Mood Disorder	1.58 (1.36–1.84)	<0.001
Urban Hospital	0.75 (0.54–1.03)	0.07
Teaching Hospital	1.13 (0.96–1.32)	0.14
Hospital Size		
Small	Reference	
Medium	1.07 (0.86–1.34)	0.54
Large	1.19 (0.96–1.46)	0.11
Year		
2002	Reference	
2003	0.84 (0.60–1.19)	0.32
2004	0.94 (0.71–1.25)	0.68
2005	1.26 (0.83–1.90)	0.27
2006	1.08 (0.79–1.48)	0.64
2007	1.04 (0.73–1.49)	0.84
2008	1.24 (0.92–1.69)	0.16
2009	1.20 (0.88–1.64)	0.24
2010	1.12 (0.81–1.54)	0.50
2011	1.17 (0.86–1.60)	0.31
Geographic Location		
Northeast	Reference	
Midwest	1.53 (1.15–2.04)	0.004
South	0.94 (0.75–1.16)	0.55
West	1.67 (1.33–2.09)	<0.001

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Figure 1:
Study Cohort Selection Flowchart

Figure 2:
Postoperative Opioid Overdoses per 1,000 Cases by Year

Figure 3:
Postoperative Opioid Overdoses per 1,000 cases by Operation Type

Table 1:

Patient Characteristics and Comparison

	Total N (%)	No overdose N (%)	Overdose N (%)	p-value
Total, N	11,327,416	11,317,958 (99.9%)	9,458 (0.1%)	
Gender, Female	7,661,566 (67.6%)	7,655,040 (67.6%)	6,527 (69.0%)	0.20
Age category (years)				<0.001
18–39	1,420,494 (12.5%)	1,419,699 (12.5%)	795 (8.4%)	
40–59	5,129,774 (45.3%)	5,126,748 (45.3%)	3,026 (32.0%)	
60–79	4,043,713 (35.7%)	4,039,079 (35.7%)	4,634 (49.0%)	
80+	733,436 (6.5%)	732,433 (6.5%)	1,003 (10.6%)	
Race				0.001
White	7,670,025 (67.7%)	7,663,016 (67.7%)	7,009 (74.1%)	
Black	889,256 (7.9%)	888,795 (7.9%)	462 (4.9%)	
Hispanic	655,010 (5.8%)	654,656 (5.8%)	354 (3.7%)	
Other	419,411 (3.7%)	419,124 (3.7%)	287 (3.0%)	
Missing	1,693,713 (15.0%)	1,692,367 (15.0%)	1,346 (14.2%)	
Income Quartile by Zip Code				0.001
\$1–24,999	2,220,556 (19.6%)	2,219,057 (19.6%)	1,499 (15.9%)	
\$25,000–34,999	2,808,733 (24.8%)	2,806,443 (24.8%)	2,290 (24.2%)	
\$35,000–44,999	2,943,662 (26.0%)	2,941,027 (26.0%)	2,635 (27.9%)	
\$45,000+	3,354,465 (29.6%)	3,351,432 (29.6%)	3,033 (32.1%)	
Surgery Type				<0.001
Pneumectomy/Lobectomy	509,523 (4.5%)	508,590 (4.5%)	933 (9.9%)	
Colecotomy	1,376,219 (12.1%)	1,374,706 (12.1%)	1,513 (16.0%)	
Spinal Fusion	2,654,226 (23.4%)	2,651,154 (23.4%)	3,072 (32.5%)	
Coronary artery bypass graft	784,544 (6.9%)	784,128 (6.9%)	416 (4.4%)	
Hysterectomy	3,772,080 (33.3%)	3,770,344 (33.3%)	1,736 (18.4%)	
Hip Arthroplasty	2,230,822 (19.7%)	2,229,036 (19.7%)	1,787 (18.9%)	
Comorbid Diseases:				

	Total N (%)	No overdose N (%)	Overdose N (%)	p-value
Chronic Obstructive Pulmonary Disease	775,322 (6.8%)	773,960 (6.8%)	1,363 (1.44%)	<0.001
Asthma	762,878 (6.7%)	761,956 (6.7%)	922 (9.7%)	<0.001
History of Smoking	2,372,861 (20.9%)	2,370,480 (20.9%)	2,382 (25.2%)	<0.001
Coronary Artery Disease	1,624,756 (14.3%)	1,623,216 (14.3%)	1,540 (16.3%)	0.03
Cerebrovascular Disease	46,919 (0.4%)	46,866 (0.4%)	53 (0.6%)	0.32
Liver Disease	196,983 (1.7%)	196,680 (1.7%)	303 (3.2%)	<0.001
Renal Disease	307,639 (2.7%)	306,642 (2.7%)	997 (10.5%)	<0.001
Diabetes	1,582,000 (14.0%)	1,580,204 (14.0%)	1,796 (19.0%)	<0.001
Obese	1,044,415 (9.2%)	1,043,176 (9.2%)	1,239 (13.1%)	<0.001
Solid Tumor	2,083,965 (18.4%)	2,081,466 (18.4%)	2,499 (26.4%)	<0.001
Hematologic Malignancy	102,222 (0.9%)	102,078 (0.9%)	144 (1.5%)	0.01
Metastatic Cancer	443,571 (3.9%)	442,931 (3.9%)	640 (6.8%)	<0.001
Rheumatoid Arthritis	184,228 (1.6%)	184,011 (1.6%)	216 (2.3%)	0.03
Osteoarthritis	343,183 (3.0%)	342,662 (3.0%)	521 (5.5%)	<0.001
History of substance abuse	156,583 (1.4%)	154,661 (1.4%)	1,922 (20.3%)	<0.001
History of Chronic Pain	137,417 (1.2%)	137,026 (1.2%)	390 (4.1%)	<0.001
Mood Disorder	887,932 (7.8%)	886,408 (7.8%)	1,524 (16.1%)	<0.001
Urban/Rural Hospital				0.98
Rural	990,924 (8.7%)	990,094 (8.7%)	830 (8.8%)	
Urban	10,336,492 (91.3%)	10,327,864 (91.3%)	8,627 (91.2%)	
Hospital Teaching Status				0.11
Nonteaching	5,772,685 (51.0%)	5,768,160 (51.0%)	4,525 (47.8%)	
Teaching	5,554,730 (49.0%)	5,549,798 (49.0%)	4,932 (52.1%)	
Hospital Size				0.02
Small	1,355,733 (12.0%)	1,354,797 (12.0%)	936 (9.9%)	
Medium	2,738,778 (24.2%)	2,736,705 (24.2%)	2,073 (21.9%)	
Large	7,232,905 (63.9%)	7,226,456 (63.8%)	6,449 (68.2%)	
Year				<0.001
2002	1,090,763 (9.6%)	1,090,083 (9.6%)	680 (7.2%)	

	Total N (%)	No overdose N (%)	Overdose N (%)	p-value
2003	1,056,287 (9.3%)	1,055,750 (9.3%)	537 (5.7%)	
2004	1,078,635 (9.5%)	1,078,008 (9.5%)	627 (6.6%)	
2005	1,093,702 (9.7%)	1,092,813 (9.7%)	889 (9.4%)	
2006	1,074,744 (9.5%)	1,073,980 (9.5%)	764 (8.1%)	
2007	1,072,256 (9.5%)	1,071,438 (9.5%)	818 (8.6%)	
2008	1,183,325 (10.4%)	1,182,085 (10.4%)	1,240 (13.1%)	
2009	1,228,605 (10.8%)	1,227,299 (10.8%)	1,306 (13.8%)	
2010	1,208,500 (10.7%)	1,207,296 (10.7%)	1,204 (12.7%)	
2011	1,240,599 (11.0%)	1,239,205 (11.0%)	1,394 (14.7%)	
Geographic Location				<0.001
Northeast	2,377,065 (21.0%)	2,375,497 (21.0%)	1,568 (16.6%)	
Midwest	2,098,597 (18.5%)	2,096,294 (18.5%)	2,303 (24.3%)	
South	4,591,409 (40.5%)	4,588,521 (40.5%)	2,888 (30.5%)	
West	2,260,345 (20.0%)	2,257,646 (19.9%)	2,699 (28.5%)	

Table 2:

Unadjusted and Adjusted Analysis

	Unadjusted Odds Ratio (95% Confidence Interval)	p-value	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Gender, Female	1.07 (0.97–1.17)	0.201	1.63 (1.46–1.81)	<0.001
Age Category (years)				
18–39	Reference		Reference	
40–59	1.05 (0.89–1.25)	0.540	0.92 (0.78–1.10)	0.37
60–79	2.05 (1.73–2.42)	<0.001	1.50 (1.26–1.79)	<0.001
80+	2.45 (1.97–3.03)	<0.001	1.72 (1.37–2.17)	<0.001
Race				
White	Reference		Reference	
Black	0.57 (0.45–0.71)	<0.001	0.72 (0.57–0.91)	0.01
Hispanic	0.59 (0.47–0.75)	<0.001	0.76 (0.60–0.97)	0.03
Other	0.75 (0.57–0.99)	0.04	0.84 (0.64–1.10)	0.21
Missing	0.87 (0.66–1.15)	0.32	0.90 (0.74–1.10)	0.31
Income Quartile by Zip Code				
\$1–24,999	Reference		Reference	
\$25,000–34,999	1.21 (1.04–1.41)	0.02	1.13 (0.97–1.32)	0.11
\$35,000–44,999	1.33 (1.12–1.57)	<0.001	1.26 (1.06–1.49)	0.01
\$45,000+	1.34 (1.14–1.57)	<0.001	1.32 (1.13–1.56)	<0.001
Surgery Type				
Pneumonectomy/Lobectomy	Reference		Reference	
Colectomy	0.60 (0.49–0.73)	<0.001	0.75 (0.60–0.92)	0.01
Spinal Fusion	0.63 (0.51–0.78)	<0.001	0.90 (0.72–1.13)	0.38
CABG	0.29 (0.22–0.38)	<0.001	0.36 (0.26–0.49)	<0.001
Hysterectomy	0.25 (0.21–0.31)	<0.001	0.45 (0.36–0.57)	<0.001
Hip Arthroplasty	0.44 (0.35–0.55)	<0.001	0.53 (0.41–0.68)	<0.001
Comorbid Diseases:				
Chronic Obstructive Pulmonary Disease	2.29 (2.01–2.61)	<0.001	1.45 (1.26–1.68)	<0.001

	Unadjusted Odds Ratio (95% Confidence Interval)	p-value	Adjusted Odds Ratio (95% Confidence Interval)	p-value
Asthma	1.50 (1.28–1.75)	<0.001	1.31 (1.12–1.53)	<0.001
History of Smoking	1.27 (1.13–1.42)	<0.001	0.87 (0.77–0.99)	0.03
Coronary Artery Disease	1.16 (1.02–1.33)	0.03	1.05 (0.90–1.22)	0.54
Cerebrovascular Disease	1.35 (0.75–2.46)	0.32	0.93 (0.51–1.70)	0.80
Liver Disease	1.87 (1.44–2.44)	<0.001	1.04 (0.79–1.38)	0.77
Renal Disease	4.23 (3.62–4.95)	<0.001	2.89 (2.45–3.41)	<0.001
Diabetes	1.44 (1.28–1.63)	<0.001	1.12 (0.99–1.27)	0.07
Obese	1.48 (1.28–1.73)	<0.001	1.34 (1.15–1.56)	<0.001
Solid Tumor	1.59 (1.41–1.80)	<0.001	1.07 (0.93–1.24)	0.33
Hematologic Malignancy	1.70 (1.17–2.46)	0.01	1.23 (0.85–1.80)	0.27
Metastatic Cancer	1.78 (1.46–2.17)	<0.001	1.27 (1.04–1.56)	0.02
Rheumatoid Arthritis	1.42 (1.04–1.93)	0.03	1.06 (0.77–1.44)	0.73
Osteoarthritis	1.87 (1.52–2.30)	<0.001	1.08 (0.87–1.35)	0.47
History of Substance Abuse	18.4 (16.11–21.03)	<0.001	14.81 (12.74–17.21)	<0.001
History of Chronic Pain	3.51 (2.73–4.52)	<0.001	1.52 (1.17–1.98)	0.002
Mood Disorder	2.26 (1.98–2.58)	<0.001	1.35 (1.18–1.55)	<0.001
Urban Hospital	1.00 (0.76–1.31)	0.98	0.79 (0.60–1.06)	0.11
Teaching Hospital	1.13 (0.97–1.32)	0.11	1.11 (0.96–1.29)	0.15
Hospital Size				
Small	Reference		Reference	
Medium	1.1 (0.87–1.39)	0.44	1.07 (0.86–1.34)	0.54
Large	1.29 (1.04–1.60)	0.02	1.19 (0.96–1.46)	0.11
Year				
2002	Reference		Reference	
2003	0.82 (0.60–1.12)	0.20	0.85 (0.63–1.16)	0.31
2004	0.93 (0.71–1.22)	0.61	0.92 (0.70–1.20)	0.53
2005	1.30 (0.88–1.93)	0.18	1.22 (0.84–1.77)	0.29
2006	1.14 (0.84–1.55)	0.40	1.05 (0.78–1.41)	0.75
2007	1.22 (0.88–1.71)	0.24	0.92 (0.66–1.29)	0.63

	Unadjusted Odds Ratio (95% Confidence Interval)	p-value	Adjusted Odds Ratio (95% Confidence Interval)	p-value
2008	1.68 (1.28–2.21)	<0.001	1.17 (0.89–1.55)	0.26
2009	1.71 (1.27–2.30)	<0.001	1.15 (0.86–1.55)	0.34
2010	1.60 (1.19–2.14)	0.002	0.99 (0.74–1.33)	0.95
2011	1.80 (1.37–2.37)	<0.001	1.04 (0.79–1.39)	0.76
Geographic Location				
Northeast	Reference		Reference	
Midwest	1.66 (1.28–2.17)	<0.001	1.63 (1.26–2.11)	<0.001
South	0.95 (0.77–1.18)	0.66	1.05 (0.87–1.28)	0.60
West	1.81 (1.45–2.26)	<0.001	1.72 (1.40–2.11)	<0.001