Pain Medicine

Pain Medicine 2014; 15: 1911–1929
Wiley Periodicals, Inc.

Risk Factors for Serious Prescription Opioid-Related Toxicity or Overdose among Veterans Health Administration Patients

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Disclosure: This research was funded by kaléo, Inc. The study was conceived, designed, executed, and reported by the authors who had sole control over the data and the decision to publish. Kaléo, Inc. reviewed and commented on the methods developed by the authors and reviewed the final manuscript for proprietary information. Drs. Murrelle, Zedler, Joyce, and Rajan are Principals of Venebio Group, LLC, which has research and consulting agreements with kaléo, Inc. and Reckitt-Benckiser Pharmaceuticals, Inc. and reports no additional conflicts of interest. The other coauthors report no conflicts of interest.

Abstract

Objective. Prescription opioid use and deaths related to serious toxicity, including overdose, have increased dramatically in the United States since 1999. However, factors associated with serious opioid-related respiratory or central nervous system (CNS) depression or overdose in medical users are not well characterized. The objective of this study was to examine the factors associated with serious toxicity in medical users of prescription opioids.

Design. Retrospective, nested, case-control analysis of Veterans Health Administration (VHA) medical, pharmacy, and health care resource utilization administrative data.

Subjects. Patients dispensed an opioid by VHA between October 1, 2010 and September 30, 2012 (N = 8,987).

Methods. Cases (N = 817) experienced life-threatening opioid-related respiratory/CNS depression or overdose. Ten controls were randomly assigned to each case (N = 8,170). Logistic regression was used to examine associations with the outcome.

Results. The strongest associations were maximum prescribed daily morphine equivalent dose (MED) ≥ 100 mg (odds ratio [OR] = 4.1, 95% confidence interval [CI], 2.6–6.5), history of opioid dependence (OR = 3.9, 95% CI, 2.6–5.8), and hospitalization during the 6 months before the serious toxicity or overdose event (OR = 2.9, 95% CI, 2.3–3.6). Liver disease, extended-release or long-acting opioids, and daily MED of 20 mg or more were also significantly associated.

Conclusions. Substantial risk for serious opioid-related toxicity and overdose exists at even relatively low maximum prescribed daily MED, especially in patients already vulnerable due to underlying demographic factors, comorbid conditions, and concomitant use of CNS depressant medications or substances. Screening patients for risk, providing education, and coprescribing naloxone for those at elevated risk may be effective at reducing serious opioid-related respiratory/CNS depression and overdose in medical users of prescription opioids.

Key Words. Prescription; Opioid; Toxicity; Overdose; Risk; Predictors

Introduction

Serious toxicity, including overdose, related to prescription opioid analgesics has increased dramatically in the United States since 1999 [1,2]. Opioids are central nervous system (CNS) depressants. Life-threatening opioid toxicity includes profound sedation/coma and severe respiratory depression that can result in death from respiratory arrest [3–5]. Prescription drug "overdose" is a type of serious toxicity in which the drug is used in amounts that exceed the individual's ability to tolerate the exposure, resulting in serious adverse effects. Serious opioid-related respiratory/CNS depression can occur unintentionally in patients using them for approved therapeutic indications ("medical users") and even at dosages in the recommended prescribing range. Medical users taking opioids as prescribed may experience circumstances that predispose them to opioid accumulation, prolonged duration of action or enhanced CNS, and consequent respiratory depression. Examples include certain comorbid conditions (e.g., impaired renal, hepatic, or respiratory function) and concomitant medications or substances (e.g., sedatives, alcohol). Opioid pain relievers were involved in nearly 17,000 deaths in 2010, representing a threefold increase since 1999 and three-fourths of all prescription drug poisoning deaths [1,2]. The alarming upward trajectory of fatal unintentional overdoses parallels increases of 29–80% in the use of prescription opioids for long-term management of chronic noncancer pain (2000–2005) in an estimated 9 million US adults per year currently [6–11]. Approximately 60% of overdoses occur in medical users of maximum prescribed daily morphine equivalent doses (MED) of 100 mg or more[1] or those who misuse opioid analgesics, typically prescribed by a single physician, to manage chronic pain [7]. The remaining 40% of overdoses occur in nonmedical users who abuse prescription opioids for recreational purposes, tend to receive prescriptions from multiple prescribers, and engage in diversion of prescription opioids to and from others [7,12,13].

The factors associated with *fatal* opioid-related overdose have been well characterized [2,7,12,14–21]. Patient-related factors include certain demographic characteristics and clinical comorbidities. Men have a higher opioid-related overdose death rate [12], but the percentage rise in deaths since 1999 is greater in women [15]. For prescription opioids, overdose death rates are highest in persons aged 45–54 years; non-Hispanic whites, American Indians and Alaskan Natives; rural and impoverished areas; and in the West and Southwest United States and the Appalachian states of Kentucky and West Virginia where the opioid analgesic prescribing rates are highest [2,8,12,18,19,22,23]. Geographic variations in overdose deaths reflect, in part, variations in opioid analgesic prescribing patterns, the number of physicians available, and state-regulated pain management policies rather than inherent patient differences [2,24]. Persons with a history of substance abuse, previous overdose, mental illness, and respiratory disease are significantly more likely to die of an opioid-related overdose [7,16,20,21,25,26]. Prescription drug-related factors significantly associated with fatal opioid-related overdose or serious toxicity include use of oxycodone, methadone, and extended-release formulations [7,12,16,18,27–29]; maximum prescribed daily MED exceeding 50 mg [21,25]; and concurrent use of other psychoactive CNS depressants (e.g., sedative–hypnotics, anxiolytics, alcohol) [1,20,26,30].

To date, most research on predictors of serious opioid-related toxicity or overdose has focused on fatal events, illicit opioids, nonmedical users of prescription opioids, or limited samples of medical users and used relatively small, geographically limited convenience samples. The objective of this study was to identify the factors independently most associated with overdose or life-threatening respiratory/CNS depression, including nonfatal events, among medical users of prescription opioids in a large, national, administrative health care database.

Methods

Study Design

A nested case-control design was used to examine factors associated with a diagnosis of serious opioid-related respiratory/CNS depression or overdose among Veterans Health Administration (VHA) patients who were dispensed an opioid by VHA. The study was exempt from Institutional Review Board review.

Study Setting and Data Source

A retrospective analysis of deidentified national administrative health care data was conducted using VHA Medical SAS datasets from October 1, 2010 through September 30, 2012. These datasets contain data for VHA-provided health care that is utilized primarily by US military veterans and a small number of nonveterans (e.g., employees, eligible family members, research participants) and include inpatient, outpatient, laboratory, radiology, pharmacy, vital signs, vital status, and enrollment information.

Study Sample

Study "cases" were defined as patients who satisfied the following criteria at any time between October 1, 2010 and September 30, 2012 (the "study period"): 1) were dispensed at least one opioid prescription by VHA (see Appendix I), identified by national drug code; and 2) had a claim for a serious opioid-related toxicity or overdose event based on International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes and Current Procedure Terminology (CPT) codes (Table 1) [7,21,31]. A serious opioid-related toxicity or overdose event was defined as follows: 1) a listed CNS or respiratory adverse effect code in addition to a listed poisoning event or external cause code occurring within ±1 day of

[1]Maximum prescribed daily morphine equivalent doses exceeding 200 mg are considered 'high-dose.' [55]

Table 1 Diagnostic codes for serious opioid-related toxicity including overdose

ICD-9-CM Diagnosis Codes	Description
Poisoning codes	
965.00	Poisoning by opium (alkaloids), unspecified
965.01	Poisoning by heroin
965.02	Poisoning by methadone
965.09	Poisoning by other opiates and related narcotic
Adverse effect codes	
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency, not elsewhere classified
780.0	Alteration of consciousness
786.03	Apnea
799.0	Asphyxia and hypoxemia
CPT codes for mechanical ventilation or critical care	
31500	Intubation, endotracheal, emergency procedure
94002	Ventilation assist and management, initiation of pressure, or volume preset ventilators for assisted or controlled breathing; hospital inpatient/observation, each subsequent day
94660	CPAP ventilation; initiation and management
94662	CNAP ventilation; initiation and management
99291	Critical care, evaluation, and management of the critically ill or critically injured patient, first 30–74 minutes
External cause codes	
E850.0	Accidental poisoning by heroin
E850.1	Accidental poisoning by methadone
E850.2	Accidental poisoning by other opiates and related narcotics
E935.0	Adverse effects of heroin
E935.1	Adverse effects of methadone
E935.2	Adverse effects of other opioids and related narcotics

CNAP = continuous negative airway pressure; CPAP = continuous positive airway pressure; ICD-9-CM, International Classification of Disease, 9th Revision, Clinical Modification.

the adverse effect; or 2) use of mechanical ventilation or critical care in addition to a listed poisoning event or external cause code occurring within ±1 day of the critical respiratory support. The first identified occurrence of opioid-related overdose or life-threatening respiratory/CNS depression ("index event") during the study period served as the "index date" for cases. All patients were required to have nonmissing age, sex, and race values in addition to continuous medical and pharmacy benefits in the 6 months before the index date (the "baseline period"). For cases, the follow-up period was calculated as the number of days after the end of the event until death, disenrollment, or the end of the study period.

For each case, 10 control patients were randomly selected and assigned from those who 1) were dispensed an opioid by VHA during the study period; 2) did not experience serious opioid-related toxicity or overdose as defined in the study; and 3) had complete data for age, sex, and race. The case index date was assigned to each of the 10 control patients, and the follow-up period for these controls was the number of days thereafter until death, disenrollment, or the end of the study period.

Baseline Variables

Baseline demographic variables included age group (18–34, 35–44, 45–54, 55–64, 65+ years), sex, race, marital status, body mass index, and the US Census region of the patient's VHA treatment center (Northeast, North Central, South, West, other). Baseline comorbidity measures included the Charlson Comorbidity Index score, calculated as the sum of assigned comorbidity category weights [32].

Other selected baseline comorbidities were stratified as pain-related and nonpain-related [33–36]. Pain-related comorbid conditions included low back disorders, other back/neck disorders, neuropathic disorders, fibromyalgia, headache/migraine, burns, traumatic injury, and motor vehicle accidents. Nonpain-related comorbidities included psychoactive substance use disorders including substance abuse and nonopioid substance dependence, tobacco use disorder, post-traumatic stress disorder, bipolar disorder, attention deficit hyperactivity disorder, schizophrenia, anxiety disorder, obsessive-compulsive–disorder, cardiovascular disease, endocarditis, viral and alcoholic hepatitis), pancreatitis, sexually transmitted

disease, herpes simplex infection, skin infections/abscesses, sleep apnea, and obesity.

Additional baseline variables included the number of opioid prescriptions dispensed by VHA, opioid used (categorized by active ingredient, formulation [extended-release/long-acting vs short-acting], and route [oral, parenteral, transdermal, other]), and the maximum prescribed daily MED. For each opioid prescription dispensed during the baseline period, the product of the number of units dispensed and the opioid strength per unit (milligrams) was divided by the number of days supplied. The resulting opioid daily dose dispensed (milligrams per day) was then multiplied by a conversion factor derived from published sources to estimate the daily dose in morphine equivalents (MED) (see Table 2) [37–42]. The maximum prescribed daily MED during the baseline period was calculated for each patient by summing the daily MED for all opioid prescriptions dispensed to the patient during those 6 months. It reflects the maximum *prescribed* daily dose and not necessarily the actual amount *consumed*. Nonopioid medications also dispensed by VHA which can potentiate opioid-associated serious adverse effects, such as psychoactive drugs and nonopioid analgesics, were included as baseline variables [1,28]. Baseline health care utilization measures included the number of inpatient admissions and outpatient emergency department (ED), office, and pharmacy visits (Table 6).

Outcome Variable

The occurrence of serious opioid-related toxicity or overdose as defined by listed ICD-9-CM and CPT codes was the primary outcome variable (Table 1). All analyses were conducted at the patient level. For patients who experienced more than one episode of serious opioid-related respiratory/CNS depression or overdose during the study period, only the index event was evaluated.

Statistical Analysis

Baseline covariates and the outcome measure were summarized descriptively. Tests for normality were conducted, and medians and interquartile ranges (IQRs) were calculated for continuous variables that were not normally distributed. Frequencies and percentages were calculated for categorical variables. Student's *t*-tests or Wilcoxon Rank Sum tests were used, as appropriate, to examine differences in continuous variables of interest between cases and controls. Chi-squared tests of proportion were used to examine bivariate associations for categorical variables.

Multivariable analysis was performed using conditional logistic regression to examine factors potentially associated with the index event of serious opioid-related toxicity or overdose. The covariates included in the regression model were age, sex, race/ethnicity, marital status, US Census region, comorbidities, prescription opioid characteristics, the maximum prescribed daily MED, selected nonopioid prescription medications, and baseline health care resource utilization. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) and *P* values were calculated. *P* values less than 0.05 were considered statistically significant. One full, main effects, logistic regression model was run. Model discrimination was evaluated by the c-statistic which reflects the area under the receiver operating characteristic curve and ranges from 0.5 (no discrimination between cases and controls) to 1.0 (perfect discrimination) [41]. [43] Only the first (index) event of serious opioid-related toxicity or overdose was modeled for case patients who experienced more than one episode during the study period.

Table 2 Prescription opioids and morphine equivalent conversion factors

Opioid*	Morphine Equivalent Conversion Factor†,‡ (per mg of Opioid)
Short acting	
Meperidine hydrochloride	0.1
Codeine	0.15
Tramadol	0.2
Hydrocodone	1.0
Morphine sulfate	1.0
Oxycodone	1.5
Oxymorphone	3.0
Hydromorphone	4.0
Fentanyl citrate (transmucosal)	0.13§
Extended release/long-acting	
Morphine sulfate extended-release	1.0
Oxycodone hydrochloride controlled-release	1.5
Methadone	3.0
Fentanyl (transdermal)	2.4¶, **

* Some drug products contained an opioid in combination with a nonopioid (e.g., acetaminophen, aspirin) (Appendix II). No MED was calculated for the two controls who used sublingual buprenorphine.
† Sources of morphine equivalent conversion factors: Von Korff [37] and Leppert and Luczak [69].
‡ For each opioid dispensed, the daily MED (mg per day) was calculated as follows (see text): (number of units dispensed × strength of unit [mg] × MED conversion factor)/number of days supply.
§ Converting transmucosal fentanyl to morphine equivalents assumes 50% bioavailability of transmucosal fentanyl and that 100 μg of transmucosal fentanyl is equivalent to 12.5–15 mg of morphine.
¶ Converting transdermal fentanyl to morphine equivalents assumes that each patch has a conversion factor of 2.4 and remains in place for 3 days. The daily MED (mg per day) was calculated as follows:
(number of patches dispensed × 3 days per patch × strength of patch [μg/h] × MED conversion factor)/number of days supply.
** Prescription Drug Monitoring Program Training and Technical Assistance Center (no specific author) [41].
MED = morphine equivalent dose.

All analyses were conducted using SAS version 9.3 [44].

Results

Sixteen patients were excluded from the analysis due to missing age, sex, or race data. We identified 921 patients with a claim of life-threatening opioid-related respiratory/CNS depression or overdose and at least 6 months of continuous medical and pharmacy benefits before the event, 817 of whom were also dispensed an opioid by VHA. Among these 817 cases, 16 experienced more than one episode during the study period. Among those who received an opioid prescription from VHA during the study period, 8,170 control patients without overdose were identified who met selection criteria (Figure 1).

Descriptive Analysis

The median age was 62 years for both cases and controls (IQR, 10 and 16, respectively). As shown in Table 3, cases were more likely than controls to be non-Hispanic white, divorced, separated or widowed, and to reside in the western US Census region.

Compared with controls, patients with serious opioid-related toxicity or overdose were more likely to be diagnosed with other diseases and health conditions. The mean CCI score, which reflects general health status, was higher for cases than for controls (3.9 vs 1.7, $P < 0.0001$), indicating poorer overall health in the cases. As shown in Table 4, cases reported particularly significantly higher frequency during the 6-month baseline period of chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis); depression; skin ulcers; hypertension; malignancy; opioid dependence, substance abuse, nonopioid substance dependence, and tobacco use disorder; viral hepatitis; mental health disorders including anxiety, post traumatic stress, and bipolar disorders; cardiovascular disease; sleep apnea; back and neck disorders; neuropathic disorders; and traumatic injury (e.g., fracture, dislocation, contusion, laceration, wound).

VHA prescription drug dispensing data during the 6-month baseline period indicated that, overall, cases were prescribed opioids significantly more often than controls, in larger variety, with a higher proportion of extended-release or long-acting (ER/LA) formulations and with a higher mean maximum prescribed daily MED (Table 5). The mean number of opioid prescriptions dispensed in the baseline period was 6.8 among cases, compared with 2.5 among controls ($P < 0.0001$). Prescription opioid active ingredients varied significantly between cases and controls, with more hydrocodone, methadone, oxycodone, and morphine, but less tramadol, dispensed to cases than controls. Both ER/LA and short-acting formulations as well as oral opioids were prescribed to cases more often than to controls. The mean maximum prescribed MED was 122 mg per day in cases and 48 mg per day in controls, with significantly more cases receiving prescriptions for MED ≥50 mg per day and ≥100 mg per day. All selected nonopioid drugs were also prescribed to cases significantly more often than to controls (Table 5).

As shown in Table 6, cases had significantly greater health care resource utilization than controls during the baseline period, including outpatient office and ED visits, hospital-

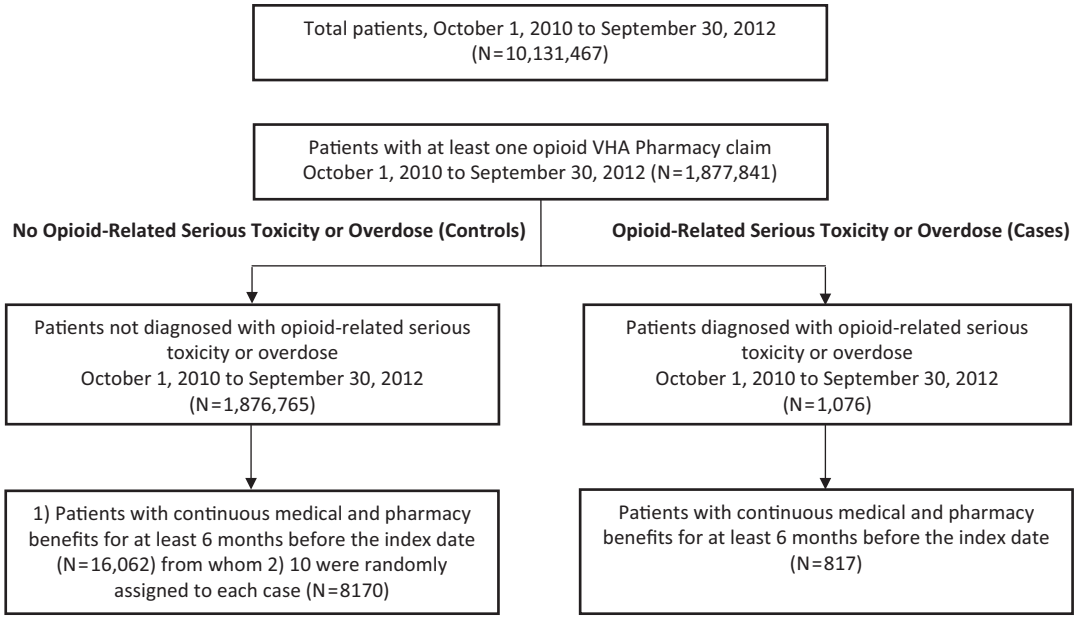

Figure 1 Sample selection flowchart.

Table 3 Baseline demographic characteristics

	Cases (N = 817)		Controls (N = 8,170)		
Characteristics	N	SD, %	N	SD, %	*P*
Age (years), median (IQR)	62.0	10.0	62.0	16.0	<0.001
Age group (years)					
18–34	27	3.3	565	6.9	<0.001
35–44	31	3.8	619	7.6	<0.001
45–54	115	14.1	1,240	15.2	0.402
55–64	377	46.1	2,672	32.7	<0.001
65+	267	32.7	3,074	37.6	0.005
Male	753	92.2	7,528	92.1	0.980
Race/ethnicity					
Non-Hispanic white	555	67.9	4,546	55.6	<0.001
Non-Hispanic black	83	10.2	1,300	15.9	<0.001
Hispanic	32	3.9	431	5.3	0.094
Other	147	18.0	1,893	23.2	0.001
Marital status					
Never married	102	12.5	1,227	15.0	0.052
Married	351	43.0	4,246	52.0	<0.001
Separated	20	2.5	41	0.5	<0.001
Divorced	285	34.9	2,268	27.8	<0.001
Widowed	59	7.2	388	4.8	0.002
BMI (kg/m^2)					
Underweight (<18.5)	29	3.6	72.0	0.9	<0.001
Normal (18.5–24.9)	193	23.6	1,197	14.7	<0.001
Overweight (25.0–29.9)	224	27.4	2,070	25.3	0.193
Obese (≥30.0)	306	37.5	2,667	32.6	0.005
Missing	65	8.0	2,164	26.5	<0.001
US Census region					
Northeast	75	9.2	824	10.1	0.411
North Central	190	23.3	1,745	21.4	0.208
South	270	33.1	3,258	39.9	<0.001
West	257	31.5	1,842	22.6	<0.001
Other	25	3.1	501	6.1	<0.001

BMI = body mass index; IQR = interquartile range; SD = standard deviation.

izations, and pharmacy visits. An ED visit occurred during the baseline period in 65% of cases compared with 21% of controls. Nearly half of the cases were hospitalized during the baseline period at least once compared with 9% of controls.

During the 2-year study period, 159/817 case patients died (19.5%) compared with 282/8,170 controls (3.5%). Twenty of the deaths in the case patients occurred during a VHA-treated episode of serious toxicity or overdose for an index event fatality rate of 2.4% (20/817).

Multivariable Analysis

The logistic regression model for the dichotomous outcome of serious opioid-related respiratory/CNS depression or overdose resulted in multiple, independent, statistically significant associations. To improve the estimate stability, the marital status categories "separated" (N = 20/817 cases) and "divorced" (N = 285/817 cases) were combined into one category. Endocarditis was not included in the final logistic regression as it was reported in only one case patient. The final model yielded a c-statistic of 0.89. As displayed in Figure 2, significant independent demographic predictors of serious opioid toxicity included ages 55–64 years and 65 and above, non-Hispanic white race, never married, widowed, and those receiving care in the western region of the United States.

Concomitant health conditions that were most strongly associated with the occurrence of serious opioid-related toxicity or overdose were opioid dependence, moderate or severe liver disease, skin ulcers, metastatic solid tumor, and pancreatitis. Other comorbidities significantly associated with the outcome included renal disease, bipolar disorder, traumatic injury chronic pulmonary disease, warfarin use, substance abuse, and sleep apnea (Figure 3).

Prescription opioids containing hydromorphone or oxycodone and those with ER/LA formulations were

Table 4 Baseline clinical characteristics

	Cases (N = 817)		Controls (N = 8,170)		
Comorbidities	N	SD, %	N	SD, %	*P*
CCI score, mean (SD)	3.9	3.3	1.7	2.0	<0.001
Individual CCI comorbidities					
Myocardial infarction	28	3.4	105	1.3	<0.001
Congestive heart failure	93	11.4	308	3.8	<0.001
Peripheral vascular disease	71	8.7	353	4.3	<0.001
Cerebrovascular disease	57	7.0	343	4.2	<0.001
Dementia	5	0.6	32	0.4	0.348
Chronic pulmonary disease	291	35.6	1,047	12.8	<0.001
Rheumatologic disease	6	0.7	96	1.2	0.257
Peptic ulcer disease	9	1.1	63	0.8	0.312
Mild liver disease	43	5.3	64	0.8	<0.001
Diabetes	263	32.2	1,850	22.6	<0.001
Hypertension	495	60.6	3,670	44.9	<0.001
Depression	357	43.7	1,562	19.1	<0.001
Use of warfarin	78	9.6	387	4.7	<0.001
Hemiplegia or paraplegia	13	1.6	34	0.4	<0.001
Renal disease	112	13.7	428	5.2	<0.001
Any malignancy, including leukemia and lymphoma	147	18.0	646	8.0	<0.001
Diabetes with chronic complications	92	11.3	432	5.3	<0.001
Skin ulcers	122	14.9	302	3.7	<0.001
Moderate or severe liver disease	28	3.4	19	0.2	<0.001
Metastatic solid tumor	46	5.6	59	0.7	<0.001
HIV/AIDS	11	1.4	42	0.5	0.003
Other selected comorbidities					
Nonpain related					
Substance abuse and nonopioid substance dependence	215	26.3	764	9.4	<0.001
Opioid dependence	105	12.9	97	1.2	<0.001
Endocarditis	1	0.1	9	0.1	0.920
Viral hepatitis	106	13.0	249	3.0	<0.001
Alcoholic hepatitis	3	0.4	5	0.1	0.005
Pancreatitis	24	2.9	49	0.6	<0.001
Sexually transmitted disease	12	1.5	69	0.8	0.072
Herpes simplex infection	7	0.9	45	0.6	0.272
Skin infections/abscesses	85	10.4	286	3.5	<0.001
Sleep apnea	147	18.0	652	8.0	<0.001
Tobacco use disorder	301	36.8	1,266	15.5	<0.001
PTSD	221	27.1	1,119	13.7	<0.001
Bipolar disorder	86	10.5	239	2.9	<0.001
ADHD	7	0.9	58	0.7	0.637
Schizophrenia	36	4.4	114	1.4	<0.001
Anxiety disorder	180	22.0	681	8.3	<0.001
OCD	5	0.6	19	0.2	0.045
Cardiovascular disease	172	21.1	764	9.4	<0.001
Obesity	150	18.4	1,072	13.1	<0.001
Pain related					
Low back disorders	380	46.5	2,099	25.7	<0.001
Other back/neck disorders	214	26.2	1,048	12.8	<0.001
Neuropathic disorders	170	20.8	717	8.8	<0.001
Fibromyalgia	34	4.2	157	1.9	<0.001
Headache/migraine	88	10.8	427	5.2	<0.001
Burns	4	0.5	16	0.2	0.089
Traumatic injury	212	26.0	869	10.6	<0.001
Motor vehicle accidents	7	0.9	14	0.2	<0.001

ADHD = attention deficit hyperactivity disorder; AIDS = acquired immunodeficiency syndrome; CCI = Charlson Comorbidity Index, 2008 updated (score); OCD = obsessive–compulsive disorder; PTSD = post-traumatic stress disorder; SD = standard deviation.

Table 5 Baseline prescription drugs dispensed by VHA

	Cases (N = 817)		Controls (N = 8,170)		
Prescription Drug Use	N	SD, %	N	SD, %	*P*
Opioid use	693	84.8	4,936	60.4	<0.001
By active ingredient					
Hydrocodone	314	38.4	2,633	32.2	<0.001
Oxycodone	305	37.3	876	10.7	<0.001
Buprenorphine	0	0.0	2	0.0	0.655
Tramadol	114	14	1,428	17.5	0.011
Codeine	63	7.7	561	6.9	0.365
Fentanyl	49	6.0	44	0.5	<0.001
Morphine	251	30.7	334	4.1	<0.001
Hydromorphone	38	4.7	28	0.3	<0.001
Methadone	107	13.1	139	1.7	<0.001
Oxymorphone	1	0.1	1	0.0	0.044
Other*	2	0.2	4	0.1	0.039
By formulation					
ER/LA‡	369	45.2	499	6.1	<0.001
Short acting‡	633	77.5	4,807	58.9	<0.001
Proportion of opioids = ER/LA†	0.25	0.3	<0.1	0.2	<0.001
By route					
Oral	692	84.7	4,923	60.3	<0.001
Parenteral	6	0.7	6	0.1	<0.001
Transdermal	48	5.9	44	0.5	<0.001
Number of opioid prescriptions dispensed, mean (SD)	6.8	5.9	2.5	3.4	<0.001
Number of unique opioid NDCs, mean (SD)	2.4	1.9	0.9	1.1	<0.001
Maximum prescribed daily MED (mg), mean (SD)	98.7	122.1	24.2	48.4	<0.001
1–<20	35	4.3	1,331	16.3	<0.001
20–<50	227	27.8	2,614	32.0	0.014
50–<100	163	20.0	718	8.8	<0.001
≥100	268	32.8	273	3.3	<0.001
Selected nonopioid drugs	747	91.4	5,905	72.3	<0.001
Benzodiazepines	336	41.1	1,242	15.2	<0.001
Antidepressants	565	69.2	2,886	35.3	<0.001
Nonopioid analgesics	556	68.1	4,598	56.3	<0.001
Muscle relaxants	226	27.7	1,288	15.8	<0.001
Other sedatives	125	15.3	609	7.5	<0.001
Antipsychotics	239	29.3	772	9.5	<0.001
Stimulants	14	1.7	51	0.6	<0.001

* Other opioids include meperidine and pentazocine/naloxone.
† Proportion of opioid prescriptions dispensed to a patient during baseline that contained an ER/LA formulation. Methadone is a long-acting opioid.
‡ Percentages exceed 100% due to prescription of both ER/LA and short-acting formulations in some patients.
ER/LA = extended release/long acting; MED = morphine equivalent dose; NDC = National drug code; SD = standard deviation; VHA = Veterans Health Administration.

significantly associated with increased risk of serious opioid-related toxicity or overdose. The likelihood of experiencing the outcome was related monotonically to increasing maximum prescribed daily MED of 20 mg or higher. Patients prescribed a maximum daily MED ≥100 mg during the baseline period were more than four times as likely to experience serious opioid-related toxicity or overdose compared with those prescribed MED of 1–<20 mg/day, whereas patients prescribed 50–<100 mg/day MED were 2.2 times as likely, and those prescribed 20–49 mg/day MED were 1.5 times as likely to experience life-threatening opioid-related respiratory/CNS depression or overdose (Figure 4). Coprescription of benzodiazepines, antidepressants, and antipsychotics in opioid users was significantly associated with experiencing serious toxicity or overdose.

Patients hospitalized for one or more days for any reason during the baseline period were nearly three times as likely to experience serious opioid-related toxicity compared with those who were not hospitalized.

Table 6 Baseline health care utilization

All-Cause Health Care Utilization	Cases (N = 817)		Controls (N = 8,170)		
	N	SD, %	N	SD, %	*P*
Days of hospitalization, mean (SD)	9.6	22.9	1.1	8.0	<0.001
Patients with ≥1 outpatient ED visit	534	65.4	1,740	21.3	<0.001
Patients with ≥1 outpatient office visit	792	96.9	7,333	89.8	<0.001
Patients with ≥1 inpatient hospitalization	396	48.5	739	9.1	<0.001
Patients with ≥1 prescription fill	800	97.9	7,561	92.6	<0.001
Outpatient ED visits per patient, mean (SD)	2	2.6	0.4	1	<0.001
Outpatient office visits per patient, mean (SD)	23	18.6	9.8	11.3	<0.001
Inpatient hospitalizations per patient, mean (SD)	1	1.5	0.1	0.5	<0.001
Pharmacy visits per patient, mean (SD)	24.6	15.0	12.9	10.4	<0.001

ED = emergency department; SD = standard deviation.

Full regression results, including factors that were not statistically significantly related to the outcome in the logistic model are provided in Appendix II.

Discussion

Our study produced a robust multivariable model that characterized the risk of life-threatening opioid-related respiratory/CNS depression or overdose in medical users of prescription opioids. Higher maximum prescribed daily MED, a history of opioid dependence, and hospitalization during the 6 months before the overdose or serious toxicity event were the factors most strongly associated with this outcome among an opioid-exposed cohort of predominantly US veterans. Consistent with published findings on prescription opioid overdose *deaths*, we found that certain demographic characteristics, comorbid conditions, and medication-related factors were associated with non-fatal prescription opioid-related serious toxicity or overdose as well [16,21,45]. Demographic variables previously identified as risk factors, and confirmed in the present study, included non-Hispanic white race, never married and widowed marital status, and residence in the Western United States [2,12,16,21,24,45,46]. These factors are likely to be proxies for underlying patient-related constructs, including genetic influences on drug metabolism; the social environment, such as isolation; the prescriber, including opioid-prescribing patterns; and the

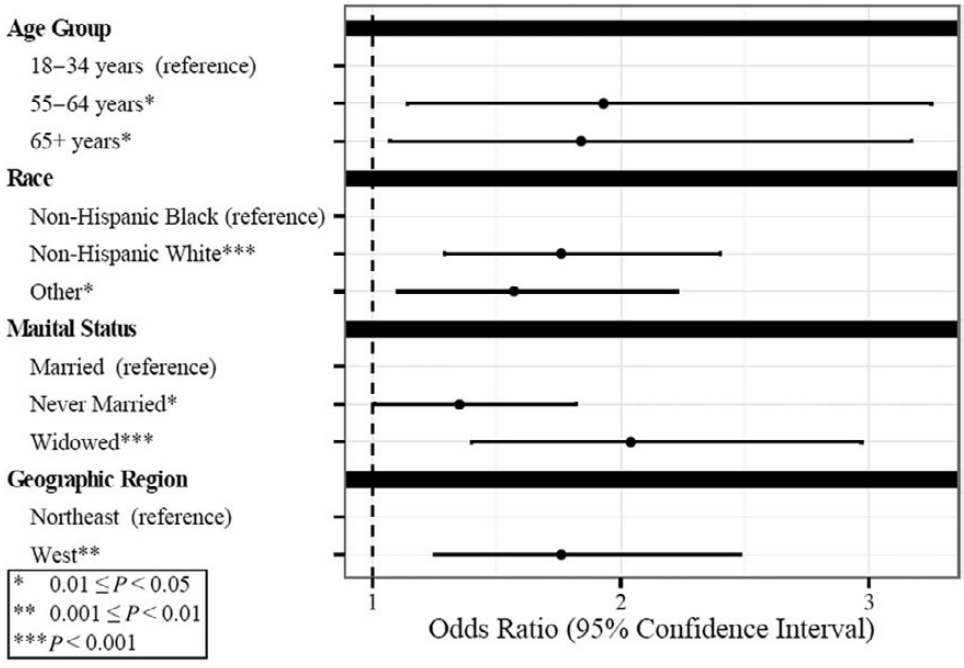

Figure 2 Logistic regression results: significant demographic factors.

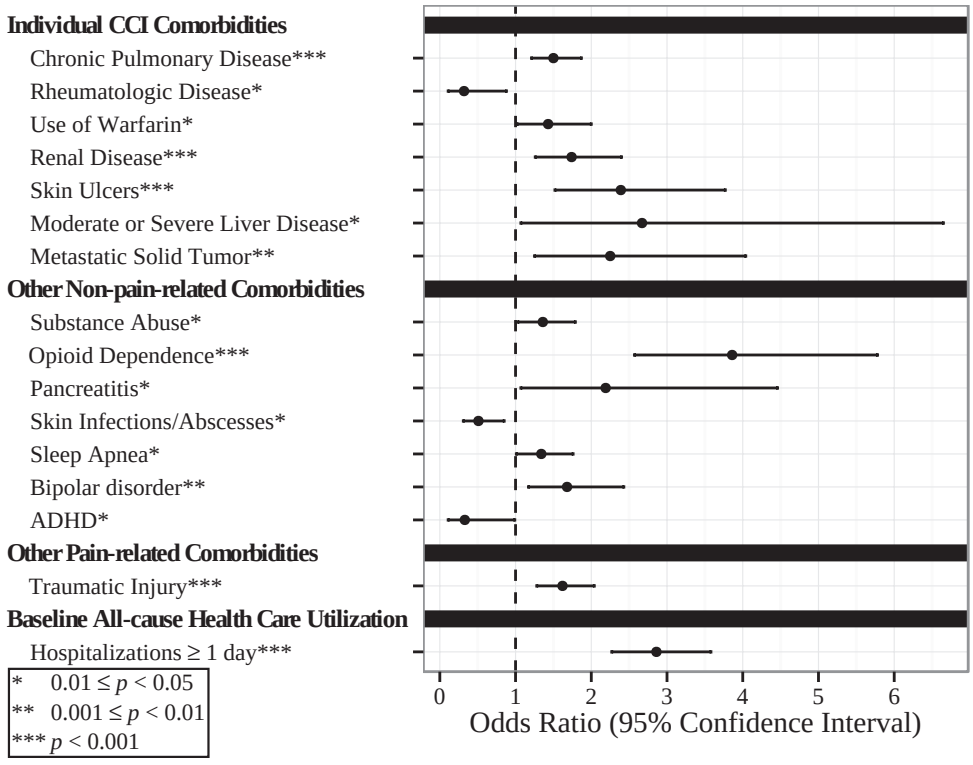

Figure 3 Logistic regression results: significant comorbid conditions and health care utilization factors.

health care system, such as access to emergency care and other medical services [24,47–52].

Some of our findings differed from those of studies of fatal opioid overdose. In contrast to the typical occurrence of opioid overdose death in middle age (peaking at 45–54 years), most case patients in our study were aged 55 years or older [8,12]. This discrepancy likely reflects the older VHA population. The older age predominance also affected the pattern of comorbidity in our study population, with chronic diseases and cancer being prevalent. Physiologically older individuals have age-related impairment in the hepatic and renal ability to metabolize and excrete certain drugs and other substances and have a greater burden of disease and associated potentially interacting concomitant medications. Such individuals are biologically vulnerable to opioid accumulation and to experiencing toxicity even when using an opioid well within its recommended dosing range. The safe use of opioids long-term to manage chronic pain in elderly patients is particularly challenging [39,53–55].

Another reported treatment challenge observed in our study population was the strong association of serious respiratory/CNS depression or overdose with substance use disorders (dependence and abuse) and mental health disorders (bipolar disorder). Abuse of alcohol, illicit opioids, and other substances is more frequent among medical users of prescription opioids than in the general population or chronic pain patients not treated with opioids [11,33,56]. We observed that polypharmacy with psychoactive drugs commonly prescribed for mental health disorders, such as benzodiazepines, antidepressants, and antipsychotics, as well as mental illness itself, was involved in approximately one-half of overdose events [1,13,56,57]. The association between serious toxicity events among opioid users in this study and pharmacotherapy for mental health disorders such as depression and anxiety may be partially mediated by the substantially higher prevalence of substance use disorders [56].

We found certain opioid characteristics to be highly associated with the likelihood of experiencing opioid-related toxicity or overdose. Use of extended-release formulations and long-acting opioids was strongly associated with an increased likelihood of overdose events, as reported previously [27,30,58]. Methadone, a long-acting opioid, was also examined as an independent determinant due to its long half-life, variable pharmacokinetics, and disproportionate involvement in 30–40% of all opioid-related deaths despite accounting for only 5–19% of US opioids prescribed [7,12,18,27,59]. In contrast to other studies that focused exclusively on *fatal* overdose, methadone alone was not independently associated with serious respiratory/CNS depression or overdose events treated at VHA facilities, falling just short of the statistical significance threshold ($P = 0.08$). It is unclear whether this difference is due to the study sample's relatively low prevalence of

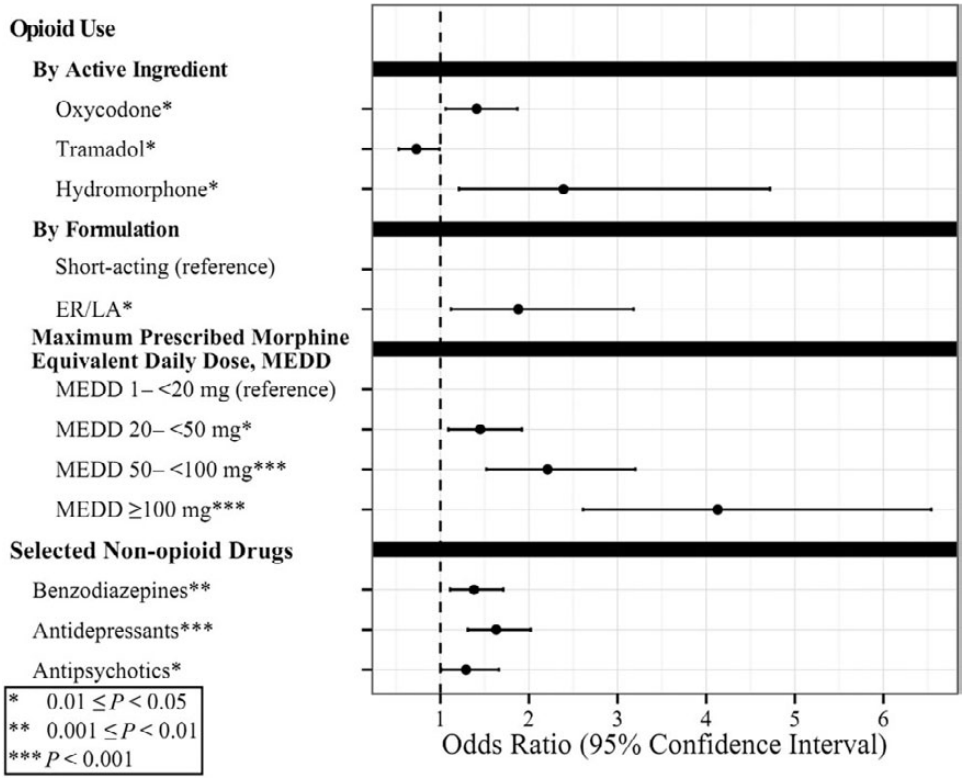

Figure 4 Logistic regression results: significant prescription drug-related factors.

methadone dispensed and fatal outcomes or to other characteristic(s) of the study sample or model specification.

Our study confirmed the known dose-related toxicity of opioids. Importantly, maximum prescribed daily MED of as little as 20 mg was associated with serious fatal and nonfatal overdose and toxicity in opioid consumers overall. Previous research identified a significant risk of overdose death for daily MED of ≥20 or 50 mg in patients with chronic noncancer pain [21,25,60]. An increasing body of scientific evidence suggests that prescriber overreliance on, and inadequate proficiency using, opioid dose conversion factors or ratios in published equianalgesic dose tables to calculate MED is an important contributor in fatal or near-fatal opioid-related CNS/respiratory depression [27,38,61–64]. The numerous published equianalgesic tables that are widely available contain inconsistent and variable conversion ratios. To reduce the risk of unintentional serious toxicity when rotating or switching opioids, updated guidelines for the safe use of equianalgesic dose tables emphasize the need to consider the opioid conversion ratio or calculated equianalgesic dose in morphine equivalents as only an approximate starting point. The calculated MED must then be adjusted for each individual patient and clinical scenario by accounting for interindividual sources of variation that can alter opioid potency. Such sources of individual variation include demographic differences (age, sex, race, ethnicity), major organ impairment (liver, kidney, adrenal), potential interactions with concomitant nonopioid medications and substances (e.g., benzodiazepines, alcohol), the direction of the opioid switch, and incomplete cross tolerance between opioids, as well as differences in the likelihood of opioid-induced hyperalgesia and physical dependence. Some differences may be due to significant genetic variants in opioid receptors, metabolism, and transport in the nervous system [65,66]. The current guidelines are based on expert opinion and have not been validated for safety or efficacy [55,61,64,67].

Of note, medical use of tramadol in our study appeared to be protective against serious opioid-related overdose (OR 0.7, 95% CI, 0.5–1.0). Tramadol, a novel synthetic opioid analgesic with monamine reuptake inhibition contributing to its analgesic effect, has low mu opioid receptor binding affinity and is not currently regulated as a controlled substance at the federal level in the United States [68–71]. However, its US prescribing information contains warnings similar to all prescription opioids regarding the risk of CNS and respiratory depression, overdose, and death. This interesting study finding warrants further investigation.

Pain is a complex, multidimensional condition with a multiplicity of interacting and contributing influences [72]. Factors involved in the likelihood of serious opioid-related toxicity or overdose in individuals treated for painful conditions relate to the patient and their social environment,

prescriber or other source of opioids, health care system, and the specific opioid and other exposures. Although pain is the most common reason a patient seeks medical care, current US data on the incidence, prevalence, and treatment of pain are not complete or consistent, partly because it is considered a symptom. Recent evidence indicates that approximately 80% of episodes of pain treated with opioids are short term [37]. However, an estimated 100–116 million US adults suffer chronic pain [53,72], and 3–4% of the adult population (9 million) are prescribed opioids each year to manage chronic noncancer pain [6–9,11]. Thus, the total population at risk of life-threatening opioid-related respiratory/CNS depression or overdose is substantial.

Our study confirms and extends findings from prior research that focused on fatal overdoses but did not differentiate between medical and nonmedical opioid users [13,16–18,21,60]. The relatively low frequency of fatal outcomes of serious opioid-related events in our VHA-treated cohort (2.4% over 2 years) suggests that the majority of such events in medical users is not fatal. However, nonfatal events do place a substantial burden on the health care system and patients [73,74].

Strengths and Limitations

Major strengths of this study include the large, national patient population as well as the rich detail of VHA administrative data. The robust statistical model included variables that are readily available from medical and pharmacy claims data. In contrast to most previous research, we examined in a comprehensive and systematic fashion the determinants associated with nonfatal as well as fatal serious toxicity and overdose related to the medical use of prescription opioids. However, the study sample included all opioid-exposed patients and was stratified by neither therapeutic indication or acuity (e.g., acute vs chronic pain conditions; chronic pain related to cancer vs noncancer) nor by the duration of opioid treatment (short term vs long term), partly to avoid potential statistical challenges with the limited number of cases available. Our study was subject to many of the limitations commonly associated with observational studies using administrative data (e.g., limited ability to infer causality and limited access to information regarding actual medication consumption/adherence, other behavioral/social elements, and therapeutic indication, with the potential for residual confounding). In addition, while VHA provides a large, national population from which to sample, generalizability is limited as the population comprises primarily older, white men who receive most of their health care within a single, closed system.

Limitations in accuracy and completeness are inherent in administrative data and include missing data, coding errors, misclassification, and undiagnosed or undocumented comorbidities such as substance use disorders. While prescriptions dispensed within the VHA system are well documented, it is possible that patients in the study also consumed opioids and other medications or substances from unreported non-VHA sources, particularly in the case cohort which had a significantly higher prevalence of substance use disorders. In addition, the serious respiratory/CNS depression and overdose rate in this sample is likely an underestimate as we evaluated only cases that fulfilled a stringent case definition and came to medical attention within VHA.

Implications for Future Research

Future studies should assess the generalizability of these findings to populations more representative of US medical users of prescription opioids, including wider age ranges and more women. With a larger dataset, selected interactions among risk factors should be evaluated, as well as the predictive utility of behavioral and other factors not routinely captured in administrative health care data (e.g., use of alcohol and other substances, other sources of opioids, therapeutic indication, social conditions, setting of the overdose or serious toxicity event, family history). Potential differences in risk factor profiles for overdose or life-threatening respiratory/CNS depression among those treated with opioids for acute vs chronic conditions, chronic noncancer pain vs chronic cancer pain, and short term vs long term should also be explored.

Conclusions

The risk of life-threatening toxicity, including overdose, in medical users of prescription opioids is an alarming, escalating public health problem. Substantial risk exists when even relatively low daily MED of opioids is used in patients who are vulnerable due to sociodemographic factors, concomitant medical and psychiatric conditions, and simultaneous use of other medications or substances. Expert guidelines recommend screening all patients before initiating opioids for pain management to identify those at elevated risk for serious adverse outcomes [26,55,75]. An extensive literature review revealed several available instruments to screen for aberrant drug-related behaviors (abuse, addiction, diversion) [55,76], but no instruments that provide useful, real-time, evidence-based information to the prescriber regarding the risk of overdose or serious respiratory/CNS depression currently exist [55]. A public health imperative is the identification of medical users of prescription opioids who are at highest risk of life-threatening toxicity for whom additional precautions should be considered. These precautions include education of the patient and caregivers, increased caution in opioid selection and dose escalation, consultation with pain management specialists, and close monitoring for the emergence of opioid-related toxicity or known risk factors for this outcome [28,55,75]. Additional measures to reduce opioid-related morbidity and mortality may include enhanced training and compliance of health care providers with evidence-based best practices for prescribing opioids, such as considering coprescribing naloxone, particularly if delivery systems can be developed that are safe and more user friendly for nonmedical first responders than the current syringe or nasal atomizer-based systems. Naloxone is a rescue medication with more than three

decades of proven effectiveness and safety in reversing life-threatening opioid-related respiratory/CNS depression or overdose [3,7,74,77–80].

The results of our study indicate that a statistically robust model based on administrative medical, pharmacy, and health care resource utilization data may help identify the demographic characteristics, comorbid conditions, concomitant medications, and opioid-related factors associated with increased risk of life-threatening toxicity and overdose. These factors help to identify the individuals most likely to benefit from preventive interventions. The development and widespread use of a risk profiling questionnaire based on these factors to guide patient treatment decisions would have the potential to significantly improve the balance between the analgesic benefit of opioid therapy and the risks of serious toxicity or overdose and other adverse outcomes, including abuse, diversion for nonmedical use, and iatrogenic addiction.

Acknowledgments

The authors of the study would like to acknowledge Juan Du, MS, of STATinMED, Inc. for statistical programming support and Elizabeth Moran of STATinMED, Inc. for medical writing support on this project.

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Appendices

Appendix I

Prescription opioid drug products

Active Ingredient(s) by Generic Name
Alfentanil hydrochloride
Buprenorphine
Butorphanol tartrate
Codeine, acetaminophen
Codeine base
Codeine phosphate
Codeine phosphate, triprolidine, pseudoephedrine hydrochloride
Codeine phosphate, chlorpheniramine maleate
Codeine phosphate, guaifenesin, pseudophedrine
Codeine phosphate, pyrilamine maleate
Codeine phosphate, acetaminophen, gamma-aminobutyric acid
Codeine phosphate, brompheniramine maleate, pseudoephedrine hydrochloride
Codeine phosphate, brompheniramine maleate, phenylephrine hydrochloride
Codeine phosphate, butalbital, acetaminophen, caffeine
Codeine phosphate, butalbital, aspirin, caffeine
Codeine phosphate, carisoprodol, aspirin

Appendix I Continued

Active Ingredient(s) by Generic Name
Codeine phosphate, chlorcyclizine hydrochloride
Codeine phosphate, dexbrompheniramine maleate, pseudoephedrine hydrochloride
Codeine phosphate, guaifenesin, pseudoephedrine hydrochloride
Codeine phosphate, phenylephrine hydrochloride
Codeine phosphate, phenylephrine hydrochloride, diphenhydramine hydrochloride
Codeine phosphate, phenylephrine hydrochloride, chlorcyclizine hydrochloride
Codeine phosphate, phenylephrine hydrochloride, chlorpheniramine maleate
Codeine phosphate, phenylephrine hydrochloride, pyrilamine maleate
Codeine phosphate, promethazine hydrochloride
Codeine phosphate, promethazine hydrochloride, phenylephrine hydrochloride
Codeine phosphate, pseudoephedrine hydrochloride, chlorcyclizine HCl
Codeine phosphate, pseudoephedrine hydrochloride, chlorpheniramine maleate
Codeine phosphate, pseudoephedrine hydrochloride
Codeine phosphate, pseudoephedrine hydrochloride, pyrilamine maleate
Codeine sulfate
Dihydrocodeine bitartrate, acetaminophen, caffeine
Dihydrocodeine bitartrate, brompheniramine maleate, phenylephrine hydrochloride
Dihydrocodeine bitartrate, brompheniramine maleate, pseudoephedrine hydrochloride
Dihydrocodeine bitartrate, guaifenesin
Dihydrocodeine bitartrate, phenylephrine hydrochloride, guaifenesin
Dihydrocodeine bitartrate, phenylephrine hydrochloride, pyrilamine maleate
Fentanyl
Fentanyl citrate, bupivacaine HCl
Hydrocodone bitartrate, acetaminophen
Hydrocodone bitartrate, homatropine methylbromide
Hydrocodone bitartrate, ibuprofen
Hydrocodone bitartrate, chlorpheniramine maleate, pseudoephedrine hydrochloride
Hydrocodone bitartrate, pseudoephedrine hydrochloride
Hydrocodone polistirex, chlorpheniramine polistirex
Hydrocodone, acetaminophen, gamma-aminobutyric acid
Hydromorphone hydrochloride
Levorphanol tartrate
Meperidine hydrochloride
Methadone hydrochloride
Morphine
Nalbuphine hydrochloride
Naloxone, buprenorphine
Oxycodone, acetaminophen
Oxycodone, aspirin
Oxycodone hydrochloride
Oxycodone hydrochloride, ibuprofen
Oxymorphone hydrochloride
Pentazocine hydrochloride, acetaminophen
Pentazocine hydrochloride, naloxone hydrochloride
Pentazocine lactate
Propoxyphene hydrochloride
Propoxyphene hydrochloride, acetaminophen
Propoxyphene napsylate
Propoxyphene napsylate, acetaminophen
Sufentanil citrate
Tapentadol
Tramadol hydrochloride
Tramadol hydrochloride, acetaminophen
Tramadol hydrochloride, gamma-aminobutyric acid
Tramadol hydrochloride, acetaminophen

Appendix II

Logistic regression results: serious opioid-related toxicity or overdose

Covariate[†]	Odds Ratio	95% CI		*P*
Age group (years)				
18–34	*Reference*			
35–44	0.9	0.5	1.8	0.826
–45–54	1.4	0.8	2.4	0.224
55–64	1.9	1.1	3.3	0.014
65+	1.8	1.1	3.2	0.028
Male	0.9	0.6	1.3	0.553
Race				
Non-Hispanic black	*Reference*			
Non-Hispanic white	1.8	1.3	2.4	<0.001
Hispanic	1.4	0.8	2.4	0.248
Other	1.6	1.1	2.2	0.013
Marital status				
Married (reference)	*Reference*			
Separated/divorced	1.1	0.9	1.4	0.404
Never married	1.4	1.0	1.8	0.044
Widowed	2.0	1.4	3.0	<0.001
Geographic region				
Northeast (reference)	*Reference*			
North central	1.3	0.9	1.8	0.184
South	1.2	0.9	1.7	0.316
West	1.8	1.3	2.5	0.001
Other	0.7	0.4	1.2	0.154
Comorbidity				
Individual CCI comorbidities				
Myocardial infarction	0.8	0.4	1.4	0.345
Congestive heart failure	1.1	0.7	1.8	0.674
Peripheral vascular disease	1.1	0.8	1.7	0.502
Cerebrovascular disease	0.7	0.4	1.1	0.132
Dementia	1.0	0.3	3.1	0.977
Chronic pulmonary disease	1.5	1.2	1.9	<0.001
Rheumatologic disease	0.3	0.1	0.9	0.027
Peptic ulcer disease	0.5	0.2	1.2	0.123
Mild liver disease	1.6	0.9	3.2	0.137
Diabetes	1.1	0.9	1.4	0.418
Hypertension	1.0	0.8	1.3	0.791
Depression	1.2	1.0	1.5	0.105
Use of warfarin	1.4	1.0	2.0	0.040
Hemiplegia or paraplegia	0.9	0.4	2.3	0.867
Renal disease	1.7	1.3	2.4	0.001
Any malignancy, including leukemia and lymphoma	1.3	1.0	1.7	0.086
Diabetes with chronic complications	1.0	0.7	1.4	0.769
Skin ulcers	2.4	1.5	3.8	<0.001
Moderate or severe liver disease	2.7	1.1	6.7	0.036
Metastatic solid tumor	2.3	1.3	4.0	0.007
HIV/AIDS	2.0	0.8	4.8	0.120
Other Selected comorbidities				
Nonpain related				
Substance abuse and nonopioid substance dependence	1.4	1.0	1.8	0.031
Opioid dependence	3.9	2.6	5.8	<0.001
Viral hepatitis	1.4	0.9	2.0	0.098
Alcoholic hepatitis	0.7	0.1	10.9	0.823
Pancreatitis	2.2	1.1	4.5	0.032
Sexually transmitted disease	1.4	0.6	3.1	0.458
Herpes simplex infection	0.8	0.3	2.2	0.639
Skin infections/abscesses	0.5	0.3	0.9	0.010
Sleep apnea	1.3	1.0	1.8	0.040
Tobacco use disorder	1.2	1.0	1.5	0.066
PTSD	1.0	0.8	1.3	0.985
Bipolar disorder	1.7	1.2	2.4	0.005

Appendix II Continued

Covariate†	Odds Ratio	95% CI		*P*
ADHD	0.3	0.1	1.0	0.048
Schizophrenia	1.6	0.9	2.8	0.105
Anxiety disorder	1.1	0.9	1.5	0.384
OCD	0.6	0.1	2.8	0.552
Cardiovascular disease	1.3	0.8	2.0	0.243
Obesity	1.1	0.8	1.4	0.498
Pain related				
Low back disorders	1.1	0.9	1.4	0.241
Other back/neck disorders	1.1	0.9	1.4	0.309
Neuropathic disorders	1.0	0.8	1.3	0.815
Fibromyalgia	1.2	0.7	2.0	0.574
Headache/migraine	1.2	0.8	1.7	0.322
Burns	0.8	0.2	3.8	0.758
Traumatic injury	1.6	1.3	2.0	<0.001
Motor vehicle accidents	2.4	0.7	7.6	0.145
Prescription drug use				
Opioids				
By active ingredient				
Hydrocodone	1.0	0.8	1.4	0.779
Oxycodone	1.4	1.1	1.9	0.017
Tramadol	0.7	0.5	1.0	0.043
Codeine	1.3	0.9	1.9	0.146
Fentanyl	0.8	0.1	6.9	0.813
Morphine	1.6	1.0	2.5	0.079
Hydromorphone	2.4	1.2	4.7	0.012
Methadone	1.6	1.0	2.7	0.079
Oxymorphone	0.3	0.0	5.4	0.377
Other*	1.7	0.1	52.5	0.775
By formulation				
Short acting	*Reference*			
ER/LA	1.9	1.1	3.2	0.018
By route				
Oral	*Reference*			
Parenteral or transdermal	2.3	0.3	18.7	0.433
Number of opioid prescriptions dispensed, mean (SD)	1.0	1.0	1.0	0.852
Number of unique opioid NDCs, mean (SD)	1.0	0.9	1.1	0.488
Maximum prescribed daily morphine equivalent dose (MED, mg/day)				
1–<20 (reference)	*Reference*			
20–<50	1.5	1.1	1.9	0.011
50–<100	2.2	1.5	3.2	<0.001
≥100	4.1	2.6	6.5	<0.001
Nonopioid drugs of interest				
Benzodiazepines	1.4	1.1	1.7	0.004
Antidepressants	1.6	1.3	2.0	<0.001
Nonopioid analgesics	0.9	0.7	1.2	0.557
Muscle relaxants	1.1	0.9	1.4	0.293
Other sedatives	1.1	0.8	1.5	0.521
Antipsychotics	1.3	1.0	1.7	0.045
Stimulants	1.9	0.8	4.6	0.179
All-cause health care utilization during the preceding 6 months				
Days of hospitalization				
0	*Reference*			
≥1	2.9	2.3	3.6	<0.001

* Other opioids included meperidine and pentazocine/naloxone. Methadone is a long-acting opioid.

ADHD = attention deficit hyperactivity disorder; CCI = Charlson Comorbidity Index; CI = confidence interval; ER/LA = extended release or long acting; MED = morphine equivalent dose; NDC = National drug code; OCD = obsessive–compulsive disorder; PTSD = post-traumatic stress disorder; SD = standard deviation.

†Covariates with frequencies less than 10 or which prevented model convergence were not included in the full model.