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Risk Factors for Serious Prescription Opioid-Induced Respiratory Depression or Overdose: Comparison of Commercially Insured and Veterans Health Affairs Populations

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Abstract

Objective. To characterize the risk factors associated with overdose or serious opioid-induced respiratory depression (OIRD) among medical users of prescription opioids in a commercially insured population (CIP) and to compare risk factor profiles between the CIP and Veterans Health Administration (VHA) population.

Subjects and Methods. Analysis of data from 18,365,497 patients in the IMS PharMetrics Plus health plan claims database (CIP) who were dispensed a prescription opioid in 2009 to 2013. Baseline factors associated with an event of serious OIRD among 7,234 cases and 28,932 controls were identified using multivariable logistic regression. The CIP risk factor profile was compared with that from a corresponding logistic regression among 817 VHA cases and 8,170 controls in 2010 to 2012.

Results. The strongest associations with serious OIRD in CIP were diagnosed substance use disorder (odds ratio [OR] = 10.20, 95% confidence interval [CI] = 9.06–11.40) and depression (OR = 3.12, 95% CI = 2.84–3.42). Other strongly associated factors included other mental health disorders; impaired liver, renal, vascular, and pulmonary function; prescribed fentanyl, methadone, and morphine; higher daily opioid doses; and concurrent psychoactive medications. These risk factors, except depression, vascular disease, and specific opioids, largely aligned with VHA despite CIP being substantially younger, including more females and less chronic disease, and having greater prescribing prevalence of higher daily opioid doses, specific opioids, and most selected nonopioids.

Conclusions. Risk factor profiles for serious OIRD among US medical users of prescription opioids with private or public health insurance were largely concordant despite substantial differences between the populations in demographics, clinical conditions, health care delivery systems, and clinical practices.

Key Words. Opioids; Risk Factors; Overdose; Respiratory Depression

Introduction

Opioid analgesics are an important therapeutic option, particularly for the estimated 100 million Americans who experience chronic pain in a given year [1–3]. Between 1999 and 2010, prescription opioid sales quadrupled in the United States [4]. Patterns of utilization of opioids vary by patient population. For example, although the available published data do not permit direct comparison by time period, the prevalence of prescription opioid use increased by 31% between 2000 and 2005 in a commercially insured US population [5], while use increased by 77% between 2004 and 2012 among Veterans Health Administration (VHA) patients [6].

Opioid use is associated with several potential adverse effects, with the most life-threatening being opioid-induced respiratory depression (OIRD) [7–9]. Annual age-adjusted US death rates involving prescription analgesics quadrupled between 2000 and 2014, from 1.5 to 5.9 per 100,000 population [10]. The US rate of emergency department (ED) visits for OIRD (prescription and illicit opioid-related) also quadrupled from 1993 to 2010 [11]; 1% to 2% were fatal [12,13], and 10% were life-threatening but nonfatal [12]. More than 90% of commercially insured patients with a nonfatal opioid overdose during long-term opioid therapy that is treated in the ED or hospital continue to be prescribed opioids after the event, and 7% experience another overdose within two years [14].

Strategies have been developed, implemented, and promoted to mitigate risk and reduce harm in response to the opioid overdose epidemic. These strategies include evidence-based treatment guidelines [15–17], prescriber education and training programs regarding appropriate opioid prescribing as part of comprehensive pain management [18], and state-based prescription drug monitoring programs [19]. In addition, the opioid reversal agent naloxone is now distributed to trained laypersons (patients, caregivers, and first responders) for use as a rescue medication in the home and other community settings [8,20,21]. Community-based programs that utilized overdose education with naloxone distribution to 152,283 laypersons during 1996 to 2014 reported 26,463 successful overdose reversals using naloxone [20] and a 50% reduction in the rate of subsequent opioid-related ED visits [22]. Most programs were initiated to address heroin-related overdoses, but their scope has expanded to include prescription opioid–involved events [23,24], which are now implicated in approximately twice as many fatal opioid overdoses each year as heroin [25].

Prescription opioid users at highest risk are likely to benefit most from preventive and potentially life-saving interventions. However, risk for overdose is complex and multifactorial and thus has not previously been readily estimated in a clinical setting. In prior work, we identified risk factors for serious OIRD among VHA medical users of prescription opioids [26] and developed a predictive screening risk index, or calculator [27], and validated it in a commercially insured population (CIP) [28]. The risk index had excellent predictive performance in both populations. The objectives of the current study were 1) to characterize the risk factors associated with serious OIRD among patients in a commercially insured population who were prescribed opioids and 2) to compare risk factor profiles between the CIP and VHA populations.

Methods

Study Design and Data Source

A nested case-control design was used to examine factors associated with serious OIRD among patients who were dispensed an opioid during the study period, as in the previous VHA risk factor identification study [26]. The Western Institutional Review Board (IRB) reviewed and determined that the study was exempt from IRB full review.

We utilized a limited PharMetrics Plus data set from the IMS Health Real-World Data Adjudicated Claims–US Database (IMS LifeLink Health Plan Claims Database, IMS Health Incorporated, Plymouth Meeting, PA, USA). Enrollment information and fully adjudicated medical and pharmacy claims on over 115 million unique, de-identified individuals since 2006 are available from health plans that are largely commercial and from self-insured employer groups, A small set of commercial Medicare and Medicaid patients is also included (data vendor, personal communication, December 5, 2016).

The prior VHA study, by comparison, analyzed data that reflected national, VHA-provided health care for US military veterans plus a small number of nonveterans (e.g., civilian employees, eligible family members, research participants).

Study Sample and Participants

In the CIP data set, 18,365,497 patients had at least one opioid pharmacy claim between January 1, 2009, and December 31, 2013, excluding opioid-containing cough/cold products. We identified patients who experienced a serious prescription OIRD event among those with nonmissing age and sex values using an algorithm that used specific diagnostic codes in the International

Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and specific critical care procedure codes in Current Procedural Terminology (Supplementary Table 1) [29]. As previously detailed [26], a serious overdose event required a listed code for prescription opioid-involved poisoning plus a code for either life-threatening respiratory or CNS depression or mechanical ventilation or critical care. The date of the first identified occurrence of OIRD during the study period (index event) was considered the index date. Eligible patients had continuous medical and pharmacy benefits in the six months before the index date (the baseline period). For each case, four control patients were randomly selected from among those who were dispensed an opioid during the study period and did not experience serious OIRD and were assigned the corresponding case index date. Controls could not be assigned to one OIRD case that occurred near the beginning of the study period due to insufficient six-month baseline data. Overall, 7,234 cases were identified and 28,932 controls assigned, for a total sample of 36,166.

In the previous VHA study, a similar approach was used to identify cases and controls [26]. Among 1,877,841 patients in the VHA data set with at least one opioid pharmacy claim between October 1, 2010, and September 30, 2012, 817 cases with an OIRD event were identified and 8,170 controls were assigned, for a total sample of 8,987.

Variables

The outcome variable of interest was the index OIRD event. For patients with more than one episode of serious OIRD during the study period, only the index event was evaluated. Independent baseline variables included demographic characteristics, the comorbidities comprising the Charlson Comorbidity Index [30,31], other selected health conditions stratified as pain- and nonpain-related [32,33], prescribed opioids and selected nonopioid medications that can potentiate serious adverse effects of opioids, and health care utilization measures. Opioids were categorized by active ingredient, formulation (short-acting vs extended-release/long-acting [ER/LA]), route, and maximum prescribed daily morphine equivalent dose (MED). MED was calculated for each opioid by multiplying the dose by a published conversion factor to estimate the daily dose in morphine equivalents [34,35]. For each patient, the maximum prescribed daily MED during the baseline period was calculated after summing the daily MED for all opioid prescriptions dispensed during those six months. Some variables were not available in both data sets, with the primary gaps being the absence of race/ethnicity, marital status, and body mass index in the CIP data set. The CIP study used an updated definition for substance use disorder (SUD) [36] that combined the variables "opioid dependence" and "nonopioid substance dependence and all substance abuse" that were used in the earlier VHA study.

Statistical Methods

To compare baseline characteristics of cases and controls, chi-square tests were used for categorical variables and Wilcoxon rank sum tests for non-normally distributed continuous variables. We performed multivariable logistic regression to identify baseline factors associated with the index event of serious OIRD. Model covariates included sex, age, US census region, comorbidities, prescription opioid characteristics, selected nonopioid prescription medications, and health care utilization. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) and P values were calculated, with a P value of less than 0.05 considered statistically significant. Model discrimination between cases and controls was evaluated by the C-statistic, which reflects the area under the receiver operating characteristic curve and ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination) [37]. All statistical analyses were conducted in R (version 3.1.2) [38] or SAS version 9.4 (SAS, Cary, NC, USA).

Results

CIP Population Characteristics

Medical users of prescription opioids in the CIP population that experienced serious OIRD were more likely to be female and older compared with controls (Table 1). A greater proportion of cases than controls lived in the West US census region and fewer in the South. The mean Charlson Comorbidity Index score in cases was more than double that in controls, consistent with poorer overall health. Every health condition assessed was more common among cases than controls, except for sexually transmitted diseases/Herpes simplex. The most prevalent diagnoses among CIP cases included low back disorders (56.0%), other back/neck disorders (49.4%), and active traumatic injury (46.0%). Hypertension, depression, and anxiety disorder were each present in nearly half of the cases, followed by diagnosed SUD (38.7%), tobacco use disorder (29.1%), and chronic pulmonary disease (27.9%).

Each opioid assessed was prescribed significantly more frequently among cases than controls except for hydrocodone, codeine, and propoxyphene. Among cases, the most frequently prescribed opioids were hydrocodone and oxycodone. ER/LA formulations were prescribed to nearly sixfold more cases (26.3%) than controls. Compared with controls, cases were prescribed a maximum MED of less than 50 mg/d only one-third as often, while an MED of 100 mg/d or greater was more than threefold as common (58.4%). All nonopioid drugs of interest, except analgesics, were prescribed more frequently among cases. Consistent with poorer overall health status, cases utilized health care resources significantly more often than controls, with ED visits in 55.3% and hospitalizations in 36.7% of cases (Table 1).

Table 1 Baseline descriptive characteristics of the commercially insured population sample

Characteristic	Cases (N = 7,234)	Controls (N = 28,932)	*P*
Demographics			
Age, median (IQR), y	51 (20)	47 (23)	<0.001
Age group, No. (%), y			
18–34	1,375 (19.0)	7,703 (26.6)	<0.001
35–44	1,152 (15.9)	5,464 (18.9)	
45–54	2,001 (27.7)	6,804 (23.5)	
55–64	1,836 (25.4)	6,151 (21.3)	
65+	870 (12)	2,810 (9.7)	
Male, No. (%)	2,945 (40.7)	12,311 (42.6)	0.005
US Census region, No. (%)			
Northeast	1,554 (21.5)	6,270 (21.7)	<0.001
Midwest	1,971 (27.2)	7,528 (26.0)	
South	2,641 (36.5)	11,953 (41.3)	
West	1,068 (14.8)	3,181 (11.0)	
Clinical			
CCI score, mean (SD)	4.3 (3.1)	2.0 (1.8)	<0.001
Individual CCI comorbidities, No. (%)			
Myocardial infarction	460 (6.4)	290 (1.0)	<0.001
Heart failure	714 (9.9)	512 (1.8)	<0.001
Peripheral vascular disease	341 (4.7)	437 (1.5)	<0.001
Cerebrovascular disease	879 (12.2)	702 (2.4)	<0.001
Dementia	41 (0.6)	41 (0.1)	<0.001
Chronic pulmonary disease	2,018 (27.9)	2,686 (9.3)	<0.001
Serious autoimmune rheumatologic disease	401 (5.5)	595 (2.1)	<0.001
Peptic ulcer disease	189 (2.6)	169 (0.6)	<0.001
Chronic hepatitis/cirrhosis	144 (2.0)	108 (0.4)	<0.001
Diabetes without chronic complications	1,440 (19.9)	3,015 (10.4)	<0.001
Hypertension	3,450 (47.7)	7,702 (26.6)	<0.001
Depression	3,473 (48.0)	2,534 (8.8)	<0.001
Warfarin treatment	400 (5.5)	720 (2.5)	<0.001
Hemiplegia or paraplegia	96 (1.3)	67 (0.2)	<0.001
Renal disease with renal impairment	644 (8.9)	562 (1.9)	<0.001
Any malignancy, including leukemia and lymphoma	679 (9.4)	1,464 (5.1)	<0.001
Diabetes with chronic complications	422 (5.8)	539 (1.9)	<0.001
Skin ulcers	344 (4.8)	257 (0.9)	<0.001
Complications of chronic liver disease	150 (2.1)	60 (0.2)	<0.001
Metastatic solid tumor	258 (3.6)	384 (1.3)	<0.001
HIV/AIDS	34 (0.5)	53 (0.2)	<0.001
Other selected comorbidities, No. (%)			
Non-pain-related			
Substance use disorder*	2,799 (38.7)	873 (3.0)	<0.001
Substance abuse and nonopioid substance dependence	2,385 (33)	644 (2.2)	<0.001
Opioid dependence	1,058 (14.6)	356 (1.2)	<0.001
Tobacco use disorder	2,106 (29.1)	2,433 (8.4)	<0.001
Bipolar disorder	868 (12.0)	430 (1.5)	<0.001
Schizophrenia	96 (1.3)	36 (0.1)	<0.001
Anxiety disorder	3,160 (43.7)	2,993 (10.3)	<0.001
PTSD	276 (3.8)	150 (0.5)	<0.001
OCD	73 (1.0)	65 (0.2)	<0.001
ADHD	280 (3.9)	534 (1.8)	<0.001
Sleep apnea	814 (11.3)	1,330 (4.6)	<0.001
Cardiovascular disease	422 (5.8)	639 (2.2)	<0.001
Endocarditis	32 (0.4)	25 (0.1)	<0.001
Viral hepatitis	215 (3.0)	172 (0.6)	<0.001

Table 1 Continued

Characteristic	Cases (N = 7,234)	Controls (N = 28,932)	P
Alcoholic hepatitis	38 (0.5)	9 (0.0)	<0.001
Nonmalignant pancreatic disease	245 (3.4)	171 (0.6)	<0.001
Sexually transmitted disease	339 (4.7)	1,298 (4.5)	0.47
Herpes simplex	60 (0.8)	224 (0.8)	0.63
Skin infections/abscesses	910 (12.6)	1,697 (5.9)	<0.001
Obesity	812 (11.2)	1,602 (5.5)	<0.001
Pain-related			
Low back disorders	4,051 (56.0)	7,365 (25.5)	<0.001
Other back/neck disorders	3,576 (49.4)	6,477 (22.4)	<0.001
Neuropathic disorders	1,467 (20.3)	2,214 (7.7)	<0.001
Fibromyalgia	1,228 (17.0)	1,636 (5.7)	<0.001
Recurrent headache	1,845 (25.5)	2,784 (9.6)	<0.001
Burns	69 (1.0)	113 (0.4)	<0.001
Active traumatic injury	3,330 (46.0)	7,370 (25.5)	<0.001
Prescription drugs			
Opioids, No. (%)			
By active ingredient			
Hydrocodone	4,240 (58.6)	18,268 (63.1)	<0.001
Oxycodone	3,520 (48.7)	7,010 (24.2)	<0.001
Morphine	1,029 (14.2)	415 (1.4)	<0.001
Fentanyl	935 (12.9)	339 (1.2)	<0.001
Hydromorphone	643 (8.9)	385 (1.3)	<0.001
Oxymorphone	213 (2.9)	81 (0.3)	<0.001
Methadone	485 (6.7)	197 (0.7)	<0.001
Buprenorphine	377 (5.2)	398 (1.4)	<0.001
Codeine	483 (6.7)	2,435 (8.4)	<0.001
Tramadol	1,315 (18.2)	4,697 (16.2)	<0.001
Propoxyphene	239 (3.3)	1,244 (4.3)	<0.001
Other[†]	123 (1.7)	218 (0.8)	<0.001
By formulation			
ER/LA	1,893 (26.3)	1,288 (4.5)	<0.001
Not ER/LA	5,271 (73.7)	27,294 (95.5)	
Missing	70 (1.0)	350 (1.2)	
By route			
Oral	6,615 (91.7)	28,342 (98.2)	<0.001
Sublingual	233 (3.2)	329 (1.1)	
Transdermal	340 (4.7)	164 (0.6)	
Injection	5 (0.1)	3 (0.0)	
Other[‡]	18 (0.0)	17 (0.0)	
Missing	23 (0.3)	77 (0.3)	
Maximum prescribed daily morphine equivalent dose group (MED, mg/d), No. (%)			
1–<20	229 (3.2)	2,557 (9.1)	<0.001
20–<50	1,271 (17.9)	13,668 (48.5)	
50–<100	1,449 (20.4)	7,522 (26.7)	
≥100	4,147 (58.4)	4,465 (15.8)	
Missing	138 (1.9)	700 (2.4)	
Selected nonopioid drugs, No. (%)			
Nonopioid analgesics	6,016 (83.2)	26,329 (91.0)	<0.001
Benzodiazepines	4,309 (59.6)	5,789 (20.0)	<0.001
Antidepressants	4,675 (64.6)	7,356 (25.4)	<0.001
Muscle relaxants	3,020 (41.7)	5,306 (18.3)	<0.001
Other sedatives	2,087 (28.8)	3,126 (10.8)	<0.001
Antipsychotics	1,390 (19.2)	991 (3.4)	<0.001

(continued)

Table 1 Continued

Characteristic	Cases (N = 7,234)	Controls (N = 28,932)	*P*
Stimulants	597 (8.3)	1,152 (4.0)	<0.001
All-cause health care utililzation			
≥1 ED visit, No. (%)	3,997 (55.3)	7,391 (25.5)	<0.001
No. of ED visits, mean (SD)	1.5 (2.7)	0.4 (1.0)	<0.001
≥1 d hospitalization, No. (%)	2,653 (36.7)	3,737 (12.9)	<0.001
Days of hospitalization, No. (SD)	3.7 (9.5)	0.7 (3.2)	<0.001

ADHD = attention deficit hyperactivity disorder; CCI = Charlson Comorbidity Index; ED = emergency department; ER/LA = extended-release/long-acting; MED = morphine equivalent dose; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder.

*The variables used in the prior VHA work, "opioid dependence" and "substance abuse and nonopioid substance dependence," were combined into a single "substance use disorder" (SUD) variable in commercially insured population, consistent with the updated definition in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) [36].

[†]Other prescription opioids in 123 cases and 218 controls included meperidine (232), pentazocine (43), dihydrocodeine (15), nalbuphine (2), and butorphanol (49).

[‡]Other routes of opioid administration in 18 cases and 17 controls included nasal (21), buccal (12), and rectal (2).

Risk Factors for OIRD in CIP

Several factors were significantly associated with serious OIRD in CIP (Table 2). The model discriminated well between cases and controls (C-statistic = 0.93). Demographic risk factors included age of 65 years or older, male sex, and residence in the West and Midwest United States. The strongest risk factors for OIRD were diagnoses of SUD and depression (Table 3A). Other highly associated health conditions (OR ≥ 2.0) included bipolar disorder, schizophrenia, complications of chronic liver disease, myocardial infarction, and cerebrovascular disease. Moderately associated comorbidities (OR = 1.0 to 2.0) included nonmalignant pancreatic disease, peptic ulcer disease, and viral hepatitis; renal and pulmonary disease, heart failure, and hypertension; anxiety and tobacco use disorders; serious autoimmune rheumatologic disease, low back and other back/neck disorders; active traumatic injury, neuropathic disorders, and recurrent headache; obesity and uncomplicated diabetes; and skin ulcers.

The strongest prescription opioid-related predictors were fentanyl, morphine, methadone, and a maximum prescribed MED of 100 mg/d or more. Opioid factors moderately associated with serious OIRD included hydromorphone, oxymorphone, hydrocodone, and oxycodone, as well as ER/LA formulation and an MED of 50 to less than 100 mg/d. Nonopioid drug predictors were concurrent benzodiazepines, muscle relaxants, antidepressants, antipsychotics, and other sedatives. Patients with an ED visit during the six-month baseline period were 25% more likely to experience serious OIRD than those without a visit.

Comparison Between OIRD Risk Factor Profiles in CIP and VHA

Of the demographic factors assessed in both CIP and VHA, age 65 years or older and residence in the West

United States were consistently associated with serious OIRD (Tables 2 and 3 and Supplementary Table 3). In CIP, the likelihood was also greater in the Midwest and in male opioid users, but lower in patients age 35 to 44 years. VHA opioid users age 55 to 64 years also had greater risk.

In both populations, diagnosed SUD was one of the strongest predictors of serious OIRD (Table 3). The second strongest risk factor in CIP, a diagnosis of depression, was not a significant predictor in VHA. However, concurrently prescribed antidepressants were moderately associated with serious OIRD in both populations. The factor most strongly associated with OIRD in VHA was a maximum prescribed MED of 100 mg/d or greater, which was also strongly associated in CIP. Other highly associated health conditions in both populations included complications of chronic liver disease and nonmalignant pancreatic disease. Additional concordant comorbidity risk factors included bipolar disorder, renal and pulmonary disease, skin ulcers, and active traumatic injury.

Comorbidity predictors unique to CIP included myocardial infarction, cerebrovascular disease, heart failure, and hypertension; schizophrenia, anxiety, and tobacco use disorders; recurrent headache, low back and other back/neck disorders, and neuropathic disorders; peptic ulcer disease and viral hepatitis; and obesity and uncomplicated diabetes.

Health conditions associated with serious OIRD only in VHA included metastatic cancer, sleep apnea, and concurrent warfarin. Notably, serious autoimmune rheumatologic disease was a risk factor for serious OIRD in CIP but was protective in VHA. Other comorbidities associated with lower likelihood of OIRD included endocarditis in CIP and skin infections/abscesses and attention deficit hyperactivity disorder in VHA.

Table 2 Multivariable logistic regression: factors associated with serious opioid-induced respiratory depression in a commercially insured population

Covariate	Odds ratio	95% confidence interval
Demographic		
Age group, y		
18–34 (reference)		
35–44	0.77	0.68–0.87
45–54	0.95	0.84–1.07
55–64	0.94	0.87–1.07
65+	1.21	1.04–1.42
Male	1.10	1.01–1.20
US census region		
Northeast (reference)		
Midwest	1.22	1.09–1.36
South	1.10	0.99–1.23
West	1.48	1.29–1.69
Clinical		
Individual CCI comorbidities		
Myocardial infarction	2.39	1.93–2.97
Heart failure	1.92	1.60–2.29
Peripheral vascular disease	0.95	0.74–1.20
Cerebrovascular disease	2.35	2.01–2.75
Dementia	0.95	0.51–1.75
Chronic pulmonary disease	1.47	1.33–1.63
Serious autoimmune rheumatologic disease	1.52	1.25–1.85
Peptic ulcer disease	1.41	1.04–1.91
Chronic hepatitis/cirrhosis	0.75	0.48–1.17
Diabetes without chronic complications	1.22	1.08–1.37
Hypertension	1.20	1.10–1.31
Depression	3.12	2.84–3.42
Warfarin treatment	0.85	0.70–1.03
Hemiplegia or paraplegia	1.22	0.78–1.89
Renal disease with renal impairment	1.93	1.61–2.31
Any malignancy, including leukemia and lymphoma	1.10	0.93–1.31
Diabetes with chronic complications	1.19	0.95–1.48
Skin ulcers	1.49	1.16–1.91
Complications of chronic liver disease	2.77	1.74–4.45
Metastatic solid tumor	1.11	0.84–1.45
HIV/AIDS	1.12	0.55–2.22
Other selected comorbidities		
Non-pain-related		
Substance use disorder	10.20	9.06–11.40
Tobacco use disorder	1.69	1.52–1.87

(continued)

Table 2 Continued

Covariate	Odds ratio	95% confidence interval
Bipolar disorder	2.18	1.83–2.60
Schizophrenia	2.06	1.17–3.69
Anxiety disorder	1.64	1.50–1.80
PTSD	1.03	0.78–1.38
OCD	0.78	0.49–1.26
ADHD	0.93	0.72–1.19
Sleep apnea	1.11	0.97–1.28
Cardiovascular disease	0.84	0.68–1.03
Endocarditis	0.39	0.20–0.79
Viral hepatitis	1.39	1.02–1.89
Alcoholic hepatitis	1.87	0.79–4.84
Nonmalignant pancreatic disease	1.97	1.46–2.66
Sexually transmitted disease	0.92	0.76–1.10
Herpes simplex	0.80	0.51–1.21
Skin infections/ abscesses	1.13	0.99–1.30
Obesity	1.26	1.09–1.44
Pain-related		
Low back disorders	1.42	1.30–1.55
Other back/neck disorders	1.15	1.05–1.26
Neuropathic disorders	1.28	1.15–1.43
Fibromyalgia	1.12	0.99–1.26
Recurrent headache	1.48	1.34–1.64
Burns	0.77	0.48–1.23
Active traumatic injury	1.38	1.27–1.50
Prescription drugs		
Opioids		
By active ingredient		
Hydrocodone	1.35	1.22–1.49
Oxycodone	1.32	1.19–1.45
Morphine	2.44	2.07–2.88
Fentanyl	2.83	2.32–3.45
Hydromorphone	1.73	1.43–2.10
Oxymorphone	1.62	1.15–2.29
Methadone	2.35	1.86–2.98
Buprenorphine	0.39	0.29–0.51
Codeine	1.10	0.95–1.29
Tramadol	1.03	0.93–1.13
Propoxyphene	0.67	0.54–0.81
Other*	1.45	1.13–1.85
By formulation		
Not ER/LA (reference)		
ER/LA	1.48	1.27–1.72
By route		
Nonoral (reference)		
Oral	1.15	0.89–1.48

(continued)

Table 2 Continued

Covariate	Odds ratio	95% confidence interval
Maximum prescribed daily morphine equivalent dose group, MED, mg/d		
1–<20 (reference)		
20–<50	0.96	0.81–1.15
50–<100	1.35	1.13–1.62
≥100	2.31	1.90–2.81
Missing	1.04	0.76–1.41
Selected nonopioid drugs		
Nonopioid analgesics	0.62	0.53–0.71
Benzodiazepines	1.77	1.63–1.92
Antidepressants	1.33	1.22–1.45
Muscle relaxants	1.40	1.28–1.53
Other sedatives	1.34	1.22–1.48
Antipsychotics	1.19	1.04–1.36
Stimulants	1.04	0.87–1.23
All-cause health care utililzation		
≥1 ED visit	1.25	1.15–1.36
≥1 d hospitalization	0.84	0.76–0.93

Model performance: C-statistic = 0.93.
ADHD = attention deficit hyperactivity disorder; CCI = Charlson Comorbidity Index; ED = emergency department; ER/LA = extended-release/long-acting; MED = morphine equivalent dose; OCD = obsessive compulsive disorder; PTSD = post-traumatic stress disorder.
*Other prescription opioids included meperidine, pentazocine, dihydrocodeine, nalbuphine, and butorphanol. Missing opioid formulation (ER/LA) and route information were analyzed in the reference group in regression modeling. Sensitivity analyses were conducted to examine the impact of this and found no appreciable difference between such models relative to those in which the missing data were excluded.

Prescription opioid-related factors associated with serious OIRD in both populations, except an MED of 100 mg/d or greater, included an MED of 50 to less than 100 mg/d, ER/LA formulation, hydromorphone, and oxycodone. Fentanyl, morphine, methadone, oxymorphone, and hydrocodone were risk factors in CIP alone, while an MED of 20 to less than 50 mg/d increased risk in VHA only. The likelihood of serious OIRD was lower with propoxyphene and buprenorphine in CIP, and with tramadol in VHA. In addition to antidepressants, concurrent benzodiazepines and antipsychotics were associated with serious OIRD in both populations. In CIP, concurrent muscle relaxants and other sedatives also increased the risk, but nonopioid analgesics were associated with lower risk of OIRD. An ED visit during the baseline six months was strongly associated with serious OIRD in VHA and moderately associated in CIP. Interestingly, a baseline hospitalization was associated with increased risk in VHA but lower likelihood of serious OIRD in CIP.

Comparison of Population Characteristics in CIP vs VHA

Several important characteristics differed between the two populations of medical users of prescription opioids. Compared with VHA (Supplementary Table 2), CIP had a substantially higher proportion of females (~41% vs 8%), younger patients, and residents in the Northeast United States but fewer in the West (Table 1). Consistent with the age and sex differential, the prevalence of fibromyalgia, recurrent headache, anxiety disorder, attention deficit hyperactivity disorder, and active traumatic injury were greater among both cases and controls in CIP than in VHA. All pain-related diagnoses except neuropathic pain were substantially more prevalent among CIP cases and controls. Conversely, VHA had a greater prevalence of common chronic conditions associated with older age, including hypertension, cardiovascular disease (except myocardial infarction), warfarin treatment, obesity, diabetes, renal and pulmonary disease, sleep apnea, malignancy, and skin ulcers. Alcoholic hepatitis and nonmalignant pancreatic disease had similar prevalence in both populations, but viral hepatitis and chronic hepatitis/cirrhosis were more common in VHA.

The distribution of mental health disorders revealed a substantially lower prevalence of schizophrenia and tobacco use disorder among CIP cases and controls than in VHA, but similar prevalence of depression (~45%) and bipolar disorder (~11%) among cases in both populations. Post-traumatic stress disorder (PTSD) was sevenfold more common among VHA cases (27.1%) as CIP cases and 27-fold more prevalent among VHA controls (13.7%) as CIP controls. The frequency of opioid dependence was similar among CIP cases (14.6%) and VHA cases (12.9%) and equally rare among controls in both populations (1.2%). However, substance abuse and nonopioid substance dependence diagnoses were somewhat more common among CIP cases (33%) than VHA cases (26.3%) but fourfold as frequent among VHA controls (9.4%) as CIP controls.

Opioids prescribed in both populations included hydrocodone, oxycodone, morphine, fentanyl, hydromorphone, methadone, buprenorphine, codeine, and tramadol. Only the CIP data set contained pharmacy dispensing claims for oxymorphone and propoxyphene. Propoxyphene was removed from the US market in late 2010, accounting for its absence during the VHA study period. Pharmacy claims for buprenorphine and methadone dispensed by licensed programs within VHA as medication-assisted treatment for opioid use disorder (OUD) were not included in the VHA data set [39], and patients receiving methadone for OUD were not identifiable in the commercially insured population [14]. Hydrocodone and oxycodone were the predominant opioids prescribed in both populations. Prescribing of hydrocodone, oxycodone, fentanyl, and hydromorphone was significantly greater in CIP than in VHA. Codeine and tramadol were prescribed to a similar degree in both populations. Only morphine and methadone were

Table 3 Factors associated with serious opioid-induced respiratory depression in a commercially insured population vs the VHA population, rank-ordered by odds ratio A) in each population and B) in CIP*

A) CIP population			B) VHA population[†]		
Covariate	OR	95% CI	Covariate	OR	95% CI
Substance use disorder	**10.20**	**9.06–11.40**	MED ≥100 mg/d	**4.13**	**2.61–6.54**
Depression	**3.12**	**2.84–3.42**	Opioid dependence	**3.86**	**2.57–5.78**
Fentanyl	**2.83**	**2.32–3.45**	≥1 ED visit	**2.88**	**2.34–3.54**
Complications of chronic liver disease	**2.77**	**1.74–4.45**	≥1 d hospitalization	**2.86**	**2.27–3.58**
Morphine	**2.44**	**2.07–2.88**	Complications of chronic liver disease	**2.67**	**1.07–6.65**
Myocardial infarction	**2.39**	**1.93–2.97**	Skin ulcers	**2.39**	**1.52–3.77**
Cerebrovascular disease	**2.35**	**2.01–2.75**	Hydromorphone	**2.39**	**1.21–4.72**
Methadone	**2.35**	**1.86–2.98**	Metastatic solid tumor	**2.25**	**1.25–4.04**
MED ≥100 mg/d	**2.31**	**1.90–2.81**	MED 50–<100 mg/d	**2.21**	**1.52–3.20**
Bipolar disorder	**2.18**	**1.83–2.60**	Nonmalignant pancreatic disease	**2.19**	**1.07–4.46**
Schizophrenia	**2.06**	**1.17–3.69**	Widowed	**2.04**	**1.40–2.97**
Nonmalignant pancreatic disease	1.97	1.46–2.66	Age 55–64 y	1.93	1.14–3.25
Renal disease with renal impairment	1.93	1.61–2.31	ER/LA	1.88	1.12–3.18
Heart failure	1.92	1.60–2.29	Age 65+ y	1.84	1.07–3.17
Benzodiazepines	1.77	1.63–1.92	Non-Hispanic white	1.76	1.29–2.40
Hydromorphone	1.73	1.43–2.10	West	1.76	1.25–2.48
Tobacco use disorder	1.69	1.52–1.87	Renal disease with renal impairment	1.74	1.26–2.40
Anxiety disorder	1.64	1.50–1.80	Bipolar disorder	1.68	1.17–2.43
Oxymorphone	1.62	1.15–2.29	Antidepressants	1.63	1.31–2.02
Serious autoimmune rheumatologic disease	1.52	1.25–1.85	Active traumatic injury	1.62	1.28–2.04
Skin ulcers	1.49	1.16–1.91	Other race/ethnicity	1.57	1.10–2.23
Recurrent headache	1.48	1.34–1.64	Chronic pulmonary disease	1.50	1.21–1.87
West	1.48	1.29–1.69	MED 20–<50 mg/d	1.45	1.09–1.92
ER/LA	1.48	1.27–1.72	Warfarin treatment	1.43	1.02–2.00
Chronic pulmonary disease	1.47	1.33–1.63	Oxycodone	1.41	1.06–1.87
Other opioids[‡]	1.45	1.13–1.85	Benzodiazepines	1.38	1.11–1.71
Low back disorders	1.42	1.30–1.55	Substance abuse and non-opioid substance dependence	1.36	1.03–1.79
Peptic ulcer disease	1.41	1.04–1.91	Never married	1.35	1.01–1.82
Muscle relaxants	1.40	1.28–1.53	Sleep apnea	1.34	1.01–1.76
Viral hepatitis	1.39	1.02–1.89	Antipsychotics	1.29	1.01–1.66
Active traumatic injury	1.38	1.27–1.50	Tramadol	*0.73*	*0.53–0.99*
Hydrocodone	1.35	1.22–1.49	Skin infections/abscesses	*0.51*	*0.31–0.85*
MED 50–<100 mg/d	1.35	1.13–1.62	ADHD	*0.33*	*0.11–0.99*
Other sedatives	1.34	1.22–1.48	Serious autoimmune rheumatologic disease	*0.32*	*0.11–0.88*
Antidepressants	1.33	1.22–1.45			
Oxycodone	1.32	1.19–1.45			
Neuropathic disorders	1.28	1.15–1.43			
Obesity	1.26	1.09–1.44			
≥1 ED visit	1.25	1.15–1.36			
Midwest	1.22	1.09–1.36			
Diabetes without chronic complications	1.22	1.08–1.37			
Age 65+ y	1.21	1.04–1.42			
Hypertension	1.20	1.10–1.31			
Antipsychotics	1.19	1.04–1.36			
Other back/neck disorders	1.15	1.05–1.26			

(continued)

Table 3 Continued

A) CIP population			VHA population[†]		
Covariate	OR	95% CI	Covariate	OR	95% CI
Male	1.10	1.01–1.20			
≥1 d hospitalization	*0.841*	*0.76–0.93*			
Age 35–44 y	*0.766*	*0.68–0.87*			
Propoxyphene	*0.665*	*0.54–0.81*			
Nonopioid analgesics	*0.614*	*0.53–0.71*			
Endocarditis	*0.392*	*0.20–0.79*			
Buprenorphine	*0.388*	*0.29–0.56*			

B) CIP population			VHA population[†]		
Covariate	OR	95% CI	Covariate	OR	95% CI
			Opioid dependence	**3.86**	**2.57–5.78**
Substance use disorder	**10.20**	**9.06–11.40**	Substance abuse and nonopioid substance dependence	1.36	1.03–1.79
Depression	**3.12**	**2.84–3.42**			
Fentanyl	**2.83**	**2.32–3.45**			
Complications of chronic liver disease	**2.77**	**1.74–4.45**	Complications of chronic liver disease	**2.67**	**1.07–6.65**
Morphine	**2.44**	**2.07–2.88**			
Myocardial infarction	**2.39**	**1.93–2.97**			
Cerebrovascular disease	**2.35**	**2.01–2.75**			
Methadone	**2.35**	**1.86–2.98**			
MED ≥100 mg/d	**2.31**	**1.90–2.81**	MED ≥100 mg/d	**4.13**	**2.61–6.54**
Bipolar disorder	**2.18**	**1.83–2.60**	Bipolar disorder	1.68	1.17–2.43
Schizophrenia	**2.06**	**1.17–3.69**			
Nonmalignant pancreatic disease	1.97	1.46–2.66	Nonmalignant pancreatic disease	**2.19**	**1.07–4.46**
Renal disease with renal impairment	1.93	1.61–2.31	Renal disease with renal impairment	1.74	1.26–2.40
Heart failure	1.92	1.60–2.29			
Benzodiazepines	1.77	1.63–1.92	Benzodiazepines	1.38	1.11–1.71
Hydromorphone	1.73	1.43–2.10	Hydromorphone	**2.39**	**1.21–4.72**
Tobacco use disorder	1.69	1.52–1.87			
Anxiety disorder	1.64	1.50–1.80			
Oxymorphone	1.62	1.15–2.29			
Serious autoimmune rheumatologic Disease	1.52	1.25–1.85	Serious autoimmune rheumatologic disease	*0.32*	*0.11–0.88*
Skin ulcers	1.49	1.16–1.91	Skin ulcers	**2.39**	**1.52–3.77**
Recurrent headache	1.48	1.34–1.64			
West	1.48	1.29–1.69	West	1.76	1.25–2.48
ER/LA	1.48	1.27–1.72	ER/LA	1.88	1.12–3.18
Chronic pulmonary disease	1.47	1.33–1.63	Chronic pulmonary disease	1.50	1.21–1.87
Other opioids[‡]	1.45	1.13–1.85			
Low back disorders	1.42	1.30–1.55			
Peptic ulcer disease	1.41	1.04–1.91			
Muscle relaxants	1.40	1.28–1.53			
Viral hepatitis	1.39	1.02–1.89			
Active traumatic injury	1.38	1.27–1.50	Active traumatic injury	1.62	1.28–2.04
Hydrocodone	1.35	1.22–1.49			
MED 50–<100 mg/d	1.35	1.13–1.62	MED 50–<100 mg/d	**2.21**	**1.52–3.20**

(continued)

Table 3 Continued

B) CIP population			VHA population[†]		
Covariate	OR	95% CI	Covariate	OR	95% CI
Other sedatives	1.34	1.22–1.48			
Antidepressants	1.33	1.22–1.45	Antidepressants	1.63	1.31–2.02
Oxycodone	1.32	1.19–1.45	Oxycodone	1.41	1.06–1.87
Neuropathic disorders	1.28	1.15–1.43			
Obesity	1.26	1.09–1.44			
≥1 ED visit	1.25	1.15–1.36	≥1 ED visit	**2.88**	**2.34–3.54**
Midwest	1.22	1.09–1.36			
Diabetes without chronic complications	1.22	1.08–1.37			
Age 65+ y	1.21	1.04–1.42	Age 65+ y	1.84	1.07–3.17
Hypertension	1.20	1.10–1.31			
Antipsychotics	1.19	1.04–1.36	Antipsychotics	1.29	1.01–1.66
Other back/neck disorders	1.15	1.05–1.26			
Male	1.10	1.01–1.20			
≥1 d hospitalization	*0.84*	*0.76–0.93*	≥1 d hospitalization	**2.86**	**2.27–3.58**
Age 35–44 y	*0.77*	*0.68–0.87*			
Propoxyphene	*0.67*	*0.54–0.81*			
Nonopioid analgesics	*0.61*	*0.53–0.71*			
Endocarditis	*0.39*	*0.20–0.79*			
Buprenorphine	*0.39*	*0.29–0.56*			
			Metastatic solid tumor	**2.25**	**1.25–4.04**
			Widowed	**2.04**	**1.40–2.97**
			Age 55–64 y	1.93	1.14–3.25
			Non-Hispanic white	1.76	1.29–2.40
			Other race/ethnicity	1.57	1.10–2.23
			MED 20–<50 mg/d	1.45	1.09–1.92
			Warfarin treatment	1.43	1.02–2.00
			Never married	1.35	1.01–1.82
			Sleep apnea	1.34	1.01–1.76
			Tramadol	*0.73*	*0.53–0.99*
			Skin infections/abscesses	*0.51*	*0.31–0.85*
			ADHD	*0.33*	*0.11–0.99*

ADHD = attention deficit hyperactivity disorder; CI = confidence interval; ED = emergency department; ER/LA = extended-release/long-acting; MED = morphine equivalent dose; OCD = obsessive compulsive disorder; OR = odds ratio; PTSD = post-traumatic stress disorder.
*Factors are presented based on their strength of association with serious opioid-induced respiratory depression. OR: >2.00 are bolded, >1.0 to 2.0 are regular font, and <1.0 are italicized.
[†]From "Appendix II. Logistic regression results: Serious opioid-related toxicity or overdose" [26].
[‡]Other prescription opioids included meperidine, pentazocine, dihydrocodeine, nalbuphine, and butorphanol.

prescribed more commonly in VHA than in CIP. Among CIP cases with and without SUD diagnoses, methadone was prescribed with similar prevalence, while buprenorphine was prescribed sevenfold more frequently among cases with SUD than without (data not shown). Each opioid evaluated, except for hydrocodone, codeine, and tramadol, was prescribed to a substantially greater proportion of cases than controls in both populations.

ER/LA formulations were prescribed 42% less frequently among cases in CIP (26.3%) than among cases in VHA (45.2%), and equally infrequently to controls in both populations (~5%). Among cases, a maximum MED of less than 100 mg/d was prescribed with similar frequency between populations, but an MED of 100 mg/d or greater was almost twice as common in CIP (58.4%) as in VHA (32.8%). Among controls in both populations, there was an inverse relationship between prescribing frequency and a maximum MED of 20 mg/d or greater, but CIP out-prescribed VHA at each level of 20 mg/d or greater, peaking at a fivefold differential for an MED of 100 mg/d or greater (15.8% in CIP vs 3.3% in VHA).

Among nonopioid medications, analgesics were concurrently prescribed to 22% more CIP cases and 62% more controls than in VHA. All psychoactive medications

except antidepressants were prescribed considerably more frequently in CIP than in VHA, although the differential was substantially less among controls than cases. Antidepressants were prescribed to approximately 67% of cases in both populations, but to 39% fewer controls in CIP than VHA. The prevalence of an ED visit or hospitalization in the six months before a serious OIRD event was 18% and 32% higher, respectively, among cases in VHA than CIP, but 19% and 30% lower, respectively, among corresponding controls.

Discussion

Serious OIRD events in commercially insured individuals were most strongly associated with SUD and depression. Other strongly associated factors included other mental health disorders; impaired liver, renal, vascular, and pulmonary function; fentanyl, methadone, and morphine; higher daily opioid doses; and concurrent psychoactive medications. Many of the factors most strongly associated with serious OIRD/overdose were concordant among US medical users of prescription opioids with either private or public (VHA) health insurance coverage, except depression, vascular disease, and specific opioids. The predominant risk factors in both populations included SUD; bipolar disorder; impaired liver, renal, and pulmonary function; higher daily opioid doses; and concurrent psychoactive medications. Each population's risk factor profile showed excellent discrimination between opioid users with and without a serious OIRD event, namely 93% in CIP and 89% in VHA.

The CIP population of 18 million opioid users yielded 7,234 cases of serious OIRD that came to medical attention over a five-year observation period (2009–2013) while the VHA population of 1.9 million opioid users contained 817 cases during two years (2010–2012). Of the factors assessed commonly in both populations, 20 were risk factors for serious OIRD in both populations while 25 were positively associated with OIRD in CIP only and five in VHA only. Many differences in the OIRD risk factor profiles between the two populations can be explained by differences in population characteristics. Patients treated with prescription opioids frequently have complex health conditions that increase their vulnerability to the central nervous system (CNS) and respiratory depressant effects of opioids. Additionally, they are likely to be prescribed multiple nonopioid medications that can interact adversely with opioids. Older adults often have polypharmacy and impaired cardiopulmonary or cerebrovascular function and hepatic metabolism or renal excretion of drugs due to comorbidity or aging. Decreased clearance of drugs in these individuals can result in toxic accumulation of active opioids or metabolites and prolonged duration of action [40,41]. Reduced ability to tolerate even mild degrees of respiratory depression or sedation in such patients can manifest as serious OIRD. Older age was more strongly associated with the occurrence of serious OIRD in VHA opioid recipients (with ~75% of the population ≥55 years) than in CIP (with ~35% ≥55 years).

A diagnosis of SUD was the single comorbidity most highly associated with experiencing serious OIRD, particularly in CIP. In medical users of prescription opioids, SUD may 1) be the indication for the prescription opioid (i.e., methadone or buprenorphine as medication-assisted treatment of OUD); 2) coexist with a pain-related condition that is, in part, managed with opioids; or 3) develop as an iatrogenic adverse consequence of treating an acute or chronic pain–related condition with prescription opioids. SUD may involve misuse or abuse of prescription or illicit opioids as well as nonopioid, psychoactive substances. The uncontrolled and unpredictable nature of the substances consumed (ingredients, dose, frequency, route) makes SUD an exceptionally high-risk situation for serious OIRD/overdose, and it often involves polydrug intoxication [42]. These challenging patients often require specialized expertise to manage opioid prescribing, even within prescribing parameters generally accepted as safe [43]. A recent ED visit was associated with serious OIRD in both populations [12], but considerably more strongly in VHA. Opioid-seeking ED visits can reflect inadequate pain control, self-medication of psychiatric distress due to mental illness, or craving/withdrawal in SUD [43,44].

A diagnosis of bipolar disorder was strongly predictive of OIRD/overdose, particularly in CIP. Despite a prevalence of almost 50% among cases in both populations, depression was a strong, independent predictor of serious OIRD in CIP only. On the other hand, anxiety disorder was twice as prevalent among cases in CIP as in VHA, and schizophrenia was fourfold more common among cases in VHA than in CIP, but each of these conditions increased the probability of OIRD only in CIP. However, concurrent antidepressants, benzodiazepines, and antipsychotics were moderately strong risk factors in both populations, as well as muscle relaxants and sedatives in CIP [45–49]. The prevalence of coprescribed antidepressants, benzodiazepines, and antipsychotics was considerably greater than the prevalence of depression, anxiety, and schizophrenia diagnoses, respectively, among cases in both populations (except less than the prevalence of schizophrenia in VHA). These observations suggest underdocumentation or diagnosis of mental illness or prescribing for alternate indications (e.g., antidepressants prescribed for neuropathic pain, fibromyalgia, migraine, anxiety, or insomnia) [50]. Alternatively, inherent pharmacologic properties of the psychoactive medications themselves may contribute to opioid-related CNS/respiratory depression and represent potentially lethal drug-opioid interactions regardless of the underlying prescribing indication. For example, benzodiazepines are coprescribed in up to 80% of medical users of prescription opioids and associated with a risk of fatal overdose up to 10-fold greater, particularly at a higher opioid MED, than in patients using opioids without concurrent benzodiazepines [14,51,52].

Diagnosed PTSD was strikingly more common among VHA opioid users that experienced serious OIRD and even more so among VHA controls, compared with CIP

cases and controls, respectively. However, after adjusting for numerous factors in multivariable modeling, PTSD was not independently associated with serious OIRD in either population, in contrast to published observations based on unadjusted analyses [53].

Anxiety disorder and recurrent headache were predictors of serious OIRD only in CIP, probably reflecting its younger age distribution and greater proportion of females. Most pain-related conditions were substantially more prevalent in CIP than VHA and were associated with serious OIRD only in CIP. Although obesity and diabetes were considerably more prevalent in VHA, they were moderately associated with OIRD only in CIP. Renal, pulmonary, liver, and nonmalignant pancreatic disease were consistent predictors of serious OIRD among opioid users in both populations, despite all but pancreatic disease having substantially greater prevalence in VHA. These findings reinforce the dangers of impaired metabolism and excretion, resulting in accumulation of active opioid or metabolites, which can enhance the duration and severity of CNS/respiratory depression. The novel and consistent finding of substantial risk of serious OIRD with nonmalignant pancreatic disease is unexplained but may relate to its common association with alcohol use disorder and chronic pain.

Opioid-related factors also differed between the populations. The risk of OIRD was consistently dose dependent in both populations [54–56]. As opioid doses are gradually increased, varying degrees of tolerance typically develop to the different mechanisms underlying their respiratory depressant effects, but tolerance may be incomplete or influenced by concomitant use of other CNS depressants [42,57–60]. An MED of 100 mg/d or greater was prescribed almost twice as commonly among cases in CIP as in VHA, and fivefold more often among CIP controls. However, increasing MED was considerably more strongly associated with OIRD in VHA, and uniquely at an MED of 20 to less than 50 mg/d, which has been noted in other VHA studies of fatal opioid overdose [54–56]. This observation likely reflects increased vulnerability of the older and possibly more clinically complex VHA patients. OIRD events in both populations may reflect 1) overly rapid titration or excessive initial dosing in patients who were opioid naïve, 2) prescribing or misuse of higher doses in patients with diagnosed SUD or psychiatric disorders, or 3) cumulative opioid-related cognitive effects resulting in confusion or misuse [42,60].

Patients prescribed ER/LA opioid formulations had greater likelihood of serious OIRD than those who used short-acting formulations [61–63]. ER/LA opioids are indicated only for long-term therapy. When consumed at recommended dosing intervals, they are expected to produce more stable blood levels than short-acting opioids at an equivalent total daily MED and thus confer less pharmacologic risk [57,60]. This assumption suggests that subpopulations of individuals with other risks for overdose may gravitate to ER/LA products. Alternatively, ER/LA opioids may have been 1)

prescribed or consumed at nonindicated intervals, 2) prescribed for acute pain or opioid-naïve individuals, or 3) high-dose formulations prescribed or consumed in higher total daily MED than short-acting opioids [17,43,64,65]. Among cases in CIP, ER/LA formulations were prescribed approximately half as often as among VHA cases, likely reflecting a younger population with more acute pain conditions.

Inherent differences between the private and public health care delivery systems and clinical practices likely contribute to differences in the OIRD risk profiles between CIP and VHA. VHA is an integrated, governmental health care system with more controlled clinical and prescribing practices and drug formulary than the breadth and heterogeneity available among the multiple commercial health insurance programs represented in CIP. Prescribing of all opioids, except morphine and methadone, was substantially greater in CIP than in VHA. Perhaps consistent with this observation, all opioids prescribed in CIP, except codeine, tramadol, propoxyphene, and buprenorphine, were associated with serious OIRD, as compared with only oxycodone and hydromorphone in VHA. Morphine and methadone were prescribed in VHA at approximately twice the frequency as in CIP, but were not significantly associated with serious OIRD in VHA (albeit with a lower bound of the 95% confidence interval of 1.0). This observation is particularly striking for methadone in light of its uniquely challenging pharmacology and substantial interindividual variability in the setting of generally older and potentially more clinically complex VHA patients with more chronic health conditions. This finding may reflect successful implementation of VHA-specific risk mitigation strategies, for example, prescriber education or methadone prescribing restrictions for pain management [15].

In CIP, serious OIRD cases with a methadone pharmacy claim were distributed similarly between those with and without diagnosed SUD (data not shown), potentially suggesting methadone use as much to manage pain as OUD. On the other hand, CIP cases prescribed buprenorphine were sevenfold as likely to have a diagnosis of SUD as not, suggesting use predominantly as medication-assisted therapy for OUD rather than for pain management. In the United States, higher-dose buprenorphine in sublingual formulation is indicated only to treat OUD, while the lower-dose transdermal formulation is approved only for pain. In CIP, buprenorphine was associated with a significantly lower risk of serious OIRD (OR = 0.39), while methadone was strongly associated with OIRD (OR = 2.35). Tramadol, a unique, synthetic opioid with low mu receptor affinity that was reclassified as a US controlled substance in August 2014, was prescribed with similar frequency among cases and controls in both populations. Tramadol was not associated with OIRD in CIP and correlated with lower OIRD likelihood in VHA. Coprescribed nonopioid analgesics were also associated with a lower risk of serious OIRD in CIP, possibly by reducing the amount of opioid required to manage pain.

Slight differences between regression models and the smaller VHA sample analyzed also may have contributed to some of the differences found. The regression models in the two populations differed slightly due mainly to differences in variables available in the source data sets. The CIP model used an updated definition for SUD and included more low-frequency prescription opioids in an "other opioids" covariate. Some variables assessed in the smaller VHA population had low endorsement frequencies, and thus potentially more unstable prevalence estimates and model-derived beta coefficients. For example, serious autoimmune rheumatologic disease was moderately associated with OIRD in CIP but had lower risk (protective) in VHA. The approximately fourfold difference alone between the two study samples increased the likelihood of statistically significant differences between cases and controls in the substantially larger CIP sample.

Strengths and Limitations

This retrospective, nested case-control study is the most comprehensive characterization published to date of serious OIRD/overdose in a national sample of privately insured, US medical users of prescription opioids. The risk factor profile derived from multivariable modeling statistically adjusted for numerous covariates, and thus identified factors independently associated with serious OIRD.

Possible limitations of the source populations studied are that approximately 89% of the prescription opioid users in the largely employer-based, commercially insured population were younger than age 65 years and the older VHA population may not be representative of all publicly insured opioid users (e.g., Medicaid, Medicare, federal and state government employees). Second, administrative health care claims data may contain missing or incomplete elements and misclassification or coding errors, especially for socially sensitive comorbidities such as SUD or other mental health conditions. In fact, the substantially lower prevalence of diagnoses of depression, anxiety, and schizophrenia in patients experiencing overdose relative to their frequency of coprescribed antidepressants, benzodiazepines, and antipsychotics, respectively, suggests underdiagnosis or documentation of mental illness. Third, claims data are unable to capture all known and potential predictors of serious OIRD, such as family history and genotype, some behavioral and social characteristics, medication adherence (i.e., the maximum prescribed daily MED may not necessarily reflect the actual amount consumed by an individual), illicit substances consumed, and medications obtained from other sources or paid for in cash, and lack details regarding the therapeutic indications for prescribed opioids (e.g., analgesia vs medication-assisted treatment of OUD) and nonopioids. Fourth, we did not assess some factors known to be important determinants of risk for serious OIRD, including previous overdose [14] and duration of opioid therapy [66], nor potentially important

interactions, such as between MED and coprescribed psychoactive medications [51] or treated vs untreated SUD or other mental illnesses. Fifth, the serious prescription OIRD outcome variable was defined by an administrative health care coding algorithm whose clinical validity and reliability have not yet been fully established. However, our ICD-9-CM coding classification for prescription opioid-involved poisoning is consistent with recommendations of Injury Surveillance Workgroup [67] and other studies using claims data [14,68,69]. Our code-based definition further reduces the possibility of misclassification of serious overdose by requiring additional codes for manifestations of life-threatening respiratory or CNS depression or its treatment. Finally, the total number of overdoses in each population was conservative as it did not include an unknown number of cases of serious OIRD that were fatal or successfully treated in prehospital settings and thus were not represented in the VHA or commercial insurance claims [14]. Whether the two populations differed in the frequency of such prehospital events is unknown.

Conclusion

Risk factor profiles for serious OIRD among US medical users of prescription opioids with either private or public health insurance were largely concordant, with the strongest predictors being substance use disorder; bipolar disorder; impaired liver, renal and pulmonary function; higher daily opioid doses; and concurrent CNS-depressant medications.

Clinical Implications

Opioid pharmacotherapy requires an individualized approach due to the potential for serious OIRD/overdose in all patients regardless of age, indication, or specific opioid. Future research to assess overdose risk and risk factor behavior in clinically important subgroups as well as to evaluate potential interactions among risk factors would yield important insight regarding the mechanism(s) by which each identified risk factor enhances risk and whether that risk differs by age group or sex, opioid indication (e.g., pain vs medication-assisted treatment of opioid use disorder), duration and regularity of opioid use (i.e., acute, episodic, or chronic), or specific comorbidities (e.g., mental health disorders or SUD) or concurrent medications (e.g., benzodiazepines). As risk for a serious adverse outcome is multifactorial, appropriate and thoughtful prescribing to mitigate risk requires multidimensional assessment and accounting for relevant demographic and psychosocial characteristics, active clinical conditions, concurrent medications and substance use, and opioid-specific pharmacologic characteristics. A validated, predictive screening risk index is available to use at the point of care in clinical settings to provide a quantitative estimate of risk of overdose and corresponding risk factor profile for individual prescription opioid users [27,28]. For patients with elevated risk and given the general concordance between risk factor profiles of the two populations studied, the existing

publicly available risk mitigation resources and strategies that the VHA has developed and successfully piloted [15] are likely generalizable to the private sector. These and other evidence-based resources should be leveraged in the general population of medical users of prescription opioids to reverse the ongoing epidemic of life-threatening OIRD.

Acknowledgments

Supplementary Data

Supplementary Data may be found online at http://painmedicine.oxfordjournals.org.

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