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Original Research Article

Development of a Risk Index for Serious Prescription Opioid-Induced Respiratory Depression or Overdose in Veterans' Health Administration Patients

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Abbreviations: CCI = Charlson Comorbidity Index; CNS = central nervous system; ER/LA = extended release/long-acting; MED = morphine equivalent dose; OSORD = overdose or serious opioid-induced respiratory depression; RIOSORD = risk index for overdose or serious opioid-induced respiratory depression; VHA = Veterans' Health Administration

Abstract

Objective. Develop a risk index to estimate the likelihood of life-threatening respiratory depression or overdose among medical users of prescription opioids.

Subjects, Design, and Methods. A case-control analysis of administrative health care data from the Veterans' Health Administration identified 1,877,841 patients with a pharmacy record for an opioid prescription between October 1, 2010 and September 30, 2012. Overdose or serious opioid-induced respiratory depression (OSORD) occurred in 817. Ten controls were selected per case ($n = 8,170$). Items for an OSORD risk index (RIOSORD) were selected through logistic regression modeling, with point values assigned to each predictor. Modeling of risk index scores produced predicted probabilities of OSORD; risk classes were defined by the predicted probability distribution.

Results. Fifteen variables most highly associated with OSORD were retained as items, including mental health disorders and pharmacotherapy; impaired

drug metabolism or excretion; pulmonary disorders; specific opioid characteristics; and recent hospital visits. The average predicted probability of experiencing OSORD ranged from 3% in the lowest risk decile to 94% in the highest, with excellent agreement between predicted and observed incidence across risk classes. The model's C-statistic was 0.88 and Hosmer–Lemeshow goodness-of-fit statistic 10.8 ($P > 0.05$).

Conclusion. RIOSORD performed well in identifying medical users of prescription opioids within the Veterans' Health Administration at elevated risk of overdose or life-threatening respiratory depression, those most likely to benefit from preventive interventions. This novel, clinically practical, risk index is intended to provide clinical decision support for safer pain management. It should be assessed, and refined as necessary, in a more generalizable population, and prospectively evaluated.

Key Words. Opioid; Risk; Respiratory Depression; Overdose; Questionnaire; Index

Introduction

Unintentional opioid-related overdose in the United States is an increasingly common yet preventable cause of death among medical users of prescription opioids [1,2]. Identifying risk factors and individuals at elevated risk is a public health imperative and necessary to implement effective preventive measures.

Serious toxicity and overdose events from prescription opioid use have risen in the United States over the last two decades and parallel a striking increase in opioid prescribing to manage acute and chronic pain [3–9]. The marked increase in opioid prescribing overall is reflected in the U.S. Veterans' Health Administration (VHA), with the percentage of all VHA patients receiving opioids growing from 18.9% in Fiscal Year 2004 to 33.4% in Fiscal Year 2014 [10].

Opioids depress the central nervous system (CNS), which may result in profound and potentially fatal respiratory depression, sedation, and coma [11–13]. Prescription opioid-related deaths in the United States have almost quadrupled since 1999, to 16,917 in 2011, with approximately 80% of fatal opioid-related overdoses classified as unintentional [3]. More than half of overdoses occur in patients who are prescribed a relatively high morphine equivalent dose (MED) of >100 mg/day or who misuse opioid analgesics [4]. However, patients using opioids with daily MED as low as 20–50 mg can experience unintentional life-threatening respiratory or CNS depression under conditions that enhance these effects or result in opioid accumulation or excessive duration of action [14–17]. Certain pre-existing conditions (e.g., liver, kidney, or pulmonary disease) or concomitant use of other medications or substances (e.g., sedative-hypnotics or alcohol) can negatively impact a patient's ability to tolerate opioid exposure, resulting in overdose and serious respiratory/CNS depression.

Predictive models and scoring systems (risk indices) that estimate the level of risk of an adverse outcome are commonly developed in medical research and clinical practice with the goal of preventing or mitigating an outcome [18]. Examples include risk of suicidality [19], cardiovascular disease [20–22], postoperative pulmonary complications [23,24], and mortality [25].

Several screening instruments assess the risk of aberrant drug-related behaviors (misuse, abuse, or addiction) in prescription opioid-treated patients, such as the Opioid Risk Tool [26], Screener and Opioid Assessment for Patients with Pain-Revised (SOAPP-R) [27], Pain Medication Questionnaire (PMQ) [28], CAGE-Adapted to Include Drugs (CAGE-AID) [29], Screening Tool for Addiction Risk (STAR) [30], and the Screening Instrument for Substance Abuse Potential (SISAP) [31]. However, no published instruments currently provide clinically useful, evidence-based risk information about the likelihood of opioid-induced overdose or life-threatening respiratory/CNS depression [32].

We previously examined potential predictors of serious prescription opioid-induced toxicity and overdose in a case-control study of US military veterans [15]. Factors with the most significant positive associations included maximum prescribed daily MED ≥ 100 mg (with a significant dose-response effect beginning at ≥ 20 mg), history of opioid dependence, hospitalization during the 6 months before the serious respiratory depression or overdose event, liver disease, and use of extended-release or long-acting opioids. Based on results from the previous study, a practical risk index was developed to estimate the likelihood of overdose or serious opioid-induced respiratory depression (OSORD) among medical users of prescription opioids.

Methods

Study Design and Setting

The risk index was developed using a retrospective, case-control analysis of administrative health care data derived from VHA Medical SAS Inpatient and Outpatient and VHA Decision Support databases. These include information from all VHA Medical Centers and Outpatient Clinics. The Western Institutional Review Board determined that this study was exempt from full IRB review.

Study Participants

This study used the same VHA population as our previous study that identified factors associated with prescription opioid-induced respiratory depression or overdose [15]. A total of 10,131,467 patients was included in the VHA Medical SAS datasets from October 1, 2010 through September 30, 2012; of these,

Table 1 Baseline descriptive characteristics of the study sample

Characteristics	Cases ($n = 817$) n (%)	Controls ($n = 8{,}170$) n (%)	P Value
DEMOGRAPHICS			
Age (years), median (IQR)	62 (10)	62 (16)	<0.001
Age Group (years)			
18–34	27 (3.3)	565 (6.9)	<0.001
35–44	31 (3.8)	619 (7.6)	
45–54	115 (14.2)	1,240 (15.2)	
55–64	377 (46.1)	2,672 (32.7)	
65+	267 (32.7)	3,074 (37.6)	
Male	753 (92.2)	7,528 (92.1)	0.98
Race			
Non-hispanic White	555 (67.9)	4,546 (55.6)	<0.001
Non-hispanic Black	8 (10.2)	1,300 (15.9)	
Hispanic	32 (3.9)	431 (5.3)	
Other	147 (18)	1,893 (23.2)	
Marital Status			
Never married	102 (12.5)	1,227 (15)	<0.001
Married	351 (43)	4,246 (52)	
Separated	20 (2.5)	41 (0.5)	
Divorced	285 (34.9)	2,268 (27.8)	
Widowed	59 (7.2)	388 (4.8)	
Body Mass Index (BMI, kg/m^2)			
Underweight (<18.5)	29 (3.6)	72 (0.9)	<0.001
Normal (18.5–24.9)	193 (23.6)	1,197 (14.7)	
Overweight (25.0–29.9)	224 (27.4)	2,070 (25.3)	
Obese (≥30.0)	306 (37.5)	2,667 (32.6)	
Missing	65 (8)	2,164 (26.5)	
U.S. Census Region			
Northeast	75 (9.2)	824 (10.1)	<0.001
North Central	190 (23.3)	1,745 (21.4)	
South	270 (33.1)	3,258 (39.9)	
West	257 (31.5)	1,842 (22.6)	
Other	25 (3.1)	501 (6.1)	
CLINICAL CHARACTERISTICS			
CCI score, mean (SD)	3.9 (3.3)	1.7 (2)	<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)	343 (4.2)	<0.001
Dementia	5 (0.6)	32 (0.4)	0.35
Chronic pulmonary disease	291 (35.6)	1,047 (12.8)	<0.001
Rheumatologic disease (serious autoimmune)	6 (0.7)	96 (1.2)	0.26
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)	646 (8)	<0.001

Table 1 *Continued*

Characteristics	Cases ($n = 817$) n (%)	Controls ($n = 8,170$) n (%)	P Value
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			
Non-pain-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)	0.92
Viral hepatitis	106 (13)	249 (3)	<0.001
Alcoholic hepatitis	3 (0.4)	5 (0.1)	0.005
Non-malignant pancreatic disease	24 (2.9)	49 (0.6)	<0.001
Sexually transmitted disease	12 (1.5)	69 (0.8)	0.07
Herpes simplex	7 (0.9)	45 (0.6)	0.27
Skin infections/abscesses	85 (10.4)	286 (3.5)	<0.001
Sleep apnea	147 (18)	652 (8)	<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)	0.64
Schizophrenia	36 (4.4)	114 (1.4)	<0.001
Anxiety disorder	180 (22)	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 disorder	170 (20.8)	717 (8.8)	<0.001
Fibromyalgia	34 (4.2)	157 (1.9)	<0.001
Chronic headache	88 (10.8)	427 (5.2)	<0.001
Burns	4 (0.5)	16 (0.2)	0.089
Active traumatic injury	212 (26)	869 (10.6)	<0.001
Motor vehicle accident	7 (0.9)	14 (0.2)	<0.001
PRESCRIPTION DRUG INFORMATION			
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
Morphine	251 (30.7)	334 (4.1)	<0.001
Tramadol	114 (14)	1,428 (17.5)	0.01
Methadone	107 (13.1)	139 (1.7)	<0.001
Codeine	63 (7.7)	561 (6.9)	0.365
Fentanyl	49 (6)	44 (0.5)	<0.001
Hydromorphone	38 (4.7)	28 (0.3)	<0.001
Oxymorphone	1 (0.1)	1 (0)	0.04
Buprenorphine	0 (0)	2 (0)	0.66
Other*	2 (0.2)	4 (0.1)	0.04
BY FORMULATION			
Extended-Release/Long-Acting (ER/LA)	369 (45.2)	499 (6.1)	<0.001
Not ER/LA	633 (77.5)	4,807 (58.5)	<0.001

Table 1 *Continued*

Characteristics	Cases ($n = 817$) *n* (%)	Controls ($n = 8,170$) *n* (%)	*P* Value
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
Maximum Prescribed Daily MED Group			
1–<20	35 (4.3)	1,331 (16.3)	<0.001
20–<50	227 (27.8)	2,614 (32)	
50–<100	163 (20)	718 (8.8)	
≥100	268 (32.8)	273 (3.3)	
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
ALL CAUSE HEALTH CARE UTILIZATION			
Days of hospitalization, mean (SD)	9.6 (22.9)	1.1 (8)	<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 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
Hospitalizations per patient, mean (SD)	1 (1.5)	0.1 (0.5)	<0.001
Pharmacy visits per patient, mean (SD)	24.6 (15)	12.9 (10.4)	<0.001

* Other opioids included meperidine and pentazocine/naloxone.

† Proportion of opioid prescriptions dispensed to a patient during baseline that contained an extended-release/long-acting formulation. Methadone is a long-acting opioid.

Abbreviations: CCI = Charlson Comorbidity Index; ED = emergency department; ER = extended-release; LA=long acting; MED = morphine equivalent dose; NDC = National Drug Code.

1,877,841 (18.5%) had at least one pharmacy record for an opioid. Only patients with complete demographic information on age, sex, and self-identified race, and continuous medical and pharmacy benefits for the 6-month baseline period before the index date were eligible for inclusion in the study. Cases were patients who experienced OSORD (index event), as defined by the *International Classification of Disease, 9th Revision*, *Clinical Modification* (ICD-9-CM) and Current Procedure Terminology (CPT) coding algorithm developed in our prior work [15]. To optimize statistical power, 10 control patients from those dispensed an opioid by VHA during the study period were randomly selected per case and assigned the same index date [33–35]. After eligibility criteria were applied, 8,987 patients were included in the present analysis (817 cases, 8,170 controls).

Variables

The outcome variable, OSORD, was defined by ICD diagnostic and CPT procedural codes [15]. Independent variables (Table 1) included demographics; the Charlson Comorbidity Index (CCI) score [36–38]; individual CCI comorbidities; other selected pain- and nonpain-related comorbidities [39–42]; prescription medication information, including opioid active ingredient, formulation, and MED [43,44], and select concomitant medications known to potentiate opioid effects; and health care utilization [15].

Data Analysis

Univariate statistics were calculated to characterize the sample. Analyses of variance, *t*-tests, and Wilcoxon Rank Sum tests, as appropriate, were used to compare continuous variables between cases and controls, while Chi-square tests were used to compare proportions of categorical variables between cases and controls.

Multivariable logistic regression was conducted to examine potential predictors of serious opioid-induced respiratory depression or overdose. All independent variables with $P < 0.25$ on bivariate testing were initially included in the model (Table 1). Variables with $P > 0.10$ were dropped from the model sequentially unless they were identified as confounders (i.e., variables that, when dropped from the model, resulted in a 20% or greater change in parameter estimates for one or more of the other variables, when compared with the original model). The final model included confounders and all variables with $P \leq 0.10$. All statistical analyses were conducted in SAS v9.3. (SAS, Cary, NC).

Risk Index Construction

Items for the risk index were selected from the model variables statistically significantly associated with OSORD. The authors balanced the scientific and statistical robustness of each variable's association with opioid overdose with the practical need for a relatively brief instrument with simplified administration by health care personnel in a busy community health care setting. Considerations included: 1) statistical strength of association in this sample; 2) confirmation in the published literature that the variable is a risk factor; 3) likely generalizability of the variable to the U.S. population of medical users of prescription opioids; and 4) feasibility of obtaining readily available, valid information for all index items.

Point values were assigned to questionnaire items by multiplying the regression-generated β coefficients by 10 and rounding to the nearest integer. For each patient, values were summed, yielding a risk index score [23,45]. The risk index scores were then used in a multiple logistic regression model with life-threatening opioid-induced respiratory depression or overdose as the outcome, to produce predicted probabilities of the outcome [23,45]. A power transformation (ln [risk index score + 25], with ln indicating natural logarithm) reduced the skewness of the risk index scores and improved model calibration [23,45].

Model performance was assessed with the Hosmer–Lemeshow test for overall model goodness-of-fit and receiver operating curves and corresponding C-statistics for model discrimination between those with and without the outcome of interest. Accepted C-statistic cutoffs for reasonable and strong discrimination are 0.7 and 0.8, respectively [46].

To test the validity of the risk index, the distribution of predicted probabilities was compared by deciles to that of the observed occurrence of serious toxicity or overdose. Patient count, average predicted probability of the outcome, and observed incidence of events were computed for each risk class.

Results

Descriptive Statistics

Baseline sample characteristics, including demographics, comorbidities, prescription medications, and health care utilization, are in Table 1. As described in Zedler et al., unadjusted analyses showed that cases were significantly more likely to be non-Hispanic; white; divorced, separated or widowed; and to have received care in the southern or western United States [15]. Cases also had a greater burden of illness as indicated by a higher mean CCI score and frequencies of most individual CCI and selected other comorbidities. Several opioid-related factors were significantly associated with OSORD, including opioid formulation, route of administration, maximum prescribed daily MED, and receipt of more opioid prescriptions overall. Cases were prescribed other potentially interacting medications more frequently and had greater baseline health care utilization than did controls [15].

Multivariable Modeling

Independent variables excluded from multivariable regression modeling due to $P > 0.25$ on bivariate analysis included dementia, peptic ulcer disease, endocarditis, herpes simplex infection, attention deficit hyperactivity disorder, and buprenorphine or codeine prescription. Demographic variables associated with higher odds of OSORD included age groups 45–54 years and $\geq$55, race/ethnicity non-Hispanic white, and marital status never married or widowed. Multiple CCI comorbidities were associated with an event, with liver disease reflecting cirrhosis and chronic hepatitis having the highest odds, followed by skin ulcers, metastatic solid tumor, renal disease, and chronic pulmonary disease. Opioid dependence[1] was the nonpain-related comorbidity with the highest likelihood (OR 4.54, 95% CI 3.12, 6.63), followed by nonmalignant pancreatic disease (OR 2.13, 95% CI 1.06, 4.25), a combined variable of bipolar disorder or schizophrenia (OR 1.95, 95% CI 1.43, 2.67), and sleep apnea (OR 1.34, 95% CI 1.03, 1.75). Active traumatic injury was the only pain-related comorbidity associated with higher odds of the outcome (OR 1.48, 95% CI 1.18, 1.87) (Table 2).

Certain medication and health care utilization variables were significantly associated with serious opioid-induced respiratory depression or overdose. Maximum prescribed daily MED $\geq$100 mg/day had the highest likelihood (OR 4.96, CI 3.24, 7.61), but MED levels $\geq$20 mg/day were monotonically associated with increased probability of an

[1]In the International Classification of Disease, 9th and 10th Revisions, substance "dependence" replaced "addiction with or without tolerance." We classified substance use disorders as "opioid dependence" (304.0x, 304.7x) or "nonopioid substance dependence and nondependent substance abuse."

Table 2 Multivariable logistic regression: Factors associated with serious opioid-induced respiratory depression or overdose*

	All Patients (Cases, $n = 817$; Controls, $n = 8,170$)			
Covariate	Odds Ratio	95% CI		*P* Value
DEMOGRAPHICS				
Age group (in years)†				
18–34 (reference)				
35–44	1.24	0.65	2.35	0.52
45–54	1.97	1.15	3.37	**0.013**
55+	2.57	1.55	4.26	**<0.001**
Race/ethnicity				
Non-Hispanic black (reference)				
Non-Hispanic white	1.71	1.27	2.31	**<0.001**
Hispanic	1.53	0.9	2.59	0.12
Other	1.56	1.1	2.2	**0.013**
Marital status‡				
Married (reference)				
Separated/divorced	1.16	0.94	1.44	0.16
Never married	1.48	1.11	1.97	**0.008**
Widowed	2.12	1.46	3.08	**<0.001**
Geographic region				
Northeast (reference)				
North Central	1.29	0.91	1.84	0.16
South	1.13	0.81	1.58	0.48
West	1.56	1.11	2.2	**0.01**
Other	0.63	0.36	1.11	0.11
CLINICAL CHARACTERISTICS				
Individual Charlson Index (CCI) comorbidities				
Congestive heart failure	1.05	0.64	1.72	0.85
Peripheral vascular disease	1.14	0.78	1.67	0.50
Cerebrovascular disease	0.66	0.41	1.06	0.09
Chronic pulmonary disease	1.57	1.27	1.94	**<0.001**
Rheumatologic disease (serious autoimmune)	0.32	0.12	0.89	**0.03**
Mild liver disease	2.42	1.39	4.19	**0.002**
Use of warfarin	1.27	0.91	1.79	0.16
Renal disease	1.59	1.17	2.17	**0.004**
Any malignancy, including leukemia and lymphoma	1.28	0.95	1.72	0.10
Skin ulcers	2.31	1.48	3.61	**<0.001**
Metastatic solid tumor	1.88	1.04	3.41	**0.04**
Other selected comorbidities:				
Non-pain-related				
Opioid dependence	4.54	3.12	6.63	**<0.001**
Non-malignant pancreatic disease	2.13	1.06	4.25	**0.03**
Skin infections/abscesses	0.46	0.28	0.76	**0.002**
Sleep apnea	1.34	1.03	1.75	**0.03**
Bipolar disorder/schizophrenia§	1.95	1.43	2.67	**<0.001**
Cardiovascular disease	1.2	0.77	1.88	0.41
Pain-related				
Headache/migraine	1.25	0.9	1.74	0.18
Traumatic injury	1.48	1.18	1.87	**<0.001**

Table 2 *Continued*

Covariate	All Patients (Cases, $n = 817$; Controls, $n = 8,170$) Odds Ratio	95% CI		*P* Value
PRESCRIPTION OPIOID USE				
By active ingredient				
Hydrocodone	0.87	0.7	1.08	0.21
Oxycodone	1.32	1.03	1.69	**0.03**
Morphine	1.28	0.77	2.14	0.35
Tramadol	0.69	0.52	0.92	**0.01**
Methadone	2.42	1.61	3.66	**<0.001**
Fentanyl	0.63	0.11	3.76	0.61
Hydromorphone	1.85	0.96	3.58	0.07
By formulation				
Not ER/LA (reference)				
Extended-release/long-acting (ER/LA)	2.48	1.27	4.88	**0.01**
Proportion of opioids = ER/LA	0.65	0.28	1.54	0.33
By route				
Oral (reference)				
Parenteral or transdermal	3.08	0.58	16.48	0.19
Maximum prescribed morphine equivalent dose (MED, mg/day)				
1-<20 (reference)				
20-<50	1.59	1.19	2.12	**0.002**
50–<100	2.51	1.73	3.63	**<0.001**
≥100	4.96	3.24	7.61	**<0.001**
NON-OPIOID PRESCRIPTION DRUG USE				
Benzodiazepines	1.49	1.22	1.83	**<0.001**
Antidepressants	1.98	1.63	2.41	**<0.001**
ALL-CAUSE HEALTH CARE UTILIZATION				
≥1 day of hospitalization	2.2	1.76	2.76	**<0.001**
≥1 ED Visit	2.88	2.34	3.54	**<0.001**
≥1 Prescription fill	0.48	0.28	0.85	**0.01**
Model performance				
C-statistic = 0.89				
Hosmer-Lemeshow goodness-of-fit statistic = 7.49 ($P > 0.05$)				

* The multivariable logistic regression model presented includes all variables retained at a *P* value of <0.10 and all variables considered to be confounders. This model was used for review and selection of items to be included in RIOSORD.

† Age categories 55–64 and 65+ were collapsed into one category, 55+, for multivariable modeling.

‡ Marital status categories *separated* and *divorced* were collapsed into one category, *separated/divorced*, for multivariable modeling.

§ The comorbidities *bipolar disorder* and *schizophrenia* were combined into one variable, *bipolar disorder/schizophrenia*, for multivariable modeling.

Abbreviations: CCI = Charlson Comorbidity Index; ED = emergency department; ER = extended release; LA = long-acting; MED = morphine equivalent dose; NDC = National Drug Code.

event. After accounting for MED, ER/LA opioids had the highest odds (OR 2.48, 95% CI 1.27, 4.88), followed by methadone (OR 2.42, 95% CI 1.61, 3.66) or oxycodone (OR 1.32, 95% CI 1.03, 1.69) prescription, and concomitant antidepressant (OR 1.98, 95% CI 1.63, 2.41) or benzodiazepine prescription (OR 1.49, 95% CI 1.22, 1.83). Additionally, prescription opioid users who visited an emergency department (ED) (OR 2.88, 95% CI 2.34, 3.54) or were hospitalized for one or more days in the 6-month baseline period (OR 2.2, 95% CI 1.76, 2.76) had higher odds of OSORD (Table 2). Four variables included in the model were associated with lower odds of experiencing an overdose event: serious autoimmune rheumatologic disease, skin infections/abscesses, tramadol prescription, and having filled at least one prescription at VHA during the baseline period.

Table 3 Risk index for overdose or serious opioid-induced respiratory depression (RIOSORD)*

Question	Points for Yes Response
In the past 6 months, has the patient had a healthcare visit (outpatient, inpatient or ED) involving any of the following health conditions?†	
Opioid dependence?‡	15
Chronic hepatitis or cirrhosis?	9
Bipolar disorder or schizophrenia?	7
Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?	5
Chronic kidney disease with clinically significant renal impairment?	5
An active traumatic injury, excluding burns (e.g., fracture, dislocation, contusion, laceration, wound)?	4
Sleep apnea?	3
Does the patient consume:	
An extended-release or long-acting (ER/LA) formulation of any prescription opioid?§ (*e.g., OxyContin, Oramorph-SR, methadone, fentanyl patch*)	9
Methadone? (*Methadone is a long-acting opioid so also check "**ER/LA formulation**"* [*9 points*])	9
Oxycodone? (*If it has an ER/LA formulation* [*e.g., OxyContin*] *also check "**ER/LA formulation**"* [*9 points*])	3
A prescription antidepressant? (*e.g., fluoxetine, citalopram, venlafaxine, amitriptyline*)	7
A prescription benzodiazepine? (*e.g., diazepam, alprazolam*)	4
Is the patient's current maximum prescribed opioid dose#:	
≥100 mg morphine equivalents per day?	16
50–<100 mg morphine equivalents per day?	9
20–<50 mg morphine equivalents per day?	5
In the past 6 months, has the patient:	
Had one or more emergency department (ED) visits?	11
Been hospitalized for one or more days?	8
Total point score (maximum 115)	

* This risk index is intended for completion by a health care professional.
† The condition does not have to be the *primary* reason for the visit but should be entered in the chart or EHR as *one* of the reasons or diagnoses for the visit.
‡ *The International Classification of Disease (9th and 10th Revisions)* codes the diagnosis of substance "addiction" as substance "dependence."
§ A patient consuming one or more opioids with an ER/LA formulation receives 9 additional points regardless of the number of different ER/LA products consumed.
# Include *all* prescription opioids consumed on a daily basis.

The model had good discrimination and calibration, with a C-statistic of 0.89 and Hosmer–Lemeshow goodness-of-fit statistic of 7.49 ($P > 0.05$) (Table 2).

Screening Risk Index

Table 3 shows the statistically significant predictors in the final model that were retained as items in the risk index, and their corresponding, assigned point values. Table 4 presents risk classes by deciles of predicted probability and the corresponding observed incidence of OSORD and risk scores. Based on risk factors present/absent during the 6 months before the index event, the average predicted probability of an event ranged from 3% in the lowest risk class to 94% in the highest, and the observed occurrence of an event increased commensurately.

The risk class model's C-statistic was 0.88 and Hosmer–Lemeshow goodness-of-fit statistic 10.8 ($P > 0.05$), indicating very good calibration and discrimination between patients with and without an event (Table 4).

Discussion

A novel screening tool was developed to estimate the risk of overdose or life-threatening respiratory depression in medical users of prescription opioids. The risk index for overdose or serious opioid-induced respiratory depression (RIOSORD) performed well in the VHA study sample in identifying patients at increased risk of such events. Higher risk scores correlated closely with increased observed occurrence of events. RIOSORD is the first

Table 4 Risk classes and predicted probabilities

Risk Class	Risk Index Score (Points)	All Patients ($n = 8,987$), n (%)	Overdose or Serious Opioid-Induced Respiratory Depression (All patients, $n = 8,987$)	
			Average Predicted Probability (95% CI)	Observed Incidence
1	0–24	7,133 (79.4)	0.03 (0.03, 0.03)	0.03
2	25–32	780 (8.7)	0.14 (0.14, 0.15)	0.14
3	33–37	306 (4.5)	0.24 (0.24, 0.24)	0.23
4	38–42	238 (2.7)	0.34 (0.34, 0.35)	0.37
5	43–46	133 (1.5)	0.46 (0.45, 0.46)	0.51
6	47–49	77 (0.9)	0.55 (0.54, 0.55)	0.55
7	50–54	101 (1.1)	0.64 (0.64, 0.65)	0.60
8	55–59	87 (1.0)	0.76 (0.75, 0.76)	0.79
9	60–66	73 (0.8)	0.85 (0.84, 0.85)	0.75
10	$\geq$67	59 (0.7)	0.94 (0.93, 0.95)	0.86
Model performance				
C-statistic = 0.88				
Hosmer–Lemeshow goodness-of-fit statistic = 10.8 ($P > 0.05$)				

instrument intended to provide healthcare professionals with clinical decision support for assessing the most serious and important adverse effect that can occur in patients being managed for pain using opioid therapy. It provides current, quantitative, evidence-based information about a patient's level of risk of serious prescription opioid-induced respiratory depression or overdose.

Risk Factors

The 15 items in RIOSORD include several factors well-documented in the literature as predictors of fatal opioid overdose. They comprise features of the prescription opioid [4,47–52]; concomitant prescribed benzodiazepines or antidepressants [1,53–56]; renal, liver, and pulmonary comorbidities and active traumatic injury; and mental health disorders including opioid dependence [9,36,57,58]. In addition, increased health care utilization in the form of a recent ED visit or hospitalization was among the most significant predictors of experiencing OSORD [59].

The total MED of the patient's daily opioid regimen was one of the variables most strongly associated with an event, in a monotonic dose-response fashion beginning, alarmingly, with an MED as low as 20 mg/day [14–17]. MED is one of the most consistently reported risk factors for fatal overdose. Accurate, reliable calculation of the patient's total daily MED entails the use of standardized morphine equivalent conversion factors. Numerous published equianalgesic tables are available, but the opioid conversion factors vary widely [40,60–64]. Therefore, to maximize RIOSORD's clinical utility and high predictive performance, inclusion of MED in the risk index requires use of a standardized automatic electronic calculator, as currently available in a mobile, tablet, or Web-based platform, to facilitate simple, rapid, accurate, and reliable calculation.

Intended Use and Interpretation of Results

Pain is the most common reason patients seek medical attention [65]. Approximately 80% of pain episodes treated with opioids in the United States are short-term [60,63]. However, an estimated 100 million to 116 million U.S. adults have chronic pain [65,66]. The prescription of opioids to manage chronic noncancer pain increased dramatically since 2000 to approximately 9 million individuals annually [5–7,9,67]. Managing acute, episodic, or chronic pain with opioids is particularly challenging due to the multidimensionality of pain and the multitude of influences affecting opioid efficacy and safety. RIOSORD, which is based on a multivariable regression model, integrates independent risk factors and adjusts for confounding influences. As a result, RIOSORD can provide valuable decision support to health care professionals to manage pain more safely and effectively, particularly in complex patients who are biologically vulnerable to serious opioid-related CNS or respiratory depression. RIOSORD supports but does not replace the health care provider's judgment in clinical decision-making.

RIOSORD is intended as a screening tool to be used by a health care professional before prescribing opioids, to assess a patient's baseline risk of opioid-induced respiratory depression or overdose. It also can be employed periodically during ongoing opioid treatment to re-evaluate risk based on changes in a patient's clinical condition or medication regimen. Explaining the RIOSORD score to a patient creates an opportunity to discuss the benefits and risks associated with the use of opioids. It also facilitates patient education regarding the word

overdose and the importance of adjusting modifiable risk factors (e.g., adhering to prescribed treatment for comorbidities such as sleep apnea, or minimizing use of neurodepressive psychoactive substances and medications). For example, the provider may begin a discussion with, "Patients with risk scores similar to yours" (e.g., 50 points) "were predicted to have an *x*% chance" (e.g., 76%) "of experiencing a life-threatening opioid emergency such as an overdose with slow or very shallow breathing and unresponsiveness. This can occur under certain conditions despite taking your opioid medication exactly as prescribed. You can reduce your risk by…" (e.g., "using your CPAP device for sleep apnea, following opioid dose instructions, and not drinking alcohol").

Patients identified as having increased risk are the most likely to benefit from preventive and potentially lifesaving interventions. Options include patient and caregiver education, increased attention when selecting an opioid or increasing dose, consulting pain management experts, possible pharmacogenetic testing, and heightened vigilance for serious opioid-related adverse effects or the emergence of known risk factors. Naloxone, a highly effective opioid antagonist, is recommended for patients at increased risk for opioid overdose, including those on chronic opioid therapy [68–75]. In 2014, the U.S. Food and Drug Administration approved the first naloxone product for use outside medically supervised settings by family members or caregivers as a rescue medication in the event of a known or suspected overdose as manifested by respiratory and/or CNS depression [73].

Strengths and Limitations

RIOSORD was developed using extensive administrative health care data in the U.S. VHA population. Limitations common in observational studies using administrative data include limited or no information about : 1) potentially relevant patient behavior, social characteristics, and family history (such as familial substance use disorders); 2) adherence to dosing instructions and actual use of prescribed medication; 3) substances, medications, and treatment obtained outside VHA; and 4) therapeutic indications for prescribed medications. As such, the predictive ability of RIOSORD, like other tools derived from observational data, is subject to residual confounding by currently unknown or excluded contributory factors. Administrative data can be limited by incompleteness, coding errors, and misclassification, particularly for comorbidities including mental health and substance use disorders. A gold standard administrative (claims) code-based definition for the outcome of serious opioid-related respiratory/CNS depression or overdose does not exist currently, and the diagnostic accuracy of our coding algorithm has not been validated yet against linked patient medical records. In addition, the VHA population includes relatively few women and younger patients; the study sample might not accurately reflect the broader U.S. population of medical users of prescription opioids.

The risk factors selected as risk index items were chosen partly because accurate, complete responses should be readily identified by a health care professional in a patient's medical record in the context of a typical brief provider-patient visit, or from medical and pharmacy administrative (claims) data. The completion of RIOSORD by a health care professional is intended to reduce response gaps or errors that may decrease its predictive accuracy and performance. This index does not include all known risk factors, such as family history of substance use disorders. In addition, some variables associated with an event in the VHA sample were excluded, such as age, race/ethnicity, and geographic location, because they differed from published findings from studies of fatal opioid-related overdose in non-VHA populations. The limited number of cases in the study sample and unknown external generalizability of findings precluded stratifying the analysis by the duration of opioid therapy or the acuity and type of therapeutic indication (e.g., cancer-relatedness).

Implications for Future Research

While RIOSORD performed well in the VHA patient population, it should be assessed and further validated in a separate population that is more representative of U.S. medical users of prescription opioids. It also should be evaluated in clinically defined subgroups of prescription opioid users, based on characteristics of the pain condition (e.g., chronic vs acute and cancer vs noncancer). RIOSORD will also benefit from prospective reliability and validity testing across a broad spectrum of patients. RIOSORD can be formatted for electronic administration via Web or mobile platform to improve its real-world deployment by enabling automated MED calculation, risk scoring, and calculation of risk class.

Conclusion

RIOSORD is the first-known published risk index to provide current, evidence-based information to health care providers regarding the risk of overdose or life-threatening CNS/respiratory depression in medical users of prescription opioids. Its performance should be further assessed, and refined as necessary, in a larger, more generalizable population, as well as prospectively. Once validated, this index will assist health care professionals in identifying patients who are at increased risk of serious opioid-induced respiratory depression or overdose and help with decision-making regarding interventions to mitigate their risk.

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