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

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

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

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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].

Opoids 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) | Controls (n = 8,170) | P Value |
|------------------------------------------|-----------------|----------------------|---------|
| **DEMOGRAPHICS**                         |                 |                      |         |
| Age (years), median (IQR)                |                 |                      | <0.001  |
| Age Group (years)                        |                 |                      |         |
| 18–34                                    | 62 (10)         | 62 (16)              | <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                                     |                 |                      | <0.001  |
| Non-hispanic White                       | 555 (67.9)      | 4,546 (55.6)         |         |
| 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                           |                 |                      | <0.001  |
| Never married                            | 102 (12.5)      | 1,227 (15)           |         |
| 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/m²)             |                 |                      | <0.001  |
| Underweight (<18.5)                      | 29 (3.6)        | 72 (0.9)             |         |
| 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                       |                 |                      | <0.001  |
| Northeast                                | 75 (9.2)        | 824 (10.1)           |         |
| 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**             |                 |                      | <0.001  |
| CCI score, mean (SD)                     | 3.9 (3.3)       | 1.7 (2)              |         |
| **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                             | 485 (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  |
| Characteristics                                      | Cases (n = 817) | Controls (n = 8,170) | 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) vs. 764 (9.4) <0.001
- Opioid dependence: 105 (12.9) vs. 97 (1.2) <0.001
- Endocarditis: 1 (0.1) vs. 9 (0.1) 0.92
- Viral hepatitis: 106 (13) vs. 249 (3) <0.001
- Alcoholic hepatitis: 3 (0.4) vs. 5 (0.1) 0.005
- Non-malignant pancreatic disease: 24 (2.9) vs. 49 (0.6) <0.001
- Sexually transmitted disease: 12 (1.5) vs. 69 (0.8) 0.07
- Herpes simplex: 7 (0.9) vs. 45 (0.6) 0.27
- Skin infections/abscesses: 85 (10.4) vs. 286 (3.5) <0.001
- Sleep apnea: 147 (18) vs. 652 (8) <0.001
- Tobacco use disorder: 301 (36.8) vs. 1,266 (15.5) <0.001
- PTSD: 221 (27.1) vs. 1,119 (13.7) <0.001
- Bipolar disorder: 86 (10.5) vs. 239 (2.9) <0.001
- ADHD: 7 (0.9) vs. 58 (0.7) 0.64
- Schizophrenia: 36 (4.4) vs. 114 (1.4) <0.001
- Anxiety disorder: 180 (22) vs. 681 (8.3) <0.001
- OCD: 5 (0.6) vs. 19 (0.2) 0.045
- Cardiovascular disease: 172 (21.1) vs. 764 (9.4) <0.001
- Obesity: 150 (18.4) vs. 1,072 (13.1) <0.001

**Pain-related**

- Low back disorders: 380 (46.5) vs. 2,099 (25.7) <0.001
- Other back/neck disorders: 214 (26.2) vs. 1,048 (12.8) <0.001
- Neuropathic disorder: 170 (20.8) vs. 717 (8.8) <0.001
- Fibromyalgia: 34 (4.2) vs. 157 (1.9) <0.001
- Chronic headache: 88 (10.8) vs. 427 (5.2) <0.001
- Burns: 4 (0.5) vs. 16 (0.2) 0.089
- Active traumatic injury: 212 (26) vs. 869 (10.6) <0.001
- Motor vehicle accident: 7 (0.9) vs. 14 (0.2) <0.001

**PRESCRIPTION DRUG INFORMATION**

**Opioid use**

- 693 (84.8) vs. 4,936 (60.4) <0.001

**BY ACTIVE INGREDIENT**

- Hydrocodone: 314 (38.4) vs. 2,633 (32.2) <0.001
- Oxycodone: 305 (37.3) vs. 876 (10.7) <0.001
- Morphine: 251 (30.7) vs. 334 (4.1) <0.001
- Tramadol: 114 (14) vs. 1,428 (17.5) 0.01
- Methadone: 107 (13.1) vs. 139 (1.7) <0.001
- Codeine: 63 (7.7) vs. 561 (6.9) 0.365
- Fentanyl: 49 (6) vs. 44 (0.5) <0.001
- Hydromorphone: 38 (4.7) vs. 28 (0.3) <0.001
- Oxymorphone: 1 (0.1) vs. 1 (0) 0.04
- Buprenorphine: 0 (0) vs. 2 (0) 0.66
- Other*: 2 (0.2) vs. 4 (0.1) 0.04

**BY FORMULATION**

- Extended-Release/Long-Acting (ER/LA): 369 (45.2) vs. 499 (6.1) <0.001
- Not ER/LA: 633 (77.5) vs. 4,807 (58.5) <0.001
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).

**Table 1 Continued**

| Characteristics | Cases (n = 817) | Controls (n = 8,170) | 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 (5.5) | <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) | <0.001 |
| 50–<100 | 163 (20) | 718 (8.8) | <0.001 |
| ≥100 | 268 (32.8) | 273 (3.3) | <0.001 |
| **Selected Nonopioid Drugs** | | | |
| 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 (98.8) | <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.

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 \( P < 0.10 \). 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 \( \beta \) 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 (in [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 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

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1In 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” (304.6x, 304.7x) or “nonopioid substance dependence and nondependent substance abuse.”

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

| Covariate                              | All Patients (Cases, n = 817; Controls, n = 8,170) | 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  |
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 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                                                          |
| Oxycodeone                             | 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.
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...
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

| Risk Class | Risk Index Score (Points) | All Patients \(n = 8,987\), \(n (%)\) | 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/≥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 \((P > 0.05)\)

Table 4  Risk classes and predicted probabilities

| Risk Class | Risk Index Score (Points) | All Patients \(n = 8,987\), \(n (%)\) | 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/≥67    |                          | 59 (0.7)                     | 0.94 (0.93, 0.95)                    | 0.86              |
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 neurodepressant 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 life-saving 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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