Validation of a Screening Risk Index for Overdose or Serious Prescription Opioid-Induced Respiratory Depression

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BACKGROUND

Prescription opioid use and deaths from overdose or opioid-induced respiratory depression have increased dramatically in the United States since 1999.[1] There were more than 4 times as many opioid-related fatalities in 2010 as there were in 1999[2] and annual opioid-related deaths have remained at these levels through 2013.[3-5]

Several instruments have been developed to assess the risk of opioid abuse; however, no instruments currently exist that provide useful, real-time, evidence-based information to a healthcare professional regarding the risk of overdose or serious opioid-induced respiratory depression (OSORD) in medical users of prescription opioids. This research builds upon previous work involving the development of a risk index using US Veterans Health Administration (VHA) administrative data to predict a patient's likelihood of experiencing an OSORD event.[6,7]

OBJECTIVE

To validate and extend the Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) in a larger population more representative of US medical users of prescription opioids.

METHODS

Study Design

Retrospective, nested, case-control study of 18,365,497 US patients with a pharmacy claim for an opioid between January 1, 2009, and December 31, 2013. The study was exempted from IRB review.

Data Source

IMS PharMetrics Plus™ is the largest US database of integrated commercial health plan claims information. It comprises medical and pharmacy claims and enrollment information for more than 150 million unique enrollees since 2006, including 40 million active lives in 2012. It represents patients in the majority of 3-digit zip codes who are covered through 85% of the Fortune 100 companies, as well as 90% of US hospitals and 80% of US physicians.

Study Sample

Study cases were patients who experienced an opioid overdose or life-threatening respiratory or CNS depression event as defined by an algorithm comprising International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) and Current Procedure Terminology (CPT-4) codes.[6]

For each case, 4 control patients were randomly selected and assigned from those who did not experience OSORD. The case index date was assigned to each of the 4 control patients.

All eligible cases and controls had non-missing age and sex values, continuous medical/pharmacy benefits during the 6-month baseline period before the index date, and were dispensed at least 1 opioid prescription (excluding cough and cold opioids) during the 6-month baseline period.

Case Definition (Outcome Variable)

An OSORD event was defined as (1) a listed, serious respiratory or CNS adverse effect ICD code (780.0, 780.01-780.03, 780.09, 581.81, 581.82, 786.03, 799.0, 799.01, 799.02, 799.1) in addition to a listed opioid poisoning code (965.0, 965.00-965.02, 965.09) or external cause code (E850.0-E850.2, E935.0-E935.2) occurring within ± 1 day of the adverse effect, or (2) use of mechanical ventilation or critical care in addition to a listed opioid poisoning or external cause code occurring within ± 1 day of the critical respiratory support ICD or CPT code. The first identified event during the study period (index event) served as the index date for cases. Cases that involved heroin alone (965.01 or E935.0) were excluded.

Covariates

Sex, age, US Census region, Charlson Comorbidity Index (CCI) score, selected pain- and non–pain-related comorbidities, prescription opioid (active ingredient, formulation, route of administration), maximum prescribed daily morphine equivalent dose (MED, mg/day), selected non-opioid prescription drugs known to potentiate opioid effects, and healthcare utilization (all measured during the baseline period). Covariates in the previously developed VHA RIOSORD were modified as necessary to accommodate differences in the available IMS data.

Statistical Analysis

- Used multivariable logistic regression modeling to identify the RIOSORD covariates significantly associated with an index event in the IMS population
- Assigned point values to the most statistically significant RIOSORD predictors in the IMS data set based on their Ƀ-coefficients in the model[8]
- Calculated RIOSORD scores for IMS patients[9]
- Used multivariable logistic regression modeling of the risk index scores and the OSORD outcome to produce predicted probabilities of OSORD in the IMS data set. Risk classes were defined by the predicted probability distribution[9]
- Compared the predicted probability of OSORD, by risk classes, with the observed incidence in the IMS data set

RESULTS

Sample Characteristics

Among the ~18 million IMS patients with an opioid claim during the baseline period, we identified 7,234 case patients who experienced OSORD and 28,932 controls who did not (total N=36,166). Compared with controls, cases were slightly older and more likely to be female. 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, both related and not related to pain. Several opioid-related factors were significantly associated with OSORD, including certain active ingredients, Extended-Release and Long-Acting (ER/LA) formulations, an oral route of administration, and higher maximum prescribed daily MED. Cases were prescribed other potentially interacting medications more frequently and had greater baseline health care utilization (ED visits and hospital admissions) compared to controls.

Multivariable Modeling: OSORD-Associated Variables

The covariates most strongly associated with experiencing OSORD in the IMS population included eight coexisting health conditions (neuropsychiatric disorders and impaired drug metabolism or excretion) and eight prescription drug factors (specific opioid drug characteristics and concomitant benzodiazapines or antidepressants) (**Table 1**). The model had a C-statistic of 0.90, indicating excellent discrimination between cases and controls.

Risk Index Configuration

Sixteen variables were retained as items in RIOSORD (**Figure 1**) from among all model covariates statistically significantly associated with overdose or serious opioid-induced respiratory depression in the IMS population. In selecting the RIOSORD items, an effort was made to balance (1) the scientific and statistical robustness of each included factor's association with OSORD against (2) the practical need for a relatively brief instrument with optimum simplicity and accuracy when completed by a healthcare professional in the context of a typical busy community care setting.

Table 1. Multivariable Logistic Regression Model: RIOSORD Covariates

	Overall (N=36,166) (Cases = 7,234; Controls = 28,932)				Overall (N=36,166) (Cases = 7,234; Controls = 28,932)			
Covariate (During 6-month Baseline Period)	**Odds Ratio**	**95% Confidence Limits**		**Covariate (During 6-month Baseline Period)**	**Odds Ratio**	**95% Confidence Limits**	
Demographics				**Comorbidities**			
Sex Male	1.03	0.95	1.11	Charlson Comorbidity Index (CCI)			
Age Category 35-54 vs 18-34	1.05	0.95	1.15	Congestive Heart Failure	2.06	1.74	2.44
Age Category 55+ vs 18-34	1.16	1.04	1.29	Peripheral Vascular Disease	0.91	0.72	1.14
Patient region Midwest vs Northeast	1.20	1.08	1.33	Cerebrovascular Disease	2.52	2.18	2.92
Patient region South vs Northeast	1.09	0.98	1.20	Chronic Pulmonary Disease	1.72	1.56	1.89
Patient region West vs Northeast	1.39	1.23	1.58	Serious Autoimmune Rheumatologic Disease	1.47	1.23	1.77
Prescription Drug Use				Chronic Hepatitis/Cirrhosis	1.39	0.96	2.00
Opioid Drugs				Warfarin Prescription	0.79	0.66	0.95
By Active Ingredient				Chronic Renal Disease	2.17	1.83	2.57
Hydrocodone	1.30	1.20	1.41	Any Malignancy, including Leukemia and Lymphoma	1.09	0.93	1.29
Oxycodone	1.50	1.38	1.64	Skin Ulcers	1.50	1.18	1.90
Tramadol	1.19	1.08	1.31	Metastatic Solid Tumor	0.95	0.73	1.23
Fentanyl	3.72	3.10	4.46	Other Selected Pain and Non-Pain Comorbidities			
Morphine	2.93	2.49	3.43	Substance Use Disorder	12.74	11.46	14.16
Hydromorphone	2.04	1.69	2.45	Non-malignant Pancreatic Disease	2.07	1.56	2.75
Methadone	2.80	2.22	3.51	Skin Infections/Abscesses	1.14	1.00	1.30
By Formulation				Sleep Apnea	1.33	1.16	1.52
Not ER/LA(reference)				Bipolar Disorder/Schizophrenia	2.85	2.44	3.32
ER/LA	1.73	1.51	1.99	Cardiovascular Disease	0.98	0.81	1.20
By Route Oral (vs Non-Oral Reference)	1.90	1.54	2.34	Chronic Headache	1.73	1.57	1.90
Max Prescribed Daily MED ≥100 mg/day	2.04	1.87	2.24	Active Traumatic Injury	1.53	1.41	1.65
Non-Opioid Drugs of Interest, n (%)				**All-cause Health Care Utilization**			
Benzodiazepines	2.35	2.18	2.54	≥1 Day of Hospitalization	1.12	1.02	1.23
Antidepressants	2.19	2.03	2.36	≥1 ED Visit	1.52	1.41	1.65

Figure 1: Risk Assessment for Overdose or Serious Opioid-Induced Respiratory Depression

Step 1: Determine Score for Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) → **Step 2: Identify Risk Class** for OSORD

Question[1]	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?[2]	
Substance use disorder (abuse or dependence)? **includes opioids, antidepressants, sedatives/anxiolytics, alcohol, amphetamines, cannabis, cocaine, hallucinogens*	25
Bipolar disorder or schizophrenia?	10
Stroke (cerebrovascular accident, CVA) or other cerebrovascular disease?	9
Chronic kidney disease with clinically significant renal impairment?	8
Heart failure?	7
Non-malignant pancreatic disease (e.g., acute or chronic pancreatitis)?	7
Chronic pulmonary disease (e.g., emphysema, chronic bronchitis, asthma, pneumoconiosis, asbestosis)?	5
Chronic headache (e.g., migraine)?	5
Does the patient consume:	
Fentanyl? (e.g., transdermal or transmucosal immediate-release products)	13
Morphine?	11
Methadone?	10
Hydromorphone?	7
An extended-release or long-acting (ER/LA) formulation of any prescription opioid, including the above?[3]	5
A prescription benzodiazepine? (e.g., diazepam, alprazolam)	9
A prescription antidepressant? (e.g., fluoxetine, citalopram, venlafaxine, amitriptyline)	8
Is the patient's current maximum prescribed opioid dose ≥ 100 mg morphine equivalents per day? (Include all prescription opioids consumed on a daily basis)	7
Total point score (maximum 146)	

Risk Class	RIOSORD Score (Points)	Average Probability of OSORD
1	0-4	2%
2	5-7	5%
3	8-9	7%
4	10-17	15%
5	18-25	30%
6	26-41	55%
7	≥42	83%

OSORD, overdose or serious opioid-induced respiratory depression
[1]This questionnaire is intended for completion and interpretation by a healthcare professional. It is not a replacement for clinical judgment and is intended to guide and inform clinical decision-making for patients who are prescribed opioids.
[2]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.
[3]A patient consuming 1 or more opioids with an ER/LA formulation receives 5 additional points for 'ER/LA formulation of any prescription opioid' regardless of the number of different ER/LA products consumed.

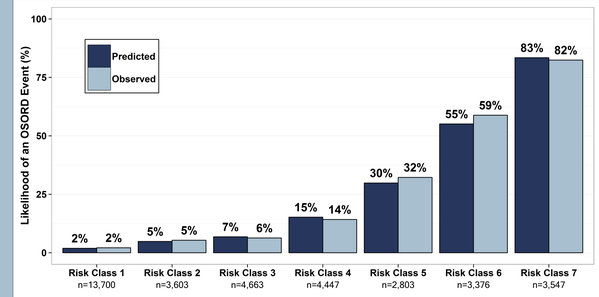
Risk Index Configuration (continued)

A point value was assigned to each statistically significant factor retained in RIOSORD by multiplying its β-coefficient from the logistic regression model in the IMS population by 10 and rounding to the nearest integer. The RIOSORD score for each patient was the sum of points for all risk index items.

Multivariable Modeling: Predicted Probability of OSORD

Predicted probabilities of experiencing overdose or serious respiratory depression were produced from the RIOSORD scores in the IMS study sample using logistic regression (C-statistic 0.91). The predictive validity of RIOSORD was assessed by comparing the distribution of predicted probabilities, by percentiles, with the observed incidence of the outcome in the study sample. Among 7 risk classes, the average predicted probability of an event ranged from 2% in the lowest risk class to 83% in the highest, and the observed occurrence of an event increased commensurately (Figure 2).

Figure 2. Predicted Probability (Risk Classes, by Percentiles) vs Observed Incidence of Overdose or Serious Opioid-induced Respiratory Depression



CONCLUSIONS

The Risk Index for Overdose or Serious Opioid-induced Respiratory Depression (RIOSORD) is the first known screening instrument developed to provide real-time, evidence-based information to the healthcare professional regarding the risk of overdose or serious respiratory depression in medical users of prescription opioids. The predictive performance of the RIOSORD in a large commercial health plan database was excellent and similar to its performance in the VHA database in which it was first developed.[7] RIOSORD performed well in identifying in this independent dataset the medical users of prescription opioids who were at increased risk of an event. The strongest predictors were consistent between the VHA[6] and commercial database and included both coexisting clinical conditions and characteristics of prescribed medications. Further prospective evaluation and refinement of RIOSORD in real-world clinical settings, and in clinically defined patient subgroups, should be undertaken.

Patients identified as having elevated risk are most likely to benefit from interventions to mitigate that risk. Such precautions include education of the patient and caregivers, increased caution in opioid selection and dose escalation, consultation with pain management specialists, close monitoring for the emergence of OSORD or known risk factors for it, as well as prescription of naloxone for administration by family members or caregivers as a rescue medication in the event of a suspected opioid emergency such as overdose.

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