

Naloxone Dispensing in Patients at Risk for Opioid Overdose After Total Knee Arthroplasty Within the Veterans Health Administration

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Background: Naloxone prescribing among patients undergoing surgery is not well described. This cohort study was designed to examine patients' risk factors for opioid overdose and their association with naloxone prescribing among veterans undergoing total knee arthroplasty (TKA) after a system-wide Overdose Education and Naloxone Distribution (OEND) initiative.

Methods: A retrospective analysis of Veterans Health Administration (VHA) records was performed and consisted of 38,011 veterans undergoing primary TKA from 2013 to 2016. Patient overdose risk was determined using a validated risk index for overdose or serious opioid-induced respiratory depression (RIOSORD) based on patient diagnoses, health care utilization, and prescription drug use. Naloxone dispensing was examined from the year before surgery until 7 days after discharge. These rates were examined the year prior to

implementation of a national OEND initiative (2013), the year of implementation (2014), and 2 years following implementation (2015-2016).

Results: In 2013, 3.3% of patients presenting for TKA had moderate or high risk for overdose and none were prescribed naloxone. By 2016, after OEND implementation, 2.2% of patients presenting for TKA had moderate or high risk for overdose, but only 10.9% of the moderate-risk and 12.7% of the high-risk patients were prescribed naloxone.

Conclusions: Patients presenting for TKA routinely have risk factors for opioid overdose and significant proportions are at moderate or high risk for overdose. Despite this, most patients at moderate and high risk do not receive perioperative naloxone. Risk mitigation strategies using validated tools such as RIOSORD may help identify surgical patients at greatest risk for opioid overdose who could benefit from OEND.

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Fed Pract. 2022;39(2).
Published online February 10.
doi:10.12788/fp.0227

Opioid overdose is a major public health challenge, with recent reports estimating 41 deaths per day in the United States from prescription opioid overdose.^{1,2} Prescribing naloxone has increasingly been advocated to reduce the risk of opioid overdose for patients identified as high risk. Naloxone distribution has been shown to decrease the incidence of opioid overdoses in the general population.^{3,4} The Centers for Disease Control and Prevention (CDC) *Guideline for Prescribing Opioids for Chronic Pain* recommends considering naloxone prescription for patients with a history of overdose or substance use disorder, opioid dosages ≥ 50 morphine equivalent daily dose (MEDD), and concurrent use of benzodiazepines.⁵

Although the CDC guidelines are intended for primary care clinicians in outpatient settings, naloxone prescribing is also relevant in the postsurgical setting.⁵ Many surgical patients are at risk for opioid overdose and data from the Veterans Health Administration (VHA) has shown that risk of opioid overdose is 11-fold higher in the 30 days following discharge from a surgical

admission, when compared with the subsequent calendar year.^{6,7} This likely occurs due to new prescriptions or escalated doses of opioids following surgery. Overdose risk may be particularly relevant to orthopedic surgery as postoperative opioids are commonly prescribed.⁸ Patients undergoing total knee arthroplasty (TKA) may represent a vulnerable population to overdose as it is one of the most commonly performed surgeries for the treatment of chronic pain, and is frequently performed in older adults with medical comorbidities.^{9,10}

Identifying patients at high risk for opioid overdose is important for targeted naloxone dispensing.⁵ A risk index for overdose or serious opioid-induced respiratory depression (RIOSORD) tool has been developed and validated in veteran and other populations to identify such patients.¹¹ The RIOSORD tool classifies patients by risk level (1-10) and predicts probability of overdose or serious opioid-induced respiratory depression (OSORD). A patient's level of risk is based on a weighted combination of the 15 independent risk factors most highly associated with OSORD, including comorbid conditions,

TABLE 1 RIOSORD Risk Factors and Classes Among TKA Patients^a

Characteristics	2013 (N = 8368)	2014 (N = 9309)	2015 (N = 10,182)	2016 (N = 10,152)
Demographics				
Age, mean (SD)	64.3 (8.6)	64.9 (8.5)	65.0 (8.3)	65.5 (8.4)
Sex, No. (%)				
Female	1125 (7.0)	1323 (7.0)	1421 (6.8)	1573 (7.8)
Male	7243 (93.0)	7986 (93.0)	8761 (93.2)	8579 (92.2)
White race, No. (%)	6125 (78.6)	6719 (78.3)	7277 (77.4)	7128 (76.6)
Comorbidity risk factors, No. (%)				
Schizophrenia	129 (1.5)	148 (1.6)	182 (1.8)	159 (1.6)
Opioid use disorder	256 (3.1)	329 (3.5)	325 (3.2)	303 (3.0)
Bipolar	385 (4.6)	453 (4.9)	486 (4.8)	424 (4.2)
Liver disease	604 (7.2)	708 (7.6)	770 (7.6)	740 (7.3)
Chronic kidney disease	990 (11.8)	1022 (11.0)	1031 (10.1)	993 (9.8)
Sleep apnea	1564 (18.7)	1624 (17.4)	1812 (17.8)	1630 (16.1)
Lung disease	2150 (25.7)	2286 (24.6)	2446 (24.0)	2288 (22.5)
Medications, No. (%)				
≥ 100 MEDD	274 (3.3)	264 (2.8)	244 (2.4)	224 (2.2)
≥ 50 MEDD	669 (8.0)	639 (6.9)	667 (6.6)	543 (5.3)
Total opioids	5277 (63.1)	5487 (58.9)	5704 (56.0)	5127 (50.5)
Long-acting opioids	708 (8.5)	723 (7.9)	715 (7.0)	588 (5.8)
Benzodiazepines	1102 (13.2)	1122 (12.1)	1080 (10.6)	893 (8.8)
RIOSORD class, No. (%)				
Low risk (1-4)	8089 (96.7)	9014 (96.8)	9867 (96.9)	9924 (97.8)
Moderate risk (5-7)	211 (2.5)	212 (2.3)	229 (2.2)	165 (1.6)
High risk (8-10)	68 (0.8)	83 (0.9)	86 (0.8)	63 (0.6)

Abbreviations: MEDD, morphine equivalent daily dose; RIOSORD; risk index for overdose or serious opioid-induced respiratory depression; TKA, total knee arthroplasty.

^aCommonly described independent overdose risk factors from RIOSORD presented.

prescription drug use, and health care utilization.¹² Using the RIOSORD tool, the VHA Opioid Education and Naloxone Distribution (OEND) program is a risk mitigation initiative that aims to decrease opioid-related overdose morbidity and mortality. This is achieved via opioid overdose education for prevention, recognition, and response and includes outpatient naloxone prescription.^{13,14}

Despite the comprehensive OEND program, there exists very little data to guide postsurgical naloxone prescribing. The prevalence of known risk factors for overdose in surgical patients remains unknown, as does the prevalence of perioperative naloxone distribution. Understanding overdose risk factors and naloxone prescribing patterns in surgical patients may identify potential targets for OEND efforts. This study retrospectively estimated RIOSORD scores for TKA patients between 2013 to 2016 and described naloxone distribution based on RIOSORD scores and risk factors.

METHODS

We identified patients who had undergone primary TKA at VHA hospitals using Current Procedural Terminology (CPT), *Inter-*

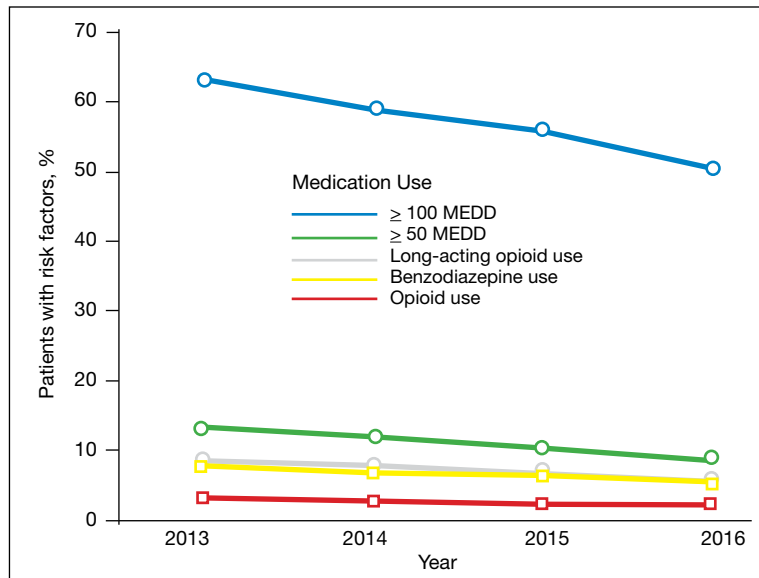
tional Classification of Diseases, Ninth Revision (ICD-9) procedure codes, and data extracted from the VHA Corporate Data Warehouse (CDW) of electronic health records (EHRs). Our study was granted approval with exemption from informed consent by the Durham Veteran Affairs Healthcare System Institutional Review Board.

This retrospective cohort study included all veterans who underwent elective primary TKA from January 1, 2013 through December 31, 2016. We excluded patients who died before discharge.

Outcomes

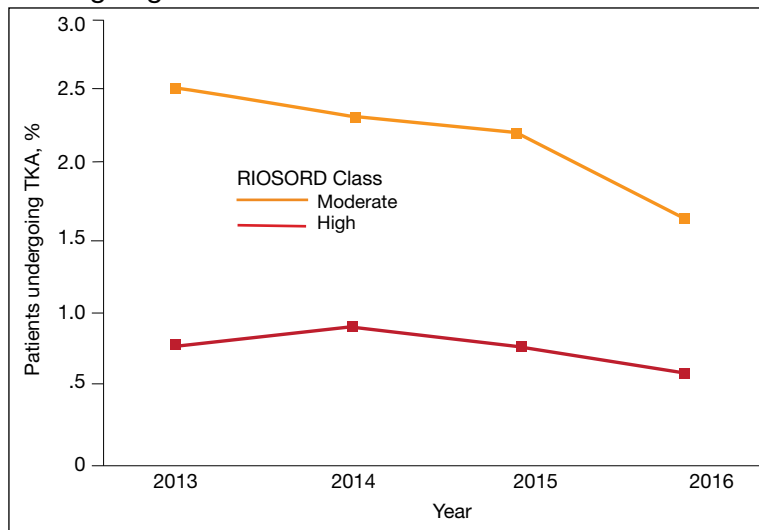
Our primary outcome was being dispensed an outpatient naloxone prescription following TKA. Naloxone dispensing was identified by examining CDW outpatient pharmacy records with a final dispense date from 1 year before surgery through 7 days after discharge following TKA. To exclude naloxone administration that may have been given in a clinic, prescription data included only records with an outpatient prescription copay. Naloxone dispensing in the year before surgery was chosen to estimate likely preoperative possession of naloxone which could be available in

FIGURE 1 Risks Factors Over Time



Abbreviation: MEDD, morphine equivalent daily dose

FIGURE 2 Prevalence of Risk Groups Among Patients Undergoing TKAs



Abbreviations: RIOSORD, risk index for overdose or serious opioid-induced respiratory depression; TKA, total knee arthroplasty.

the postoperative period. Naloxone dispensing until 7 days after discharge was chosen to identify any new dispensing that would be available in the postoperative period. These outcomes were examined over the study time frame on an annual basis.

Patient Factors

Demographic variables included age, sex, and race/ethnicity. Independent risk factors

for overdose from RIOSORD were identified for each patient.¹⁵ These risk factors included comorbidities (opioid use disorder, schizophrenia, bipolar disorder, liver disease, chronic kidney disease, sleep apnea, or lung disease) and prescription drug use (use of opioids, benzodiazepines, long-acting opioids, ≥ 50 MEDD or ≥ 100 MEDD). ICD-9 and ICD-10 diagnosis codes were used to identify comorbidities. Risk classes on day of surgery were identified using a RIOSORD algorithm code. Consistent with the display of RIOSORD risk classes on the VHA Academic Detailing Service OEND risk report, patients were grouped into 3 groups based on their RIOSORD score: classes 1 to 4 (low risk), 5 to 7 (moderate risk), and 8 to 10 (high risk).

Descriptive statistics were used to summarize data on patient demographics, RIOSORD risk factors, overdose events, and naloxone dispensing over time.

RESULTS

The study cohort included 38,011 veterans who underwent primary TKA in the VHA between January 1, 2013 and December 30, 2016. In this cohort, the mean age was 65 years, 93% were male, and 77% were White patients (Table 1). The most common comorbidities were lung disease in 9170 (24.1%) patients, sleep apnea in 6630 (17.4%) patients, chronic kidney disease in 4036 (10.6%) patients, liver disease in 2822 (7.4%) patients, and bipolar disorder in 1748 (4.6%) patients.

In 2013, 63.1% of patients presenting for surgery were actively prescribed opioids. By 2016, this decreased to 50.5%. Benzodiazepine use decreased from 13.2 to 8.8% and long-acting opioid use decreased from 8.5 to 5.8% over the same period. Patients taking ≥ 50 MEDD decreased from 8.0 to 5.3% and patients taking ≥ 100 MEDD decreased from 3.3 to 2.2%. The prevalence of moderate-risk patients decreased from 2.5 to 1.6% and high-risk patients decreased from 0.8 to 0.6% (Figure 1). Cumulatively, the prevalence of presenting with either moderate or high risk of overdose decreased from 3.3 to 2.2% between 2013 to 2016.

Naloxone Dispensing

In 2013, naloxone was not dispensed to any patients at moderate or high risk for

overdose between 365 days prior to surgery until 7 days after discharge (Table 2 and Figure 2). Low-risk group naloxone dispensing increased to 2 (0.0%) in 2014, to 13 (0.1%), in 2015, and to 86 (0.9%) in 2016. Moderate-risk group naloxone dispensing remained at 0 (0.0%) in 2014, but increased to 8 (3.5%) in 2015, and to 18 (10.9%) in 2016. High-risk group naloxone dispensing remained at 0 (0.0%) in 2014, but increased to 5 (5.8%) in 2015, and to 8 (12.7%) in 2016 (Figure 3).

DISCUSSION

Our data demonstrate that patients presenting for TKA between 2013 and 2016 routinely had individual risk factors for overdose related to either prescription drug use or comorbidities. We also show that, although the number of patients at moderate and high risk for opioid overdose is decreasing, 2.2% of TKA patients remain at moderate or high risk for opioid overdose based on a weighted combination of these individual risk factors using RIOSORD. As demand for primary TKA is projected to grow to 3.5 million procedures by 2030, using prevalence from 2016, we estimate that 76,560 patients may present for TKA across the US with moderate or high risk for opioid overdose.⁹ Following discharge, this risk may be even higher as this estimate does not yet account for post-operative opioid use. We demonstrate that through a VHA OEND initiative, naloxone distribution increased and appeared to be targeted to those most at risk using a simple validated tool like RIOSORD.

Presence of an individual risk factor for overdose was present in as many as 63.1% of patients presenting for TKA, as was seen in 2013 with preoperative opioid use. The 3 highest scoring prescription use-related risk factors in RIOSORD are use of opioids ≥ 100 MEDD (16 points), ≥ 50 MEDD (9 points), and long-acting formulations (9 points). All 3 decreased in prevalence over the study period but by 2016 were still seen in 2.2% for ≥ 100 MEDD, 5.3% for ≥ 50 MEDD, and 5.8% for long-acting opioids. This decrease was not surprising given implementation of a VHA-wide opioid safety initiative and the OEND program, but this could also be related to changes in patient selection for surgery in

TABLE 2 Naloxone Dispensing by RIOSORD Class

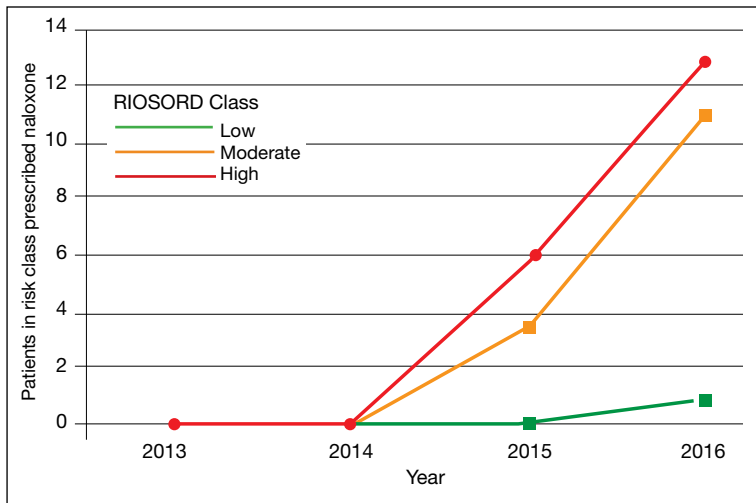
RIOSORD Class	2013	2014	2015	2016
Low risk				
Total, No.	8089	9014	9867	9924
Naloxone dispensed, No. (%)	2 (0.0)	2 (0.0)	13 (0.1)	86 (0.9)
Moderate risk				
Total, No.	211	212	229	165
Naloxone dispensed, No. (%)	0 (0.0)	0 (0.0)	8 (3.5)	18 (10.9)
High risk				
Total, No.	68	83	86	63
Naloxone dispensed, No. (%)	0 (0.0)	0 (0.0)	5 (5.8)	8 (12.7)

Abbreviation: RIOSORD; risk index for overdose or serious opioid-induced respiratory depression.

the context of increased awareness of the opioid epidemic. Despite the trend toward safer opioid prescribing, by 2016 over half of patients (50.5%) who presented for TKA were already taking opioids, with 10.6% (543 of 5127) on doses ≥ 50 MEDD.

We observed a decrease in RIOSORD risk each year, consistent with decreasing prescription-related risk factors over time. This was most obvious in the moderate-risk group. It is unclear why a similar decrease was not as obvious in the high-risk group, but this in part may be due to the already low numbers of patients in the high-risk group. This may also represent the high-risk group being somewhat resistant to the initiatives that shifted moderate-risk patients to the low-risk group. There were proportionately more patients in the moderate- and high-risk groups in the original RIOSORD population than in our surgical population, which may be attributed to the fewer comorbidities seen in our surgical population, as well as the higher opioid-prescribing patterns seen prior to the VA OEND initiative.¹²

Naloxone prescribing was rare prior to the OEND initiative and increased from 2013 to 2016. Increases were most marked in those in moderate- and high-risk groups, although naloxone prescribing also increased among the low-risk group. Integration of RIOSORD stratification into the OEND initiative likely played a role in targeting increased access to naloxone among those at highest risk of overdose. Naloxone dispensing increased for every group, although a significant proportion of moderate- and high-risk patients, 89.1% and

FIGURE 3 Naloxone Dispensed

Abbreviation: RIOSORD, risk index for overdose or serious opioid-induced respiratory depression.

87.3%, respectively, were still not dispensed naloxone by 2016. Moreover, our estimates of perioperative naloxone access were likely an overestimate by including patients dispensed naloxone up to 1 year before surgery until 7 days after surgery. The aim was to include patients who may not have been prescribed naloxone postoperatively because of an existing naloxone prescription at home. Perioperative naloxone access estimates would have been even lower if a narrower window had been used to approximate perioperative access. This identifies an important gap between those who may benefit from naloxone dispensing and those who received naloxone. This in part may be because OEND has not been implemented as routinely in surgical settings as other settings (eg, primary care). OEND efforts may more effectively increase naloxone prescribing among surgical patients if these efforts were targeted at surgical and anesthesia departments. Given that the Comprehensive Addiction and Recovery Act of 2016 requires an assessment of patient risk prior to opioid prescribing and VHA efforts to increase utilization of tools like the Stratification Tool for Opioid Risk Mitigation (STORM), which estimates patient risk when initiating an opioid prescription and includes naloxone as one of many risk mitigation strategies, we anticipate that rates of naloxone prescribing will increase over time.

Limitations

Our study captures a large number of patients across VHA hospitals of varying size nationwide, including a mix of those with and without academic medical center affiliations. This veteran population may not represent the US commercially insured population (CIP). Zedler and colleagues highlighted the differences in prevalence of individual risk factors: notably, the CIP had a substantially higher proportion of females and younger patients.¹¹ VHA had a greater prevalence of common chronic conditions associated with older age. The frequency of opioid dependence was similar among CIP and VHA. However, substance abuse and nonopioid substance dependence diagnoses were 4-fold more frequent among VHA controls as CIP controls. Prescribing of all opioids, except morphine and methadone, was substantially greater in CIP than in VHA.¹¹ Despite a difference in individual risk factors, a CIP-specific RIOSORD has been validated and can be used outside of the VHA to obviate the limitations of the VHA-specific RIOSORD.¹¹

Other limitations include our estimation of naloxone access. We do not know whether naloxone was administered or have a reliable estimate of overdose incidence in this postoperative TKA population. Also, it is important to note that RIOSORD was not developed for surgical patients. The use of RIOSORD in a postoperative population likely underestimates risk of opioid overdose due to the frequent prescriptions of new opioids or escalation of existing MEDD to the postoperative patient. Our study was also retrospective in nature and reliant on accurate coding of patient risk factors. It is possible that comorbidities were not accurately identified by EHR and therefore subject to inconsistency.

CONCLUSIONS

Veterans presenting for TKA routinely have risk factors for opioid overdose. We observed a trend toward decreasing overdose risk which coincided with the Opioid Safety and OEND initiatives within the VHA. We also observed an increase in naloxone prescription for moderate- and high-risk patients undergoing TKA, although most of these patients still did not receive naloxone

as of 2016. More research is needed to refine and validate the RIOSORD score for surgical populations. Expanding initiatives such as OEND to include surgical patients presents an opportunity to improve access to naloxone for postoperative patients that may help reduce opioid overdose in this population.

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Author disclosures

The authors report no actual or potential conflicts of interest or outside sources of funding with regard to this article.

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Ethics and consent

This study was reviewed by the Durham Veteran Affairs Healthcare System Institutional Review Board and granted exemption from informed consent.

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