

Association of Opioid-Related Adverse Drug Events With Clinical and Cost Outcomes Among Surgical Patients in a Large Integrated Health Care Delivery System

Shahid Shafi, MD, MBA, MPH; Ashley W. Collinsworth, ScD, MPH; Laurel A. Copeland, PhD; Gerald O. Ogola, PhD, MPH, MS; Taoran Qiu, MS; Maria Kouznetsova, PhD, MPH; I-Chia Liao, MPH; Natalie Mears, BA; An T. Pham, PharmD, MBA; George J. Wan, PhD, MPH; Andrew L. Masica, MD, MSCI

 Supplemental content

IMPORTANCE Opioids are commonly used for pain control during and after invasive procedures. However, opioid-related adverse drug events (ORADEs) are common and have been associated with worse patient outcomes.

OBJECTIVES To examine the incidence of ORADEs in patients undergoing hospital-based surgical and endoscopic procedures and to evaluate the association of ORADEs with clinical and cost outcomes.

DESIGN, SETTING, AND PARTICIPANTS In this retrospective study of clinical and administrative data, ORADEs were identified using *International Classification of Diseases, Ninth Revision* diagnosis codes for known adverse effects of opioids or by opioid antagonist use. Multivariable regression analysis was used to measure the association of ORADEs with outcomes after adjusting for potential confounding factors. The setting was 21 acute care hospitals in a large integrated health care delivery system. Participants were 135 379 patients (aged ≥ 18 years, admitted from January 1, 2013, to September 30, 2015) who underwent surgical and endoscopic procedures and were given opioids.

EXPOSURE Opioid use, reported as morphine milligram equivalent doses.

MAIN OUTCOMES AND MEASURES Opioid-related adverse drug events and their association with inpatient mortality, discharge to another care facility, length of stay, cost of hospitalization, and 30-day readmission.

RESULTS Among 135 379 adult patients in this study (67.5% female), 14 386 (10.6%) experienced at least one ORADE. Patients with ORADEs were more likely to be older, of white race/ethnicity, and male and have more comorbidities. Patients with ORADEs received a higher total dose of opioids (median morphine milligram equivalent dose, 46.8 vs 30.0 mg; $P < .001$) and for a longer duration (median, 3.0 vs 2.0 days; $P < .001$). In adjusted analyses, ORADEs were associated with increased inpatient mortality (odds ratio [OR], 28.8; 95% CI, 24.0-34.5), greater likelihood of discharge to another care facility (OR, 2.9; 95% CI, 2.7-3.0), prolonged length of stay (OR, 3.1; 95% CI, 2.8-3.4), high cost of hospitalization (OR, 2.7; 95% CI, 2.4-3.0), and higher rate of 30-day readmission (OR, 1.3; 95% CI, 1.2-1.4). ORADEs were associated with a 2.9% increase in absolute mortality, an \$8225 increase in cost for the index hospitalization, and a 1.6-day increase in length of stay for the index hospitalization.

CONCLUSIONS AND RELEVANCE Opioid-related adverse drug events were common among patients undergoing hospital-based invasive procedures and were associated with significantly worse clinical and cost outcomes. Hospital-acquired harm from ORADEs in the surgical patient population is an important opportunity for health systems to improve patient safety and reduce cost.

Author Affiliations: Center for Clinical Effectiveness, Baylor Scott & White Health, Dallas, Texas (Shafi, Collinsworth, Ogola, Qiu, Kouznetsova, Masica); Robbins Institute for Health Policy and Leadership, Baylor University, Waco, Texas (Collinsworth); Center for Applied Health Research, Baylor Scott & White Health, Temple, Texas (Copeland, Liao, Mears); Health Economics & Outcomes Research, Mallinckrodt Pharmaceuticals, Hampton, New Jersey (Pham, Wan); currently with the School of Pharmacy, University of California, San Francisco (Pham).

Corresponding Author: Shahid Shafi, MD, MBA, MPH, Center for Clinical Effectiveness, Baylor Scott & White Health, 8080 N Central Expressway, Ste 500, Dallas, TX 75206 (shahid.shafi@bswhealth.org).

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Opioid addiction and deaths from opioid overdose have reached epidemic levels in the United States.¹ Policy-makers, public health agencies, and health care professionals are developing strategies to minimize the use of prescription opioids in the community.² However, much less attention has been paid to the harm caused by short-term opioid use in hospitals. Hospital-based opioid use is a known source of the growing opioid epidemic, with studies³⁻⁶ demonstrating increased risk of chronic opioid use after surgery in both opioid-naïve patients and patients with a history of drug abuse. More than 7.3 million patients undergo inpatient surgical and endoscopic procedures in the United States each year; opioids, such as morphine sulfate, fentanyl citrate, and meperidine hydrochloride, are commonly used to manage moderate to severe postoperative pain.^{7,8} Although these drugs are extremely effective analgesics, adverse effects are common and can be life threatening. Opioid-related adverse drug events (ORADEs) exhibit a full spectrum of severity, ranging from mild pruritus/dermatitis to acute respiratory failure requiring mechanical ventilation.⁹⁻¹¹ The incidence of ORADEs among surgical patients has ranged from 1.8% to 13.6%, and patients with ORADEs experience higher rates of inpatient mortality and 30-day readmission as well as prolonged length of stay (LOS) and high cost of hospitalization.⁹⁻¹²

Current knowledge of ORADEs, particularly in the hospital setting, is limited to a few studies.¹⁰⁻¹³ The objectives of this study were to examine the incidence of ORADEs in patients undergoing hospital-based surgical and endoscopic procedures and to evaluate the association of ORADEs with clinical and cost outcomes of surgical patients in a large integrated health care delivery system with multiple acute care hospitals. The study hypothesis was that ORADEs occurred commonly among hospitalized patients undergoing surgical and endoscopic procedures and were associated with worse patient outcomes, including increased inpatient mortality, higher likelihood of discharge to another care facility, prolonged LOS, higher cost of hospitalization, and higher rate of 30-day readmission.

Methods

Study Design

This investigation was a retrospective study based on clinical and administrative data from 21 Baylor Scott & White Health (BSWH) acute care hospitals. This study was approved by the BSWH Research Institute institutional review board.

Study Population

The study included inpatients who underwent surgical and endoscopic procedures from January 1, 2013, to September 30, 2015; were 18 years or older; had at least one qualifying colorectal, general abdominal, obstetric/gynecological, orthopedic, spine, cardiac, cardiovascular, or endoscopic procedure (eAppendix in the Supplement); and received one or more opioids (eTable 1 in the Supplement). We identified qualifying procedures by *Current Procedural Terminology* or *International Classification of Diseases, Ninth Revision (ICD-9)* procedure

Key Points

Question What are the incidence and consequences of opioid-related adverse drug events in patients undergoing hospital-based surgical and endoscopic procedures within a large, integrated health care delivery system?

Findings In this study of clinical and administrative data that included 135 379 patients, 14 386 (10.6%) experienced opioid-related adverse drug events. These events were associated with significantly worse patient outcomes, including increased inpatient mortality, greater likelihood of discharge to another care facility, prolonged length of stay, high cost of hospitalization, and higher rate of 30-day readmission.

Meaning Opioid-related adverse drug events occur commonly during episodes for hospital-based surgical and endoscopic procedures and are associated with worse patient outcomes.

codes. We excluded patients who were prisoners, were pregnant (other than those undergoing obstetric procedures associated with childbirth), were discharged to hospice, had a do not resuscitate (DNR) order, were receiving preoperative mechanical ventilation, or had ORADE symptoms that were present on admission. Patients with hospice and DNR status were excluded because these patients likely had a terminal condition not related to ORADEs.

Measures

We collected patient demographics, including age, income (based on zip code), race/ethnicity, sex, and payer type. Clinical variables were the following: body mass index (BMI [calculated as weight in kilograms divided by height in meters squared]); American Society of Anesthesiologists (ASA) score; Charlson Comorbidity Index; presence of specific comorbidities, including anxiety, benign prostatic hypertrophy, depression, hypertension, and sleep apnea; and any history of alcohol or drug abuse. Comorbidities were identified by ICD-9 diagnosis codes that were present on admission. We also examined opioid type, dose, and duration during the entire hospital stay, including opioids used before, during, and after the procedure. Opioid doses were converted to morphine milligram equivalent doses based on a conversion formula from the Centers for Disease Control and Prevention (CDC).¹⁴

The primary outcome was the incidence of ORADEs, defined as occurrence of one or more well-known adverse effects of opioids (eTable 2 in the Supplement). These events included respiratory, gastrointestinal, and central nervous system complications identified by ICD-9 diagnosis codes or documented use of an opioid antagonist. Each type of ORADE was classified as mild, moderate, or severe by our clinical judgment of potential for patient harm. We also examined the association of ORADEs with inpatient mortality, discharge to another care facility, LOS of the index hospitalization, cost of hospitalization, and 30-day readmission to any of the health care delivery system hospitals. We created binary variables to identify patients with prolonged LOS or high cost of hospitalization, defined as those exceeding 1 SD above the mean after excluding extreme outliers that were above the 99th percentile based on methods from prior studies.¹⁰⁻¹²

Readmissions within 30 days were defined according to the Centers for Medicare & Medicaid Services criteria for unplanned admissions¹⁵ and only included readmissions to acute care hospitals within the BSWH health care delivery system. Cost data for index hospitalizations were available from 13 of 21 hospitals. We did not calculate readmission costs.

Statistical Analysis

Patients with any ORADE were compared with patients with no ORADE. First, we conducted a univariate analysis to examine unadjusted differences in patient characteristics and outcomes between patients with and without ORADEs. Differences in categorical variables were compared using χ^2 tests and Fisher exact tests. Differences in continuous variables that did not violate normality assumptions were analyzed with independent *t* tests and those with other distributions using Mann-Whitney tests and Wilcoxon rank sum tests.

Next, we conducted multivariable regression analyses to estimate risk-adjusted association between outcomes and occurrence of ORADEs. For binary outcomes, random-intercept logistic regression models were used to assess differences in odds of inpatient mortality, prolonged LOS, high cost of hospitalization, and 30-day readmission. For continuous outcomes, a random-intercept log-gamma regression model was used to determine risk-adjusted differences in LOS and cost of hospitalization. Age, race/ethnicity, sex, payer type, Charlson Comorbidity Index, and any history of alcohol or drug abuse were included as fixed-effect covariates in all regression models. Hospital facility was included as a random intercept to account for within-hospital clustering. The median BMI was similar between groups; however, BMI was missing for 25 160 patients (18.6%). Including BMI in the model altered the estimates by less than 5%. The ASA score was missing for 68 008 patients (50.2%). Hence, to maximize the number of observations included in the final models, BMI and ASA score were excluded.

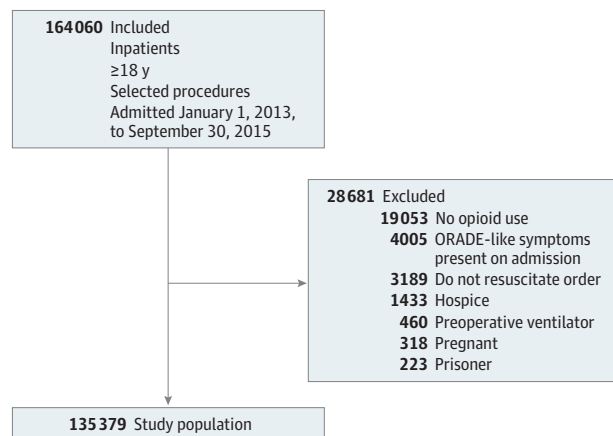
The discriminative ability for the logistic regression models was assessed using C statistics obtained from the area under the receiver operating characteristic curve. C statistics were fairly high at 0.92 (inpatient mortality), 0.82 (discharge to another care facility), and 0.68 (30-day readmission). Goodness of fit for the log-gamma regression models also was somewhat high, with adjusted R^2 values of 0.71 for both LOS and cost of hospitalization.

All statistical analyses were conducted using SAS (Enterprise Guide 7.1; SAS Institute Inc). Two-sided $P < .05$ was considered statistically significant.

Results

A total of 135 379 patients were included in the study (Figure). Of these, 14 386 patients (10.6%) experienced at least one ORADE. Patients with ORADEs were more likely than patients without ORADEs to be older, non-Hispanic, of white race/ethnicity, male, and Medicare beneficiaries (Table 1). Consistent with older age, patients with ORADEs had significantly more comorbidities, with higher ASA scores and Charlson

Figure. Study Population Inclusion and Exclusion Criteria



ORADE indicates opioid-related adverse drug event. For those included, the selected procedures are listed in the eAppendix in the Supplement.

Comorbidity Index values. A history of alcohol or drug abuse was uncommon but was more likely in patients with ORADEs. There were no significant differences between groups in terms of the mean BMI or estimated income.

Patients with ORADEs received opioids for more days (median, 3.0 vs 2.0 days; $P < .001$) and with higher morphine milligram equivalent doses (median morphine milligram equivalent dose, 46.8 vs 30.0 mg; $P < .001$) during hospitalization. However, the median daily doses and types of opioids were similar between the 2 groups (Table 1). The most commonly used opioids were hydrocodone bitartrate, morphine, fentanyl, hydromorphone hydrochloride, and tramadol hydrochloride.

Seventy-three percent of patients with ORADEs experienced only a single ORADE (eTable 3 in the Supplement). The most common events were respiratory, including ventilator use (eTable 2 in the Supplement). Other common events were ileus, nausea and vomiting, confusion/delirium, postoperative bradycardia, and pruritus/dermatitis.

The ORADE rate and average daily opioid use for specific procedures are listed in eTable 4 in the Supplement. Endoscopic procedures had the highest number of patients with ORADEs ($n = 3681$), followed by open abdominal and cardiac procedures. Open thoracic procedures had the highest rate (37.6%) of ORADEs. The median daily morphine milligram equivalent doses were higher for patients with ORADEs for almost all procedures. This difference was statistically significant in 16 of 34 (47.1%) categories. Notably, the median daily morphine milligram equivalent doses were significantly lower for patients with ORADEs undergoing joint replacements, open gynecological procedures, and cesarean sections.

Patients with ORADEs experienced significantly worse risk-adjusted outcomes (Table 2). After adjusting for age, race/ethnicity, sex, payer type, Charlson Comorbidity Index, and any history of alcohol or drug abuse, patients with ORADEs had significantly higher odds of inpatient mortality (OR, 28.8; 95% CI, 24.0-34.5), discharge to another care facility (OR, 2.9; 95% CI, 2.7-3.0), and 30-day readmission (OR, 1.3; 95% CI, 1.2-1.4). Patients with ORADEs also were significantly more likely to require

Table 1. Patient Characteristics and Unadjusted Outcomes in the Univariate Analysis

Variable	No.	ORADE (n = 14 386)	No ORADE (n = 120 993)	P Value
Age, mean (SD), y	135 379	60.3 (16.6)	47.5 (19.8)	<.001
BMI, median (IQR) ^a	110 219	28 (24-33)	29 (25-34)	.06
Hispanic ethnicity, No. (%)	21 684	1386 (9.6)	20 298 (16.8)	<.001
Income based on zip code, median (IQR), \$	135 379	70 551 (58 130-91 136)	72 504 (59 531-94 172)	.64
White race/ethnicity, No. (%)	98 583	10 806 (75.1)	87 777 (72.5)	<.001
Female sex, No. (%)	91 371	7200 (50.0)	84 171 (69.6)	<.001
Payer type, No. (%)				
Commercial	58 126	4601 (32.0)	53 522 (44.2)	
Medicaid	21 424	918 (6.4)	20 506 (16.9)	
Medicare	43 295	7448 (51.8)	35 847 (29.6)	<.001
Others	3779	466 (3.2)	3313 (2.7)	
Self or uninsured	8755	953 (6.6)	7802 (6.4)	
ASA score, No./total No. (%)				
1	2442	124 (0.9)	2318 (1.9)	
2	26 789	1419 (9.9)	25 370 (21.0)	
3	29 210	3751 (26.1)	25 459 (21.0)	<.001
≥4	8930	2855 (19.8)	6075 (5.0)	
Missing	68 008	6237 (43.4)	61771 (51.1)	
Charlson Comorbidity Index, mean (SD)	135 379	4.0 (2.9)	2.2 (2.7)	<.001
Comorbidities, No. (%)				
Anxiety	10 545	1600 (11.1)	8945 (7.4)	<.001
Benign prostatic hypertrophy	4700	861 (6.0)	3839 (3.2)	<.001
Depression	13 364	1949 (13.5)	11 415 (9.4)	<.001
Hypertension	55 864	9064 (63.0)	46 800 (38.7)	<.001
Sleep apnea	10 483	2038 (14.2)	8445 (7.0)	<.001
Any history of alcohol or drug abuse, No. (%)	6379	1263 (8.8)	5116 (4.2)	<.001
Unadjusted outcomes, median (IQR)				
Duration of opioid use, d	135 379	3.0 (1.0-6.0)	2.0 (1.0-3.0)	<.001
Morphine milligram equivalent doses, mg				
Maximum daily	135 379	23 (10-50)	20 (10-40)	<.001
Daily	135 379	15 (8-32)	15 (8-30)	<.001
Total during hospitalization	135 379	47 (15-145)	30 (12-80)	<.001
Outcome				
Inpatient mortality, No. (%)	880	727 (5.1)	153 (0.1)	<.001
Discharge to another care facility, No. (%)	116 572	8799 (61.2)	107 773 (89.1)	<.001
LOS, median (IQR), d	135 379	8 (5-15)	3 (2-5)	<.001
Cost of hospitalization, median (IQR), \$	97 572	25 818 (14 844-48 619)	8174 (5411-15 148)	<.001
30-d Readmission, No. (%)	10 094	1607 (11.2)	8487 (7.0)	<.001

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; LOS, length of stay; ORADE, opioid-related adverse drug event.

^a Data missing for some patients (25 160 for BMI and 68 008 for ASA score).

prolonged LOS (OR, 3.1; 95% CI, 2.8-3.4) and have high cost of hospitalization (OR, 2.7; 95% CI, 2.4-3.0). After risk adjustment, ORADEs were associated with a 2.9% increase in absolute mortality, an \$8225 increase in cost for the index hospitalization, and a 1.6-day increase in LOS for the index hospitalization.

Most patients with ORADEs had at least one ORADE that was moderate (55.8%) or severe (37.3%) (eTable 5 in the Supplement). These patients were significantly older, had higher ASA scores and Charlson Comorbidity Index values, and experienced worse outcomes than patients with mild ORADEs. The

risk-adjusted odds of dying were significantly higher for patients with severe ORADEs compared with patients with mild ORADEs (OR, 29.9; 95% CI, 7.4-120.6) (Table 3). Compared with patients with mild ORADEs, patients with severe or moderate ORADEs had significantly longer adjusted LOS (9.9 and 1.8 days longer, respectively), as well as increased odds of prolonged LOS and high cost of hospitalization. Adjusted costs were approximately \$44 000 and \$7000 higher for patients with severe or moderate ORADEs, respectively, compared with patients with mild ORADEs.

Table 2. Risk-Adjusted Clinical and Cost Outcome Estimates for Patients With and Without ORADEs^a

Outcome	Value (95% CI) ^b		Difference
	ORADE	No ORADE	
Inpatient mortality, %	3.0 (2.8-3.3)	0.1 (0.1-0.2)	2.9
Discharge to another care facility, % ^c	20.0 (19.5-20.6)	10.4 (10.2-10.6)	9.6
LOS, d	6.8 (6.7-6.8)	5.2 (5.1-5.3)	1.6
Cost of hospitalization, \$ ^d	25 599 (24 974-26 104)	17 374 (17 191-17 547)	8225
30-d Readmission, %	8.9 (8.5-9.4)	7.1 (7.0-7.3)	1.8

Abbreviations: LOS, length of stay; ORADEs, opioid-related adverse drug events.

^a Estimates were calculated using a random intercept logistic regression model (inpatient mortality, discharge to other facility, 30-day readmission) and a random intercept log-γ regression model (cost, LOS) that accounted for facility clustering. *P* < .001 for all comparisons.

^b Adjusted for age, race/ethnicity, sex, payer type, Charlson Comorbidity Index, and any history of alcohol or drug abuse.

^c Excludes patients who died during the index hospitalization.

^d Data only available for 13 hospitals and refer to the hospitalization during which the procedure of interest was performed.

Discussion

There are 2 main findings in this study. First, ORADEs are a common occurrence among patients undergoing invasive procedures. Approximately 88% of study patients received opioids; of these 135 379 patients, 10.6% experienced an ORADE. Second, most ORADEs were moderate or severe with respect to potential for harm and were associated with significantly worse outcomes, including higher risk of inpatient mortality and 30-day readmission, longer LOS, and higher cost of hospitalization. Occurrence of ORADEs was associated with an increase of 1.6 days in LOS and \$8225 more in cost for the index hospitalization. Extrapolating this average incremental cost per hospitalization over the entire study population experiencing ORADEs (*n* = 14 386) results in more than \$118 million of variable (and potentially avoidable) costs to the health system over a 3-year period.

The use of opioids for postsurgical pain control is an important patient safety and quality issue, yet there are many gaps in knowledge regarding this topic.¹⁶ ORADE rates may vary across hospitals and health systems because of differences in factors like patient mix, prescribing patterns, and reporting; nonetheless, our findings are consistent with national and local studies among surgical patients. We included a more comprehensive list of surgical and endoscopic procedures compared with previous studies but found similar ORADE rates and associated harm. In a retrospective study using a national database, Oderda et al¹¹ found that ORADEs occurred in 12% of 319 898 patients undergoing selected gastrointestinal, obstetric/gynecological, and orthopedic surgical procedures. Patients with ORADEs had significantly higher adjusted mean costs of care (\$22 077 vs \$17 370) and longer LOS (7.6 vs 4.2 days).¹¹ Similarly, Minkowitz et al¹² found that 12% of patients undergoing high-volume, gastrointestinal, obstetric/gynecological, and orthopedic surgical procedures in an 11-hospital health system experienced ORADEs, and these patients had significantly longer LOS (10 vs 6 days), higher mean costs of care (\$29 782 vs \$16 045), and greater 30-day readmission rates (14% vs 9%). Kessler et al¹⁰ found that 14% of patients experienced an ORADE and had significantly longer LOS, higher costs of care, and greater odds of death and 30-day readmission.

We found that patients with ORADEs tended to be older men with higher ASA scores, multiple comorbidities, and a history of alcohol or drug abuse. These results are consistent with previous findings that older age, male sex, prior opioid use, higher Charlson Comorbidity Index, and obesity were associated with ORADEs.¹⁰ Notably, we found that BMI was similar in patients with and without ORADEs; however, BMI data were missing for 18.6% of patients in our study. The finding that older and sicker patients with multiple comorbidities are more likely to experience an ORADE is not unexpected. These ORADEs may be caused by slower rate of drug metabolism, limited physical reserves, and drug-disease or drug-drug interactions. For example, an older patient with chronic obstructive pulmonary disease who receives opioids likely has a higher risk of a respiratory depression. More research is needed to determine specific predictors of ORADEs so that analgesia may be customized to individual patients to minimize risk of harm.

Variations in opioid prescribing patterns may also influence ORADE rates. We did not examine specific prescribing patterns of physicians but found that the median daily morphine milligram equivalent doses of opioids and ORADE frequency varied considerably across procedures. We found multiple procedures in which patients who experienced ORADEs received significantly higher median daily morphine milligram equivalent doses of opioids. Conversely, we also noted that patients undergoing joint replacements, open gynecological procedures, and cesarean sections who experienced ORADEs received significantly lower daily doses of opioids than patients who did not experience ORADEs. These findings suggest that factors besides opioid dosing influence ORADE rates for patients undergoing certain types of procedures. For example, hospitals that fail to provide patients with adequate pain relief may incur low scores on publicly reported patient satisfaction surveys (eg, Hospital Consumer Assessment of Healthcare Providers and Systems [<http://www.hcahpsonline.org/>]).

The magnitude and consequences of opioid abuse in the community are well documented.¹⁷ However, the magnitude of opioid-related harm in our hospitals has not received enough attention in the media or professional societies.¹⁸ The findings of our study indicate that many patients experience harm from opioids administered in hospitals. ORADEs are not now routinely reported as hospital quality measures. This study al-

Table 3. Clinical and Cost Outcome Estimates by ORADE Severity

Variable	Risk-Adjusted Value (95% CI) ^a	P Value
Outcome		
Inpatient mortality, OR		
Severe vs mild	29.9 (7.4-120.6)	<.001
Moderate vs mild	2.2 (0.5-8.8)	.29
Discharge to another care facility, OR ^b		
Severe vs mild	4.0 (3.4-4.8)	<.001
Moderate vs mild	1.0 (0.8-1.1)	.64
Outlier LOS, OR		
Severe vs mild	4.3 (3.0-6.1)	<.001
Moderate vs mild	0.9 (0.6-1.3)	.62
Outlier cost of hospitalization, OR ^c		
Severe vs mild	4.2 (3.0-6.0)	<.001
Moderate vs mild	0.8 (0.5-1.1)	.12
30-d Readmission, OR		
Severe vs mild	1.0 (0.8-1.3)	.96
Moderate vs mild	1.2 (0.9-1.4)	.21
Index Hospitalization^d		
Adjusted LOS, d		
Severe vs mild	9.9 (9.1-10.7)	<.001
Moderate vs mild	1.8 (1.0-2.6)	<.001
Cost, \$ ^c		
Severe vs mild	43 716 (40 100-47 332)	<.001
Moderate vs mild	6860 (3401-10 319)	<.001

Abbreviations: LOS, length of stay; OR, odds ratio; ORADE, opioid-related adverse drug event.

^a Adjusted for age, race/ethnicity, sex, payer type, Charlson Comorbidity Index, and any history of alcohol or drug abuse.

^b Excludes patients who died during the index hospitalization.

^c Data only available for 13 hospitals.

^d Refers to the hospitalization during which the procedure of interest was performed.

lowed us to examine the extent of the problem, as well as patient and opioid characteristics associated with ORADEs after invasive procedures. The total magnitude of ORADEs is likely much higher if all patients are taken into account. Our results indicate that it is important for hospitals to monitor and report ORADEs, including causes and associations, and to identify and implement strategies to reduce opioid use while improving outcomes and reducing costs.

More than 80% of patients who undergo surgery experience acute postoperative pain, and evidence suggests that less than half of these patients have adequate pain relief.^{19,20} Poor pain control also adversely influences functional recovery, LOS, and quality of life.^{16,21} Opioids remain the primary pharmacotherapy for postoperative analgesia, particularly for moderate to severe pain.⁷ Concerns about the potential short-term and long-term harm associated with opioid use have prompted guidelines calling for the use of other analgesics and judicious use of opioids.¹⁹ The American Pain Society recommends the use of multimodal anesthesia techniques, such as regional blocks in combination with systemic opioids, noting that systemic opioids might not be required in all patients.¹⁹ Other analgesics may include intravenous or oral nonsteroidal anti-inflammatory drugs, such as acetamino-

phen. However, the authors of the guidelines note that more research is needed to generate knowledge regarding optimal pain management strategies.

The enhanced recovery after surgery (ERAS) pathway has been shown to reduce opioid use in the postoperative hospital setting.²¹ ERAS pathways use a standardized multimodal analgesic regimen with nonopioid analgesics or techniques to minimize the use of opioids and related adverse events, with the goal of improving and expediting patients' recovery after surgery.²¹ ERAS pathways generally promote the use of opioids only on an as-needed basis when nonopioid analgesics fail. Researchers have reported significant decreases in inpatient opioid use after implementation of ERAS pathways.¹⁹ While opioids will likely remain an important form of postsurgical pain control, the use of ERAS pathways combined with traditional quality improvement techniques, including education and continuous measurement of ORADE rates with reporting and feedback, should improve their safety.²²⁻²⁵

Limitations

This study has several limitations. It is a retrospective study with all of its inherent limitations, including the inability to adjust for unobserved covariates. Specifically, the study demonstrates associations among inpatient opioid use, ORADEs, and clinical and cost outcomes but does not establish causal relationships. The most important limitation is lack of information on timing of ORADEs relative to opioid administration. Hence, it is not possible to determine if adverse events were a direct consequence of opioid use or owing to other causes or drugs. Attributing all documented adverse events based on ICD-9 codes to opioid use may overestimate the frequency of ORADEs. Conversely, more common but mild adverse drug events, such as nausea and vomiting, pruritus, constipation, and delirium, may not be captured by ICD-9 coding.¹¹ Because the study population was limited to a single health care delivery system, our results may not be generalizable to other hospitals. However, our findings are consistent with the existing literature. Unfortunately, the small number of hospitals prohibited any meaningful comparison by hospital type. Conversion to morphine milligram equivalent doses was based on the CDC's standard table; however, this method does not account for all routes of opioid administration for all drugs, including intravenous fentanyl. Also, in a given patient at a given time, the effects of opioids are highly variable depending on bioavailability of the drug. We included patients based on selected procedures without excluding specific diagnostic groups in which opioid use may be more prevalent, such as patients with cancer. Drug abuse history was determined by ICD-9 codes and not limited to opioid abuse. We were not able to determine specific type and duration of drug abuse or identify opioid use before the procedure. Cost data were missing from a few centers located in central Texas. Readmission rates were likely underestimated because we did not capture readmissions outside of the BSWH health care delivery system. Finally, we classified ORADE severity using our clinical judgment of potential harm and not by actual harm experienced by the patient. However, our finding that severe ORADEs were associated with worse outcomes compared with mild events validates our classification.

Conclusions

Opioid-related adverse drug events were common after surgical and endoscopic procedures and were associated with significantly worse clinical and cost outcomes, including in-

creased inpatient mortality, greater likelihood of discharge to another care facility, prolonged LOS, higher cost of hospitalization, and greater likelihood of 30-day readmission. Hospital-acquired harm from ORADEs in the surgical population is an important opportunity for health system patient safety interventions and cost variability reduction programs.

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Study concept and design: Shafi, Collinsworth, Pham, Wan, Masica.

Acquisition, analysis, or interpretation of data: Shafi, Collinsworth, Copeland, Ogola, Qiu, Kouznetsova, Liao, Mears, Pham, Masica.

Drafting of the manuscript: Collinsworth, Ogola, Liao, Mears, Pham.

Critical revision of the manuscript for important intellectual content: Shafi, Collinsworth, Copeland, Ogola, Qiu, Kouznetsova, Pham, Wan, Masica.

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