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ORIGINAL RESEARCH

Opioid Utilization and Opioid-Related Adverse Events in Nonsurgical Patients in US Hospitals

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BACKGROUND: Recent studies in the outpatient setting have demonstrated high rates of opioid prescribing and overdose-related deaths. Prescribing practices in hospitalized patients are unexamined.

OBJECTIVE: To investigate patterns and predictors of opioid utilization in nonsurgical admissions to US hospitals, variation in use, and the association between hospital-level use and rates of severe opioid-related adverse events.

DESIGN, SETTING, AND PATIENTS: Adult nonsurgical admissions to 286 US hospitals.

MEASUREMENTS: Opioid exposure and severe opioid-related adverse events during hospitalization, defined using hospital charges and *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

RESULTS: Of 1.14 million admissions, opioids were used in 51%. The mean ± standard deviation daily dose received in oral morphine equivalents was 68 ± 185 mg; 23% of exposed received a total daily dose of ≥100 mg oral morphine equivalents. Opioid-prescribing rates ranged from 5% in the lowest-prescribing hospital to 72% in the highest-prescribing hospital (mean, 51% ± 10%). After adjusting for patient characteristics, the adjusted opioid-prescribing rates ranged from 33% to 64% (mean, 50% ± standard deviation 4%). Among exposed, 0.60% experienced severe opioid-related adverse events. Hospitals with higher opioid-prescribing rates had higher adjusted relative risk of a severe opioid-related adverse event per patient exposed (relative risk: 1.23 [1.14-1.33] for highest-prescribing compared with lowest-prescribing quartile).

CONCLUSIONS: The majority of hospitalized nonsurgical patients were exposed to opioids, often at high doses. Hospitals that used opioids most frequently had increased adjusted risk of a severe opioid-related adverse event per patient exposed. Interventions to standardize and enhance the safety of opioid prescribing in hospitalized patients should be investigated. *Journal of Hospital Medicine* 2014;9:73–81. © 2013 Society of Hospital Medicine

Recent reports have drawn attention to the high and increasing rates of opioid prescribing and overdose-related deaths in the United States.[1–9] These studies have focused on community-based and emergency department prescribing, leaving prescribing practices in the inpatient setting unexamined. Given that pain is a frequent complaint in hospitalized patients, and that the Joint Commission mandates assessing pain as a vital sign, hospitalization is potentially a time of heightened use of such medications and could significantly contribute to nosocomial complications and subsequent outpatient use.[10] Variation in prescribing practices, unrelated to patient characteristics, could be a marker of inappropriate prescribing practices and poor quality of care.

Using a large, nationally representative cohort of admissions from July 2009 to June 2010, we sought to determine patterns and predictors of opioid utilization in nonsurgical admissions to US medical centers, hospital variation in use, and the association between hospital-level use and the risk of opioid-related adverse events. We hypothesized that hospitals with higher rates of opioid use would have an increased risk of an opioid-related adverse event per patient exposed.

METHODS

Setting and Patients

We conducted a retrospective cohort study using data from 286 US nonfederal acute-care facilities contributing to the database maintained by Premier (Premier Healthcare Solutions, Inc., Charlotte, NC). This database, created to measure healthcare utilization and quality of care, is drawn from voluntarily participating hospitals and contains data on approximately 1 in every 4 discharges nationwide.[11] Participating hospitals are similar in geographic distribution and metropolitan (urban/rural) status to hospitals nationwide, although large, nonteaching hospitals are slightly overrepresented in Premier. The database contains patient demographics, *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) codes, hospital demographics, and a date-

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stamped log of all charges during the course of each hospitalization, including diagnostic tests, therapeutic treatments, and medications with dose and route of administration. The study was approved by the institutional review board at Beth Israel Deaconess Medical Center and granted a waiver of informed consent.

We studied a cohort of all adult nonsurgical admissions to participating hospitals from July 1, 2009, through June 30, 2010. We chose to study nonsurgical admissions, as patients undergoing surgical procedures have a clear indication for, and almost always receive, opioid pain medications. We defined a nonsurgical admission as an admission in which there were no charges for operating-room procedures (including labor and delivery) and the attending of record was not a surgeon. We excluded admissions with unknown gender, since this is a key demographic variable, and admissions with a length of stay greater than 365 days, as these admissions are not representative of the typical admission to an acute-care hospital. At the hospital level, we excluded hospitals contributing <100 admissions owing to resultant lack of precision in corresponding hospital prescribing rates, and hospitals that did not prescribe the full range of opioid medications (these hospitals had charges for codeine only), as these facilities seemed likely to have unusual limitations on prescribing or incomplete data capture.

Opioid Exposure

We defined opioid exposure as presence of ≥ 1 charge for an opioid medication during the admission. Opioid medications included morphine, hydrocodone, hydromorphone, oxycodone, fentanyl, meperidine, methadone, codeine, tramadol, buprenorphine, levorphanol, oxymorphone, pentazocine, propoxyphene, tapentadol, butorphanol, dezocine, and nalbuphine. We grouped the last 9 into an "other" category owing to infrequent use and/or differing characteristics from the main opioid drug types, such as synthetic, semisynthetic, and partial agonist qualities.

Severe Opioid-Related Adverse Events

We defined severe opioid-related adverse events as either naloxone exposure or an opioid-related adverse drug event diagnosis code. Naloxone use in an adult patient exposed to opioids is one of the Institute for Healthcare Improvement's Trigger Tools for identifying adverse drug events[12] and previously has been demonstrated to have high positive predictive value for a confirmed adverse drug event.[13] We defined naloxone exposure as presence of ≥ 1 charge for naloxone. We excluded charges on hospital day 1 to focus on nosocomial events. We defined opioid-related adverse drug events using ICD-9-CM diagnosis codes for poisoning by opioids (overdose, wrong substance given, or taken in error; ICD-9-CM 965.02, 965.09, E850.1, E850.2) and drugs causing adverse effects in therapeutic use (ICD-9-CM E935.1, E935.2), as specified in prior analyses by the Agency for Healthcare Research and Quality (AHRQ).[14,15] To avoid capturing adverse events associated with outpatient use, we required the ICD-9-CM code to be qualified as not present on admission using the present on admission indicator required by the Centers for Medicare and Medicaid Services for all discharge diagnosis codes since 2008.[16]

Covariates of Interest

We were interested in the relationship between both patient and hospital characteristics and opioid exposure. Patient characteristics of interest included (1) demographic variables, such as age, sex, race (self-reported by patients at the time of admission), marital status, and payer; (2) whether or not the patient spent any time in the intensive care unit (ICU); (3) comorbidities, identified via ICD-9-CM secondary diagnosis codes and diagnosis-related groups using Healthcare Cost and Utilization Project Comorbidity Software, version 3.7, based on the work of Elixhauser et al[17,18]; (4) primary ICD-9-CM discharge diagnosis groupings, selected based on hypothesized associations with receipt of opioids, and based on the Clinical Classifications Software (CCS)—a diagnosis and procedure categorization scheme maintained by the AHRQ, and defined in the Appendix[19]; (5) and non–operating-room-based procedures potentially necessitating opioids during the admission, selected from the 50 most common ICD-9-CM procedure codes in our cohort and grouped as cardiovascular procedures (catheterization and insertion of vascular stents), gastrointestinal procedures (upper and lower endoscopy), and mechanical ventilation, further defined in the Appendix. Hospital characteristics of interest included number of beds, population served (urban vs rural), teaching status, and US census region (Northeast, Midwest, South, West).

Statistical Analysis

We calculated the percent of admissions with exposure to any opioid and the percent exposed to each opioid, along with the total number of different opioid medications used during each admission. We also calculated the percent of admissions with parenteral administration and the percent of admissions with oral administration, among those exposed to the individual categories, and in aggregate. Because medications after discharge were unavailable in Premier's dataset, we report the percent of patients with a charge for opioids on the day of discharge.

We determined the daily dose of an opioid by taking the sum of the doses for that opioid charged on a given day. The average daily dose of an opioid was determined by taking the sum of the daily doses and dividing by the number of days on which ≥ 1 dose was charged. To facilitate comparison, all opioids, with the exception of those for which standard equivalences are unavailable (tramadol, other opioid

TABLE 1. Patient and Hospital Characteristics*

Patient characteristics, N = 1,139,419	N	%
Age group, y		
18–24	37,464	3
25–34	66,541	6
35–44	102,701	9
45–54	174,830	15
55–64	192,570	17
65–74	196,407	17
75+	368,906	32
Sex		
Male	527,062	46
Female	612,357	54
Race		
White	711,993	62
Black	176,993	16
Hispanic	54,406	5
Other	196,027	17
Marital status		
Married	427,648	38
Single	586,343	51
Unknown/other	125,428	11
Primary insurance		
Private/commercial	269,725	24
Medicare traditional	502,301	44
Medicare managed care	126,344	11
Medicaid	125,025	11
Self-pay/other	116,024	10
ICU care		
No	1,023,027	90
Yes	116,392	10
Comorbidities		
AIDS	5724	1
Alcohol abuse	79,633	7
Deficiency anemias	213,437	19
RA/collagen vascular disease	35,210	3
Chronic blood-loss anemia	10,860	1
CHF	190,085	17
Chronic pulmonary disease	285,954	25
Coagulopathy	48,513	4
Depression	145,553	13
DM without chronic complications	270,087	24
DM with chronic complications	70,732	6
Drug abuse	66,886	6
Hypertension	696,299	61
Hypothyroidism	146,136	13
Liver disease	38,130	3
Lymphoma	14,032	1
Fluid and electrolyte disorders	326,576	29
Metastatic cancer	33,435	3
Other neurological disorders	124,195	11
Obesity	118,915	10
Paralysis	38,584	3
PVD	77,334	7
Psychoses	101,856	9
Pulmonary circulation disease	52,106	5
Renal failure	175,398	15
Solid tumor without metastasis	29,594	3
Peptic ulcer disease excluding bleeding	536	0
Valvular disease	86,616	8
Weight loss	45,132	4
Primary discharge diagnoses		
Cancer	19,168	2
Musculoskeletal injuries	16,798	1
Pain-related diagnoses†	101,533	9
Alcohol-related disorders	16,777	1
Substance-related disorders	13,697	1
Psychiatric disorders	41,153	4
Mood disorders	28,761	3
Schizophrenia and other psychotic disorders	12,392	1
Procedures		
Cardiovascular procedures	59,901	5
GI procedures	31,224	3
Mechanical ventilation	7853	1
Hospital characteristics, N = 286		
Number of beds		
<200	103	36
201–300	63	22
301–500	81	28
>500	39	14
Population served		
Urban	225	79
Rural	61	21
Teaching status		
Nonteaching	207	72
Teaching	79	28
US Census region		
Northeast	47	16
Midwest	63	22
South	115	40
West	61	21

NOTE: **Abbreviations:** AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; DM, diabetes mellitus; GI, gastrointestinal; ICU, intensive care unit; PVD, peripheral vascular disease; RA, rheumatoid arthritis; US, United States.

*Patient characteristics presented for each admission do not take into account multiple admissions of the same patient.

†Pain-related diagnoses include abdominal pain, headache, nonspecific chest pain, pancreatic disorders, musculoskeletal back problems, and calculus of urinary tract.

category, oral fentanyl, epidural route for all), were converted to oral morphine equivalents using a standard equivalence conversion table.[20,21] We excluded from our dosage calculations those charges for which standard morphine equivalence was unavailable, or for which dosage was missing. We also excluded from our dosage calculations any dose that was >3 standard deviations (SD) above the mean dose for that opioid, as such extreme values seemed physiologically implausible and more likely to be a data entry error that could lead to significant overestimation of the mean for that opioid.

All multivariable models used a generalized estimating equation (GEE) via the "genmod" procedure in SAS, with a Poisson distribution error term and a log link, controlling for repeated patient admissions with an autoregressive correlation structure.

To identify independent predictors of opioid receipt, we used a GEE model of opioid receipt where all patient and hospital characteristics listed in Table 1 were included as independent variables.

To assess hospital variation in opioid prescribing after adjusting for patient characteristics, we used a GEE model of opioid receipt, controlling for all patient characteristics listed in Table 1. We then took

TABLE 2. Rate of Exposure, Route of Administration, and Average Dose of Opioids Received, Overall and by Opioid (N = 1,139,419)

	Exposed		Parenteral Administration		Oral Administration		Dose Received, in Oral Morphine Equivalents	
	N	%*	N	%†	N	%†	Mean	SD‡
All opioids	576,373	51	378,771	66	371,796	65	68	185
Morphine	224,811	20	209,040	93	21,645	10	40	121
Hydrocodone	162,558	14	0	0	160,941	99	14	12
Hydromorphone	146,236	13	137,936	94	16,052	11	113	274
Oxycodone	126,733	11	0	0	125,033	99	26	37
Fentanyl	105,052	9	103,113	98	641	1	64	75
Tramadol	35,570	3	0	0	35,570	100	—	—
Meperidine	24,850	2	24,398	98	515	2	36	34
Methadone	15,302	1	370	2	14,781	97	337	384
Codeine	22,818	2	178	1	22,183	97	9	15
Other§	45,469	4	5821	13	39,618	87	—	—

NOTE: **Abbreviations:** SD, standard deviation.

*Percentages exposed to different opioids add up to more than total receiving any opioid since patients may be exposed to >1 opioid during their hospitalization.

†Denominator is the number exposed. Percentages may add up to < or >100% owing to missing route information or receipt of both parenteral and oral routes, respectively.

‡On days on which opioids were received. Charges for tramadol, "other" category opioids, oral fentanyl (0.7% of fentanyl charges), and epidural-route opioids (3.5% of fentanyl charges, 0.1% of morphine charges, and 0.1% of hydromorphone charges) were not included in dosage calculations due to lack of standard conversion factor to morphine equivalents. Charges with missing dose were also excluded (2% of total remaining opioid charges).
§Includes the following opioids: buprenorphine, levorphanol, oxymorphone, pentazocine, propoxyphene, tapentadol, butorphanol, dezocine, and nalbuphine.

the mean of the predicted probabilities of opioid receipt for the patients within each hospital in our cohort to derive the hospital prescribing rate adjusted for patient characteristics. We report the mean, SD, and range of the prescribing rates for the hospitals in our cohort before and after adjustment for patient characteristics.

To assess whether patients admitted to hospitals with higher rates of opioid prescribing have higher relative risk of severe opioid-related adverse events, we stratified hospitals into opioid-prescribing rate quartiles and compared the rates of opioid-related adverse events—both overall and among opioid exposed—between quartiles. To adjust for patient characteristics, we used a GEE model in which severe opioid-related adverse event (yes/no) was the dependent variable and hospital-prescribing rate quartile and all patient characteristics in Table 1 were independent variables. We also performed a sensitivity analysis in which we assessed the association between hospital prescribing-rate quartile and the individual components of our composite outcome. Our results were qualitatively unchanged using this approach, and only the results of our main analysis are presented.

All analyses were carried out using SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Admission Characteristics

There were 3,190,934 adult admissions to 300 acute-care hospitals during our study period. After excluding admissions with a length of stay >365 days (n = 25), missing patient sex (n = 17), and charges for operating-room procedures or a surgical attending of record (n = 2,018,553), 1,172,339 admissions were available for analysis. There were 12 hospitals with incomplete opioid-prescribing data (n = 32,794) and 2 hospitals that contributed <100 admissions each (n = 126), leaving 1,139,419 admissions in 286 hospitals in our analytic cohort. The median age of the cohort was 64 years (interquartile range, 49–79 years), and 527,062 (46%) were men. Table 1 shows the characteristics of the admissions in the cohort.

Rate, Route, and Dose of Opioid Exposures

Overall, there were 576,373 (51%) admissions with charges for opioid medications. Among those exposed, 244,760 (43%) had charges for multiple opioids during the admission; 172,090 (30%) had charges for 2 different opioids; and 72,670 (13%) had charges for ≥3 different opioids. Table 2 shows the percent exposed to each opioid, the percent of exposed with parenteral and oral routes of administration, and the mean daily dose received in oral morphine equivalents.

Among the medications/routes for which conversion to morphine equivalents was possible, dosage was missing in 39,728 out of 2,294,673 opioid charges (2%). The average daily dose received in oral morphine equivalents was 68 mg. A total dose of ≥50 mg per day was received in 39% of exposed, and a total dose of ≥100 mg per day was received in 23% of exposed. Among those exposed, 52% (26% of overall admissions) had charges for opioids on the day of discharge.

Rates of Opioid Use by Patient and Hospital Characteristics

Table 3 reports the association between admission characteristics and opioid use. Use was highest in

TABLE 3. Association Between Admission Characteristics and Opioid Use (N = 1,139,419)

	Exposed, N = 576,373	Unexposed, N = 563,046	% Exposed	Adjusted RR*	95% CI
Patient characteristics					
Age group, y					
18–24	17,360	20,104	46	(ref)	
25–34	37,793	28,748	57	1.17	1.16-1.19
35–44	60,712	41,989	59	1.16	1.15-1.17
45–54	103,798	71,032	59	1.11	1.09-1.12
55–64	108,256	84,314	56	1.00	0.98-1.01
65–74	98,110	98,297	50	0.84	0.83-0.85
75+	150,344	218,562	41	0.71	0.70-0.72
Sex					
Male	255,315	271,747	48	(ref)	
Female	321,058	291,299	52	1.11	1.10-1.11
Race					
White	365,107	346,886	51	(ref)	
Black	92,013	84,980	52	0.93	0.92-0.93
Hispanic	27,592	26,814	51	0.94	0.93-0.94
Other	91,661	104,366	47	0.93	0.92-0.93
Marital status					
Married	222,912	204,736	52	(ref)	
Single	297,742	288,601	51	1.00	0.99-1.01
Unknown/other	55,719	69,709	44	0.94	0.93-0.95
Primary insurance					
Private/commercial	143,954	125,771	53	(ref)	
Medicare traditional	236,114	266,187	47	1.10	1.09-1.10
Medicare managed care	59,104	67,240	47	1.11	1.11-1.12
Medicaid	73,583	51,442	59	1.13	1.12-1.13
Self-pay/other	63,618	52,406	55	1.03	1.02-1.04
ICU care					
No	510,654	512,373	50	(ref)	
Yes	65,719	50,673	56	1.02	1.01-1.03
Comorbidities†					
AIDS	3655	2069	64	1.09	1.07-1.12
Alcohol abuse	35,112	44,521	44	0.92	0.91-0.93
Deficiency anemias	115,842	97,595	54	1.08	1.08-1.09
RA/collagen vascular disease	22,519	12,691	64	1.22	1.21-1.23
Chronic blood-loss anemia	6444	4416	59	1.04	1.02-1.05
CHF	88,895	101,190	47	0.99	0.98-0.99
Chronic pulmonary disease	153,667	132,287	54	1.08	1.08-1.08
Coagulopathy	25,802	22,711	53	1.03	1.02-1.04
Depression	83,051	62,502	57	1.08	1.08-1.09
DM without chronic complications	136,184	133,903	50	0.99	0.99-0.99
DM with chronic complications	38,696	32,036	55	1.04	1.03-1.05
Drug abuse	37,202	29,684	56	1.14	1.13-1.15
Hypertension	344,718	351,581	50	0.98	0.97-0.98
Hypothyroidism	70,786	75,350	48	0.99	0.99-0.99
Liver disease	24,067	14,063	63	1.15	1.14-1.16
Lymphoma	7727	6305	55	1.16	1.14-1.17
Fluid and electrolyte disorders	168,814	157,762	52	1.04	1.03-1.04
Metastatic cancer	23,920	9515	72	1.40	1.39-1.42
Other neurological disorders	51,091	73,104	41	0.87	0.86-0.87
Obesity	69,584	49,331	59	1.05	1.04-1.05
Paralysis	17,497	21,087	45	0.97	0.96-0.98
PVD	42,176	35,158	55	1.11	1.11-1.12
Psychoses	38,638	63,218	38	0.91	0.90-0.92
Pulmonary circulation disease	26,656	25,450	51	1.05	1.04-1.06
Renal failure	86,565	88,833	49	1.01	1.01-1.02
Solid tumor without metastasis	16,258	13,336	55	1.14	1.13-1.15
Peptic ulcer disease excluding bleeding	376	160	70	1.12	1.07-1.18
Valvular disease	38,396	48,220	44	0.93	0.92-0.94
Weight loss	25,724	19,408	57	1.09	1.08-1.10
Primary discharge diagnoses†					
Cancer	13,986	5182	73	1.20	1.19-1.21
Musculoskeletal injuries	14,638	2160	87	2.02	2.00–2.04
Pain-related diagnoses‡	64,656	36,877	64	1.20	1.20-1.21
Alcohol-related disorders	3425	13,352	20	0.46	0.44-0.47

TABLE 3. *Continued*

	Exposed, N = 576,373	Unexposed, N = 563,046	% Exposed	Adjusted RR*	95% CI
Substance-related disorders	8680	5017	63	1.03	1.01-1.04
Psychiatric disorders	7253	33,900	18	0.37	0.36-0.38
Mood disorders	5943	22,818	21		
Schizophrenia and other psychotic disorders	1310	11,082	11		
Procedures†					
Cardiovascular procedures	50,997	8904	85	1.80	1.79-1.81
GI procedures	27,206	4018	87	1.70	1.69-1.71
Mechanical ventilation	5341	2512	68	1.37	1.34-1.39
Hospital characteristics					
Number of beds					
<200	100,900	88,439	53	(ref)	
201–300	104,213	99,995	51	0.95	0.95-0.96
301–500	215,340	209,104	51	0.94	0.94-0.95
>500	155,920	165,508	49	0.96	0.95-0.96
Population served					
Urban	511,727	506,803	50	(ref)	
Rural	64,646	56,243	53	0.98	0.97-0.99
Teaching status					
Nonteaching	366,623	343,581	52	(ref)	
Teaching	209,750	219,465	49	1.00	0.99-1.01
US Census region					
Northeast	99,377	149,446	40	(ref)	
Midwest	123,194	120,322	51	1.26	(1.25-1.27)
South	251,624	213,029	54	1.33	(1.33-1.34)
West	102,178	80,249	56	1.37	(1.36-1.38)

NOTE: **Abbreviations:** AIDS, acquired immune deficiency syndrome; CHF, congestive heart failure; CI, confidence interval; DM, diabetes mellitus; GEE, generalized estimating equation; GI, gastrointestinal; ICU, intensive care unit; PVD, peripheral vascular disease; RA, rheumatoid arthritis; ref, reference; RR, relative risk; US, United States.

*Multivariable GEE model used to account for multiple admissions of the same patient, with simultaneous control for all variables listed in this table.

†For comorbidities, primary discharge diagnoses, and procedures, the reference group is absence of that condition or procedure.

‡Pain-related diagnoses include abdominal pain, headache, nonspecific chest pain, pancreatic disorders, musculoskeletal back problems, and calculus of urinary tract.

patients between the ages of 25 and 54 years. Although use declined with age, 44% of admissions age ≥65 years had charges for opioid medication. After adjustment for patient demographics, comorbidities, and hospital characteristics, opioid use was more common in females than males, those age 25–54 years compared with those older and younger, those of Caucasian race compared with non-Caucasian race, and those with Medicare or Medicaid primary insurance. Among the primary discharge diagnoses, patients with musculoskeletal injuries, various specific and nonspecific pain-related diagnoses, and cancer were significantly more likely to receive opioids than patients without these diagnoses, whereas patients with alcohol-related disorders and psychiatric disorders were significantly less likely to receive opioids than patients without these diagnoses. Patients admitted to hospitals in the Midwest, South, and West were significantly more likely to receive opioid medications than patients in the Northeast.

Variation in Opioid Prescribing

Figure 1 shows the histograms of hospital opioid prescribing rate for the 286 hospitals in our cohort (A) before and (B) after adjustment for patient characteristics. The observed rates ranged from 5% in the lowest-prescribing hospital to 72% in the highest-prescribing hospital, with a mean (SD) of 51% (10%). After adjusting for patient characteristics, the adjusted opioid-prescribing rates ranged from 33% to 64%, with a mean (SD) of 50% (4%).

Severe Opioid-Related Adverse Events

Among admissions with opioid exposure (n = 576,373), naloxone use occurred in 2345 (0.41%) and opioid-related adverse drug events in 1174 (0.20%), for a total of 3441 (0.60%) severe opioid-related adverse events (some patients experienced both). Table 4 reports the opioid exposure and severe opioid-related adverse-event rates within hospital opioid-prescribing rate quartiles, along with the adjusted association between the hospital opioid-prescribing rate quartile and severe opioid-related adverse events. After adjusting for patient characteristics, the relative risk of a severe opioid-related adverse event was significantly greater in hospitals with higher opioid-prescribing rates, both overall and among opioid exposed.

DISCUSSION

In this analysis of a large cohort of hospitalized nonsurgical patients, we found that more than half of all patients received opioids, with 43% of those exposed receiving multiple opioids during their admission and

52% receiving opioids on the day of discharge. Considerable hospital variation in opioid use was evident, and this was not fully explained by patient characteristics. Severe opioid-related adverse events occurred more frequently at hospitals with higher opioid-prescribing rates, and the relative risk of a severe adverse event per patient prescribed opioids was also higher in these hospitals. To our knowledge, this is the first study to describe the scope of opioid utilization and the relationship between utilization and severe opioid-related adverse events in a sample of nonsurgical patients in US acute-care facilities.

Our use of naloxone charges and opioid-specific ICD-9-CM coding to define an opioid-related adverse event was intended to capture only the most severe opioid-related adverse events. We chose to focus on these events in our analysis to maximize the specificity of our outcome definition and thereby minimize confounding in our observed associations. The rate of less-severe opioid-related adverse events, such as nausea, constipation, and pruritis, is likely much higher and not captured in our outcome definition. Prior analyses have found variable rates of opioid-related adverse events of approximately 1.8% to 13.6% of exposed patients.[22–24] However, these analyses focused on surgical patients and included less-severe events. To our knowledge, ours is the first analysis of severe opioid-related adverse events in nonsurgical patients.

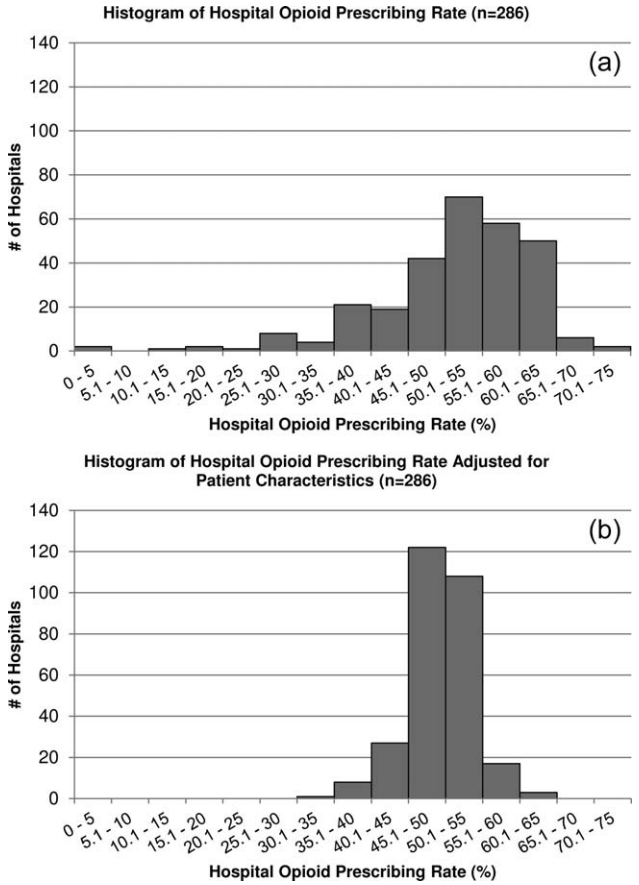

FIG. 1. Histograms of hospital opioid prescribing rate (A) before and (B) after adjustment for patient characteristics.

Our finding that severe opioid-related adverse events increase as opioid prescribing increases is consistent with that which has been demonstrated in the community setting, where rates of opioid-related adverse events and mortality are higher in communities with higher levels of opioid prescribing.[2,8,25] This finding is expected, as greater use of a class of medications with known side effects would be expected to result in a higher overall rate of adverse events. More concerning, however, is the fact that this relationship persists when focusing exclusively on opioid-exposed patients. Among similar patients receiving opioids at different hospitals, those hospitalized in facilities with higher opioid-prescribing rates have higher rates of severe opioid-related adverse events. This suggests that hospitals that use opioids more frequently do not do so more safely. Rather, the increased overall prescribing rates are associated with heightened risk for a serious adverse event per patient exposed and may reflect unsafe prescribing practices.

Furthermore, our results demonstrate both regional and hospital variation in use of opioids not fully explained by patient characteristics, similar to that which has been demonstrated for other drugs and heathcare services.[26–30] The implications of these findings are limited by our lack of information on pain severity or prior outpatient treatment, and our resultant inability to evaluate the appropriateness of opioid use in this analysis. Additionally, although we controlled for a large number of patient and hospital

TABLE 4. Association Between Hospital Opioid-Prescribing Rate Quartile and Risk of an Opioid-Related Adverse Event

Quartile	No. of Patients	Opioid Exposed, n (%)	Opioid-Related Adverse Events, n (%)	Adjusted RR in All Patients, RR (95% CI), N = 1,139,419*	Adjusted RR in Opioid Exposed, RR (95% CI), N = 576,373*
1	349,747	132,824 (38)	719 (0.21)	(ref)	(ref)
2	266,652	134,590 (50)	729 (0.27)	1.31 (1.17-1.45)	1.07 (0.96-1.18)
3	251,042	139,770 (56)	922 (0.37)	1.72 (1.56-1.90)	1.31 (1.19-1.44)
4	271,978	169,189 (62)	1071 (0.39)	1.73 (1.57-1.90)	1.23 (1.12-1.35)

NOTE: **Abbreviations:** CI, confidence interval; GEE, generalized estimating equation; ref, reference; ref, reference; RR, relative risk.

*Adjusted for repeated admissions and patient characteristics presented in Table 1 using a multivariable GEE model with a Poisson error term distribution, log link, and autoregressive correlation structure.

characteristics, there could be other significant predictors of use not accounted for in our analysis. However, it seems unlikely that differential pain severity or patient characteristics between patients in different regions of the country could fully explain a 37% relative difference in prescribing between the lowest- and highest-prescribing regions, after accounting for the 44 patient-level variables in our models. Whereas variation in use unrelated to patient factors could represent inappropriate prescribing practices, it could also be a marker of uncertainty regarding what constitutes appropriate prescribing and high-quality care in this realm. Although guidelines advocate for standard pain assessments and a step-up approach to treatment,[31–33] the lack of objective measures of pain severity and lack of evidence-based recommendations on the use of opioids for noncancer pain[34] will almost certainly lead to persistent variation in opioid prescribing despite "guideline-driven" care.

Nonetheless, our findings suggest that opportunities exist to make opioid prescribing safer in hospitalized patients. Studies aimed at elucidating the source of regional and hospital variation are necessary. Additionally, efforts should focus on identifying patient and prescribing characteristics associated with heightened risk of opioid-related adverse events. Prior studies have demonstrated that the risks of opioid medications increase with increasing age of the patient.[35,36] Although opioid use in our cohort declined with age, 44% of admissions age $\geq$65 years had charges for opioid medications. Studies in outpatients have also demonstrated that the risks of opioid overdose and overdose-related death increase with dose.[5,7] One study demonstrated a 3.7-fold increased risk of overdose at doses of 50–99 mg/day in oral morphine equivalents, and an 8.9-fold increased risk at doses of $\geq$100 mg/day, compared with doses of $\leq$20 mg/day.[7] The prevalence of high dose exposure observed in our cohort, coupled with the older age of hospitalized patients, suggests potential targets for promoting safer use in hospitalized patients through interventions such as computerized decision support and enhanced monitoring in those at highest risk.

Because medications after discharge were unavailable in our dataset, the percentage of patients given a prescription for opioid medication on discharge is unknown. However, given that opioids are often tapered rather than abruptly discontinued, our finding that 26% of hospitalized nonsurgical patients received opioids on the day of discharge suggests that a substantial proportion of patients may be discharged with a prescription for opioid medication. Given the possibility of coexistent outpatient opioid prescriptions, these findings draw attention to the importance of assuring development and streamlined accessibility of data from state prescription drug monitoring programs and suggest that increased attention should be paid to the role that inpatient opioid prescribing plays in the increased rates of chronic opioid use and overdose-related deaths in the United States.

There are additional limitations to our analysis. First, although the database used for this analysis captures a large proportion of admissions to US acute-care facilities and is similar in composition, it is possible that participating medical centers differ from nonparticipating medical centers in ways that could be associated with opioid prescribing. Additionally, although Premier performs extensive validation and correction processes to assure the quality of their data, there is still likely to be a small amount of random error in the database, which could particularly impact dosage calculations. The lack of preadmission medications in our database precluded identification of the proportion of patients newly started on opioid medications. Lastly, it is possible that the hospital prescribing-rate quartile is associated with patient characteristics unaccounted for in our analysis, and, therefore, the possibility of residual confounding still exists.

In conclusion, the majority of hospitalized nonsurgical patients are exposed to opioid medications during the course of their hospitalizations, often at high doses. More than half of those exposed are still receiving these medications on the day of discharge. We found hospital and regional variation in opioid use that was not fully explained by patient characteristics, and higher levels of hospital use were associated with higher risk of severe opioid-related adverse events in opioid-exposed patients. Further research is necessary to investigate the appropriateness of opioid use in this patient population, the sources of variation in use, and the predictors of opioid-related adverse events in hospitalized patients to allow development of interventions to make hospital use safer.

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