

Association Between Opioid and Benzodiazepine Use and Clinical Deterioration in Ward Patients

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BACKGROUND: Opioids and benzodiazepines are frequently used in hospitals, but little is known about outcomes among ward patients receiving these medications.

OBJECTIVE: To determine the association between opioid and benzodiazepine administration and clinical deterioration.

DESIGN: Observational cohort study.

SETTING: 500-bed academic urban tertiary-care hospital.

PATIENTS: All adults hospitalized on the wards from November 2008 to January 2016 were included. Patients who were “comfort care” status, had tracheostomies, sickle-cell disease, and patients at risk for alcohol withdrawal or seizures were excluded.

MEASUREMENTS: The primary outcome was the composite of intensive care unit transfer or ward cardiac arrest. Discrete-time survival analysis was used to calculate the odds of this outcome during exposed time periods compared to unexposed time periods with respect to the medications of

interest, with adjustment for patient demographics, comorbidities, severity of illness, and pain score.

RESULTS: In total, 120,518 admissions from 67,097 patients were included, with 67% of admissions involving opioids, and 21% involving benzodiazepines. After adjustment, each equivalent of 15 mg oral morphine was associated with a 1.9% increase in the odds of the primary outcome within 6 hours (odds ratio [OR], 1.019; 95% confidence interval [CI], 1.013-1.026; $P < 0.001$), and each 1 mg oral lorazepam equivalent was associated with a 29% increase in the odds of the composite outcome within 6 hours (OR, 1.29; CI, 1.16-1.45; $P < 0.001$).

CONCLUSION: Among ward patients, opioids were associated with increased risk for clinical deterioration in the 6 hours after administration. Benzodiazepines were associated with even higher risk. These results have implications for ward-monitoring strategies. *Journal of Hospital Medicine* 2017;12:428-434. © 2017 Society of Hospital Medicine

Chronic opioid and benzodiazepine use is common and increasing.¹⁻⁵ Outpatient use of these medications has been associated with hospital readmission and death,⁶⁻¹² with concurrent use associated with particularly increased risk.^{13,14} Less is known about outcomes for hospitalized patients receiving these medications.

More than half of hospital inpatients in the United States receive opioids,¹⁵ many of which are new prescriptions rather than continuation of chronic therapy.^{16,17} Less is known about inpatient benzodiazepine administration, but the prevalence may exceed 10% among elderly populations.¹⁸ Hospitalized patients often have comorbidities or physiological disturbances that might increase their risk related to use of these medications. Opioids can cause central and obstructive sleep apnea,¹⁹⁻²¹ and benzodiazepines contribute to respiratory depression and airway relaxation.²² Benzodiaz-

epines also impair psychomotor function and recall,²³ which could mediate the recognized risk for delirium and falls in the hospital.^{24,25} These findings suggest pathways by which these medications might contribute to clinical deterioration.

Most studies in hospitalized patients have been limited to specific populations^{15,26-28} and have not explicitly controlled for severity of illness over time. It remains unclear whether associations identified within particular groups of patients hold true for the broader population of general ward inpatients. Therefore, we aimed to determine the independent association between opioid and benzodiazepine administration and clinical deterioration in ward patients.

MATERIALS AND METHODS

Setting and Study Population

We performed an observational cohort study at a 500-bed urban academic hospital. Data were obtained from all adults hospitalized on the wards between November 1, 2008, and January 21, 2016. The study protocol was approved by the University of Chicago Institutional Review Board (IRB#15-0195).

Data Collection

The study utilized de-identified data from the electronic health record (EHR; Epic Systems Corporation, Verona,

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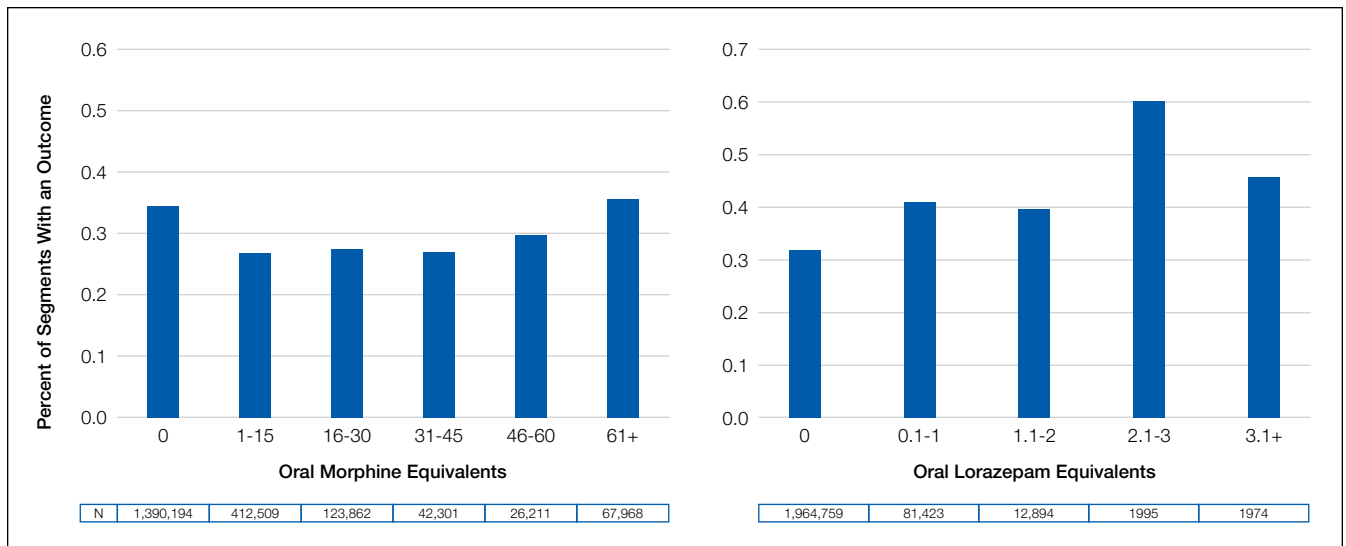


FIG. Unadjusted frequency of composite outcome stratified by medication dose.^a

^aWard cardiac arrest or intensive care unit transfer.

NOTE: N reflects the number of 6-hr ward segments associated with each dosing range, and the Y-axis shows the percentage of 6-hr segments in which an outcome occurred.

Wisconsin) and administrative databases collected by the University of Chicago Clinical Research Data Warehouse. Patient age, sex, race, body mass index (BMI), and ward admission source (ie, emergency department (ED), transferred from the intensive care unit (ICU), or directly admitted to the wards) were collected. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes were used to identify Elixhauser Comorbidity Index categories.^{29,30} Because patients with similar diagnoses (eg, active cancer) are cohorted within particular areas in our hospital, we obtained the ward unit for all patients. Patients who underwent surgery were identified using the hospital's admission-transfer-discharge database.

To determine severity of illness, routinely collected vital signs and laboratory values were utilized to calculate the electronic cardiac arrest risk triage (eCART) score, an accurate risk score we previously developed and validated for predicting adverse events among ward patients.³¹ If any vital sign or laboratory value was missing, the next available measurement was carried forward. If any value remained missing after this change, the median value for that location (ie, wards, ICU, or ED) was imputed.^{32,33} Additionally, patient-reported pain scores at the time of opioid administration were extracted from nursing flowsheets. If no pain score was present at the time of opioid administration, the patient's previous score was carried forward.

We excluded patients with sickle-cell disease or seizure history and admissions with diagnoses of alcohol withdrawal from the analysis, because these diagnoses were expected to be associated with different medication administration practices compared to other inpatients. We also excluded patients with a tracheostomy because we expected their respiratory monitoring to differ from the other patients in our cohort. Finally, because ward deaths resulting from a com-

fort care scenario often involve opioids and/or benzodiazepines, ward segments involving comfort care deaths (defined as death without attempted resuscitation) were excluded from the analysis (Supplemental Figure 1). Patients with sickle-cell disease were identified using ICD-9 codes, and encounters during which a seizure may have occurred were identified using a combination of ICD-9 codes and receipt of anti-epileptic medication (Supplemental Table 1). Patients at risk for alcohol withdrawal were identified by the presence of any Clinical Institute Withdrawal Assessment for Alcohol score within nursing flowsheets, and patients with tracheostomies were identified using documentation of ventilator support within their first 12 hours on the wards. In addition to these exclusion criteria, patients with obstructive sleep apnea (OSA) were identified by the following ICD-9 codes: 278.03, 327.23, 780.51, 780.53, and 780.57.

Medications

Ward administrations of opioids and benzodiazepines—dose, route, and administration time—were collected from the EHR. We excluded all administrations in nonward locations such as the ED, ICU, operating room, or procedure suite. Additionally, because patients emergently intubated may receive sedative and analgesic medications to facilitate intubation, and because patients experiencing cardiac arrest are frequently intubated periresuscitation, we a priori excluded all administrations within 15 minutes of a ward cardiac arrest or an intubation.

For consistent comparisons, opioid doses were converted to oral morphine equivalents³⁴ and adjusted by a factor of 15 to reflect the smallest routinely available oral morphine tablet in our hospital (Supplemental Table 2). Benzodiazepine doses were converted to oral lorazepam equivalents (Supplemental Table 2).³⁴ Thus, the independent variables were oral

TABLE 1. Characteristics of Patient Admissions During Which Opioids and Benzodiazepines Were and Were Not Administered

Patient Characteristics	Opioids			Benzodiazepines		
	Received (n = 80,463)	Never received (n = 40,055)	P value	Received (n = 25,279)	Never received (n = 95,239)	P value
Age, y (median, IQR)	56 (40-67)	61 (42-73)	<0.001	58 (47-68)	57 (38-69)	<0.001
Female, n (%)	46,244 (57.5)	22,479 (56.1)	<0.001	12,866 (50.9)	55,857 (58.7)	<0.001
Race, n (%)						
Black/African American	38,715 (48.1)	23,594 (58.9)	<0.001	10,539 (41.7)	51,770 (54.4)	<0.001
White	34,037 (42.3)	13,134 (32.8)	<0.001	12,706 (50.3)	34,465 (36.2)	<0.001
Asian	1733 (2.2)	956 (2.4)	0.01	532 (2.1)	2157 (2.3)	0.125
>1 race	1,247 (1.6)	511 (1.3)	<0.001	387 (1.5)	1,371 (1.4)	0.281
Race unknown	4731 (5.9)	1860 (4.6)	<0.001	1115 (4.4)	5476 (5.8)	<0.001
Location prior to wards, n (%)						
Operating room	14,139 (17.6)	2401 (6.0)	<0.001	1626 (6.4)	14,914 (15.7)	<0.001
Intensive care unit	8079 (10.0)	4343 (10.8)	<0.001	2408 (9.5)	10,014 (10.5)	<0.001
Emergency department	14,677 (18.2)	10,663 (26.6)	<0.001	5731 (22.7)	19,609 (20.6)	<0.001
Direct to wards	28,051 (34.9)	11,863 (29.6)	<0.001	12,151 (48.1)	27,763 (29.2)	<0.001
Procedure area	15,517 (19.3)	10,785 (26.9)	<0.001	3363 (13.3)	22,939 (24.1)	<0.001
BMI, n (%)						
Underweight (<18.5 kg/m ²)	4755 (5.9)	2302 (5.8)	0.258	1908 (7.6)	5149 (5.4)	<0.001
Normal (18.5-25 kg/m ²)	19,226 (23.9)	10,020 (25.0)	<0.001	6830 (27.0)	22,416 (23.5)	<0.001
Overweight (25-30 kg/m ²)	20,463 (25.4)	10,389 (25.9)	0.058	6598 (26.1)	24,254 (25.5)	0.04
Obese (30-40 kg/m ²)	21,886 (27.2)	10,266 (25.6)	<0.001	6060 (24.0)	26,092 (27.4)	<0.001
Superobese (>40 kg/m ²)	9219 (11.5)	4505 (11.3)	0.279	2261 (8.9)	11,463 (12.0)	<0.001
Initial ward eCART score (median, (IQR))	5 (3-10)	5 (3-10)	<0.001	5 (3-10)	5 (3-10)	<0.001
Elixhauser comorbidities						
Congestive heart failure	16,267 (20.2)	10,673 (26.7)	<0.001	6541 (25.9)	20,399 (21.4)	<0.001
Valvular disease	6715 (8.4)	3990 (10.0)	<0.001	2596 (10.3)	8109 (8.5)	<0.001
Pulmonary circulation disorder	5834 (7.3)	3328 (8.3)	<0.001	2181 (8.7)	6981 (7.3)	<0.001
Peripheral vascular disorder	8508 (10.6)	4288 (10.7)	0.485	3052 (12.1)	9744 (10.2)	<0.001
Hypertension, uncomplicated	38,666 (48.1)	20,206 (50.5)	<0.001	13,488 (55.4)	45,384 (47.7)	<0.001
Hypertension, complicated	16,544 (20.6)	10,100 (25.2)	<0.001	6300 (24.9)	20,344 (21.4)	<0.001
Paralysis	1883 (2.3)	1286 (3.2)	<0.001	847 (3.4)	2322 (2.4)	<0.001
Other neurological disorder	4045 (5.0)	3565 (8.9)	<0.001	1850 (7.3)	5760 (6.1)	<0.001
Chronic pulmonary disease	14,735 (18.3)	7620 (19.0)	0.003	4876 (19.3)	17,479 (18.4)	0.001
Diabetes, uncomplicated	19,455 (24.2)	10,886 (27.2)	<0.001	6936 (27.4)	23,405 (24.6)	<0.001
Diabetes, complicated	6957 (8.7)	3551 (8.9)	0.204	2458 (9.7)	8050 (8.5)	<0.001
Hypothyroidism	9724 (12.1)	4575 (11.4)	0.001	3759 (14.9)	10,540 (11.1)	<0.001
Renal failure	17,468 (21.7)	10,458 (26.1)	<0.001	6910 (27.3)	21,016 (22.1)	<0.001
Liver disease	6851 (8.5)	2689 (6.7)	<0.001	2879 (11.4)	6661 (7.0)	<0.001
Lymphoma	2364 (2.9)	1713 (4.3)	<0.001	1563 (6.2)	2514 (2.6)	<0.001
Metastatic cancer	14,612 (18.2)	4239 (10.6)	<0.001	6090 (24.1)	12,761 (13.4)	<0.001
Solid tumor, without metastasis	20,965 (26.1)	6137 (15.3)	<0.001	7968 (31.5)	19,134 (20.1)	<0.001
Collagen vascular disease	3927 (4.9)	1500 (3.7)	<0.001	1240 (4.9)	4187 (4.4)	0.001
Coagulopathy	13,855 (17.2)	6909 (17.3)	0.898	6561 (26.0)	14,203 (14.9)	<0.001
Obesity	13,010 (16.2)	5042 (12.6)	<0.001	3988 (15.8)	14,064 (14.8)	<0.001
Weight loss	13,115 (16.3)	4722 (11.8)	<0.001	6000 (23.7)	11,837 (12.4)	<0.001
Fluid and electrolyte disorder	34,444 (42.8)	17,493 (43.7)	0.004	14,668 (58.0)	37,269 (39.1)	<0.001
Blood loss anemia	7969 (9.9)	4,029 (10.1)	0.398	1832 (7.3)	10,166 (10.7)	<0.001
Deficiency anemia	904 (1.1)	459 (1.2)	0.729	398 (1.6)	965 (1.0)	<0.001
Alcohol abuse	4532 (5.6)	1950 (4.9)	<0.001	2138 (8.5)	4344 (4.6)	<0.001
Drug abuse	4919 (6.1)	1827 (4.6)	<0.001	1972 (7.8)	4774 (5.0)	<0.001
Psychoses	6709 (8.3)	2658 (6.6)	<0.001	3303 (13.1)	6064 (6.4)	<0.001
Depression	14,742 (18.3)	5113 (12.8)	<0.001	6861 (27.1)	12,994 (13.6)	<0.001
Obstructive sleep apnea	9518 (11.8)	4394 (11.0)	<0.001	3068 (12.1)	10,844 (11.4)	0.001

NOTE: Abbreviations: BMI, body mass index; eCART, Electronic Cardiac Arrest Risk Triage score; IQR, interquartile range.

morphine or lorazepam equivalents administered within each 6-hour window. We a priori presumed opioid doses greater than the 99th percentile (1200 mg) or benzodiazepine doses

greater than 10 mg oral lorazepam equivalents within a 6-hour window to be erroneous entries, and replaced these outlier values with the median value for each medication category.

Outcomes

The primary outcome was the composite of ICU transfer or cardiac arrest (loss of pulse with attempted resuscitation) on the wards, with individual outcomes investigated secondarily. An ICU transfer (patient movement from a ward directly to the ICU) was identified using the hospital's admission-transfer-discharge database. Cardiac arrests were identified using a prospectively validated quality improvement database.³⁵

Because deaths on the wards resulted either from cardiac arrest or from a comfort care scenario, mortality was not studied as an outcome.

Statistical Analysis

Patient characteristics were compared using Student *t* tests, Wilcoxon rank sum tests, and chi-squared statistics, as appropriate. Unadjusted and adjusted models were created using discrete-time survival analysis,³⁶⁻³⁹ which involved dividing time into discrete 6-hour intervals and employing the predictor variables chronologically closest to the beginning of each time window to forecast whether the outcome occurred within each interval. Predictor variables in the adjusted model included patient characteristics (age, sex, BMI, and Elixhauser Agency for Healthcare Research and Quality-Web comorbidities³⁰ [a priori excluding comorbidities recorded for fewer than 1000 admissions from the model]), ward unit, surgical status, prior ICU admission during the hospitalization, cumulative opioid or benzodiazepine dose during the previous 24 hours, and severity of illness (measured by eCART score). The adjusted model for opioids also included the patient's pain score. Age, eCART score, and pain score were entered linearly while race, BMI (underweight, less than 18.5 kg/m²; normal, 18.5-24.9 kg/m²; overweight, 25.0-29.9 kg/m²; obese, 30-39.9 kg/m²; and severely obese, 40 kg/m² or greater), and ward unit were modeled as categorical variables.

Since repeat hospitalization could confound the results of our study, we performed a sensitivity analysis including only 1 randomly selected hospital admission per patient. We also performed a sensitivity analysis including receipt of both opioids and benzodiazepines, and an interaction term within each ward segment, as well as an analysis in which zolpidem—the most commonly administered nonbenzodiazepine hypnotic medication in our hospital—was included along with both opioids and benzodiazepines. Finally, we performed a sensitivity analysis replacing missing pain scores with imputed values ranging from 0 to the median ward pain score.

We also performed subgroup analyses of adjusted models across age quartiles and for each BMI category, as well as for surgical status, OSA status, gender, time of medication administration, and route of administration (intravenous vs. oral). We also performed an analysis across pain score severity⁴⁰ to determine whether these medications produce differential effects at various levels of pain.

All tests of significance used a 2-sided *P* value less than 0.05. Statistical analyses were completed using Stata version 14.1 (StataCorp, LLC, College Station, Texas).

RESULTS

Patient Characteristics

A total of 144,895 admissions, from 75,369 patients, had ward vital signs or laboratory values documented during the study period. Ward segments from 634 admissions were excluded due to comfort care status, which resulted in exclusion of 479 complete patient admissions. Additionally, 139 patients with tracheostomies were excluded. Furthermore, 2934 patient admissions with a sickle-cell diagnosis were excluded, of which 95% (*n* = 2791) received an opioid and 11% (*n* = 310) received a benzodiazepine. Another 14,029 admissions associated with seizures, 6134 admissions involving alcohol withdrawal, and 1332 with both were excluded, of which 66% (*n* = 14,174) received an opioid and 35% (*n* = 7504) received a benzodiazepine. After exclusions, 120,518 admissions were included in the final analysis, with 67% (*n* = 80,463) associated with at least 1 administration of an opioid and 21% (*n* = 25,279) associated with at least 1 benzodiazepine administration.

In total, there were 672,851 intervals when an opioid was administered during the study, with a median dose of 12 mg oral morphine equivalents (interquartile range, 8-30). Of these, 21,634 doses were replaced due to outlier status outside the 99th percentile. Patients receiving opioids were younger (median age 56 vs 61 years), less likely to be African American (48% vs 59%), more likely to have undergone surgery (18% vs 6%), and less likely to have most noncancer medical comorbidities than those who never received an opioid (all *P* < 0.001) (Table 1).

Additionally, there were a total of 98,286 6-hour intervals in which a benzodiazepine was administered in the study, with a median dose of 1 mg oral lorazepam (interquartile range, 0.5-1). A total of 790 doses of benzodiazepines (less than 1%) were replaced due to outlier status. Patients who received benzodiazepines were more likely to be male (49% vs. 41%), less likely to be African-American, less likely to be obese or morbidly obese (33% vs. 39%), and more likely to have medical comorbidities compared to patients who never received a benzodiazepine (all *P* < 0.001) (Table 1).

The eCART scores were similar between all patient groups. The frequency of missing variables differed by data type, with vital signs rarely missing (all less than 1.1% except AVPU [10%]), followed by hematology labs (8%-9%), electrolytes and renal function results (12%-15%), and hepatic function tests (40%-45%). In addition to imputed data for missing vital signs and laboratory values, our model omitted human immunodeficiency virus/acquired immune deficiency syndrome and peptic ulcer disease from the adjusted models on the basis of fewer than 1000 admissions with these diagnoses listed.

Patient Outcomes

The incidence of the composite outcome was higher in admissions with at least 1 opioid medication than those without an opioid (7% vs. 4%, *P* < 0.001), and in admissions with at least 1 dose of benzodiazepines compared to those without

TABLE 2. Unadjusted Ward Outcome Rates for Patient Admissions With and Without Opioid or Benzodiazepine Administration

Outcomes, n (%)	Opioids			Benzodiazepines		
	Received (n = 80,463)	Never received (n = 40,055)	P value	Received (n = 25,279)	Never received (n = 95,239)	P value
Composite	5230 (7)	1427 (4)	<0.001	2739 (11)	3918 (4)	<0.001
ICU transfer	5177 (6)	1399 (4)	<0.001	2708 (11)	3868 (4)	<0.001
Ward cardiac arrest	174 (0.2)	70 (0.2)	0.135	87 (0.3)	157 (0.2)	<0.001

NOTE: Abbreviation: ICU, intensive care unit.

TABLE 3. Adjusted Odds of Clinical Deterioration Outcomes Within Six Hours of Receiving an Opioid or Benzodiazepine^a

Outcome	Opioids		Benzodiazepines	
	OR (95% CI)	P value	OR (95% CI)	P value
Composite	1.019 (1.013-1.026)	<0.001	1.29 (1.16-1.45)	<0.001
ICU transfer	1.019 (1.013-1.026)	<0.001	1.29 (1.14-1.43)	<0.001
Ward cardiac arrest	1.020 (0.985-1.057)	0.26	2.36 (1.43-3.90)	0.001

^aAdjustment includes patient characteristics, ward unit, surgical status, prior ICU admission, 24-hour cumulative opioid/benzodiazepine dose, and eCART score.

NOTE: Odds ratios reflect the change in odds associated with the equivalent of 15 mg oral morphine or 1 mg oral lorazepam. Abbreviations: eCART, Electronic Cardiac Arrest Risk Triage score; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.

a benzodiazepine (11% vs. 4%, $P < 0.001$) (Table 2).

Within 6-hour segments, increasing doses of opioids were associated with an initial decrease in the frequency of the composite outcome followed by a dose-related increase in the frequency of the composite outcome with morphine equivalents greater than 45 mg. By contrast, the frequency of the composite outcome increased with additional benzodiazepine equivalents (Figure).

In the adjusted model, opioid administration was associated with increased risk for the composite outcome (Table 3) in a dose-dependent fashion, with each 15 mg oral morphine equivalent associated with a 1.9% increase in the odds of ICU transfer or cardiac arrest within the subsequent 6-hour time interval (odds ratio [OR], 1.019; 95% confidence interval [CI], 1.013-1.026; $P < 0.001$).

Similarly, benzodiazepine administration was also associated with increased adjusted risk for the composite outcome within 6 hours in a dose-dependent manner. Each 1 mg oral lorazepam equivalent was associated with a 29% increase in the odds of ward cardiac arrest or ICU transfer (OR, 1.29; 95% CI, 1.16-1.44; $P < 0.001$) (Table 3).

Sensitivity Analyses

A sensitivity analysis including 1 randomly selected hospitalization per patient involved 67,097 admissions and found results similar to the primary analysis, with each 15 mg oral morphine equivalent associated with a 1.9% increase in the odds of the composite outcome (OR, 1.019; 95% CI, 1.011-1.028; $P < 0.001$) and each 1 mg oral lorazepam equivalent associated with a 41% increase in the odds of the composite outcome (OR, 1.41; 95% CI, 1.21-1.65; $P < 0.001$). Inclusion of both opioids and benzodiazepines in the adjusted model

again yielded results similar to the main analysis for both opioids (OR, 1.020; 95% CI, 1.013-1.026; $P < 0.001$) and benzodiazepines (OR, 1.35; 95% CI, 1.18-1.54; $P < 0.001$), without a significant interaction detected ($P = 0.09$). These results were unchanged with the addition of zolpidem to the model as an additional potential confounder, and zolpidem did not increase the risk of the study outcomes ($P = 0.2$).

A final sensitivity analysis for the opioid model involved replacing missing pain scores with imputed values ranging from 0 to the median ward score, which was 5. The results of these analyses did not differ from the primary model and were consistent regardless of imputation value (OR, 1.018; 95% CI, 1.012-1.023; $P < 0.001$).

Subgroup Analyses

Analyses of opioid administration by subgroup (sex, age quartiles, BMI categories, OSA diagnosis, surgical status, daytime/nighttime medication administration, IV/PO administration, and pain severity) yielded similar results to the overall analysis (Supplemental Figure 2). Subgroup analysis of patients receiving benzodiazepines revealed similarly increased adjusted odds of the composite outcome across strata of gender, BMI, surgical status, and medication administration time (Supplemental Figure 3). Notably, patients older than 70 years who received a benzodiazepine were at 64% increased odds of the composite outcome (OR, 1.64; 95% CI, 1.30-2.08), compared to 2% to 38% increased risk for patients under 70 years. Finally, IV doses of benzodiazepines were associated with 48% increased odds for deterioration (OR, 1.48; 95% CI, 1.18-1.84; $P = 0.001$), compared to a nonsignificant 14% increase in the odds for PO doses (OR, 1.14; 95% CI, 0.99-1.31; $P = 0.066$).

DISCUSSION

In a large, single-center, observational study of ward inpatients, we found that opioid use was associated with a small but significant increased risk for clinical deterioration on the wards, with every 15 mg oral morphine equivalent increasing the odds of ICU transfer or cardiac arrest in the next 6 hours by 1.9%. Benzodiazepines were associated with a much higher risk: each equivalent of 1 mg of oral lorazepam increased the odds of ICU transfer or cardiac arrest by almost 30%. These results have important implications for care at the bedside of hospitalized ward patients and suggest the need for closer monitoring after receipt of these medications, particularly benzodiazepines.

Previous work has described negative effects of opioid medications among select inpatient populations. In surgical patients, opioids have been associated with hospital readmission, increased length of stay, and hospital mortality.^{26,28} More recently, Herzig et al.¹⁵ found more adverse events in nonsurgical ward patients within the hospitals prescribing opioids the most frequently. These studies may have been limited by the populations studied and the inability to control for confounders such as severity of illness and pain score. Our study expands these findings to a more generalizable population and shows that even after adjustment for potential confounders, such as severity of illness, pain score, and medication dose, opioids are associated with increased short-term risk of clinical deterioration.

By contrast, few studies have characterized the risks associated with benzodiazepine use among ward inpatients. Recently, Overdyk et al.²⁷ found that inpatient use of opioids and sedatives was associated with increased risk for cardiac arrest and hospital death. However, this study included ICU patients, which may confound the results, as ICU patients often receive high doses of opioids or benzodiazepines to facilitate mechanical ventilation or other invasive procedures, while also having a particularly high risk of adverse outcomes like cardiac arrest and in-hospital death.

Several mechanisms may explain the magnitude of effect seen with regard to benzodiazepines. First, benzodiazepines may directly produce clinical deterioration by decreased respiratory drive, diminished airway tone, or hemodynamic decompensation. It is possible that the broad spectrum of cardiorespiratory side effects of benzodiazepines—and potential unpredictability of these effects—increases the difficulty of observation and management for patients receiving them. This difficulty may be compounded with intravenous administration of benzodiazepines, which was associated with a higher risk for deterioration than oral doses in our cohort. Alternatively, benzodiazepines may contribute to clinical decompensation by masking signs of deterioration such as encephalopathy or vital sign instability like tachycardia or tachypnea that may be mistaken as anxiety. Notably, while our hospital has a nursing-driven protocol for monitoring patients receiving opioids (in which pain is serially assessed, leading to additional bedside observation), we do

not have protocols for ward patients receiving benzodiazepines. Finally, although we found that orders for opioids and benzodiazepines were more common in white patients than African American patients, this finding may be due to differences in the types or number of medical comorbidities experienced by these patients.

Our study has several strengths, including the large number of admissions we included. Additionally, we included a broad range of medical and surgical ward admissions, which should increase the generalizability of our results. Further, our rates of ICU transfer are in line with data reported from other groups,^{41,42} which again may add to the generalizability of our findings. We also addressed many potential confounders by including patient characteristics, individual ward units, and (for opioids) pain score in our model, and by controlling for severity of illness with the eCART score, an accurate predictor of ICU transfer and ward cardiac arrest within our population.^{32,37} Finally, our robust methodology allowed us to include acute and cumulative medication doses, as well as time, in the model. By performing a discrete-time survival analysis, we were able to evaluate receipt of opioids and benzodiazepines—as well as risk for clinical deterioration—longitudinally, lending strength to our results.

Limitations of our study include its single-center cohort, which may reduce generalizability to other populations. Additionally, because we could not validate the accuracy of—or adherence to—outpatient medication lists, we were unable to identify chronic opioid or benzodiazepine users by these lists. However, patients chronically taking opioids or benzodiazepines would likely receive doses each hospital day; by including 24-hour cumulative doses in our model, we attempted to adjust for some portion of their chronic use. Also, because evaluation of delirium was not objectively recorded in our dataset, we were unable to evaluate the relationship between receipt of these medications and development of delirium, which is an important outcome for hospitalized patients. Finally, neither the diagnoses for which these medications were prescribed, nor the reason for ICU transfer, were present in our dataset, which leaves open the possibility of unmeasured confounding.

CONCLUSION

After adjustment for important confounders including severity of illness, medication dose, and time, opioids were associated with a slight increase in clinical deterioration on the wards, while benzodiazepines were associated with a much larger risk for deterioration. This finding raises concern about the safety of benzodiazepine use among ward patients and suggests that increased monitoring of patients receiving these medications may be warranted.

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