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BRIEF REPORT

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Opioid and benzodiazepine prescribing after COVID-19 hospitalization

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Abstract

Opioid and benzodiazepine prescribing after COVID-19 hospitalization is not well understood. We aimed to characterize opioid and benzodiazepine prescribing among naïve patients hospitalized for COVID and to identify the risk factors associated with a new prescription at discharge. In this retrospective study of patients across 39 Michigan hospitals from March to November 2020, we identified 857 opioid- and benzodiazepine-naïve patients admitted with COVID-19 not requiring mechanical ventilation. Of these, 22% received opioids, 13% received benzodiazepines, and 6% received both during the hospitalization. At discharge, 8% received an opioid prescription, and 3% received a benzodiazepine prescription. After multivariable adjustment, receipt of an opioid or benzodiazepine prescription at discharge was associated with the length of inpatient opioid or benzodiazepine exposure. These findings suggest that hospitalization represents a risk of opioid or benzodiazepine initiation among naïve patients, and judicious prescribing should be considered to prevent opioid-related harms.

Registration: Exempt by University of Michigan IRB (HUM00179611).

INTRODUCTION

Opioid prescribing during inpatient and perioperative care is associated with long-term opioid-related harms.[1–4] Although focus on prescribing of opioid and benzodiazepines has recently increased, little is known regarding prescribing patterns following admission for COVID-19.[3,5] COVID-19 has resulted in the hospitalization of millions of Americans, many of whom are without prior health conditions, and are opioid- and benzodiazepine-naïve.[6] Current evidence regarding prescribing in the setting of COVID-19 is limited to palliative and hospice care, and may not represent patients with high probability of survival and discharge.[7,8] Moreover, the majority of data regarding opioid prescribing are drawn from claims, which does not capture inpatient prescribing and its association with discharge prescriptions. In this statewide study, we examine data from hospitalized COVID-19 patients to evaluate the relationship between inpatient opioid and benzodiazepine exposure and a prescription at discharge, as well as characterize the patient and hospital factors prompting initiation. Understanding prescribing among opioid- and benzodiazepine-naïve COVID-19 patients can inform best practices for disease management and coordination of care after discharge.

METHODS

MI-COVID19 is a statewide collaborative quality initiative sponsored by the Blue Cross Blue Shield of Michigan and Blue Care Network, made up by 39 diverse, nonfederal hospitals. Trained abstractors collected data on a sample of hospitalized COVID-19 patients via medical record review using a standardized data dictionary and operations manual adapted from the Michigan Hospital Medicine Safety Consortium, and entered data into the MI-COVID19 registry using a structured data collection template.[9]

Patients were identified if they displayed signs and symptoms of COVID-19 on admission, and the final criteria for enrollment required a diagnosis of COVID-19 as defined through either a positive test, ICD10 code (U07.1), or documentation of strong clinical suspicion when tests were unavailable. We excluded patients who were not opioid- or benzodiazepine-naïve prior to hospitalization, defined by documentation of a prescription fill for either medication in the 30 days prior to admission. This included outpatient notes, documentation in the medication administration record (MAR), or medication lists. Patients were excluded if they required mechanical ventilation, due to the pain control requirements of invasive ventilation, and to mitigate the inclusion of patients undergoing procedural care (Supporting Information: Appendix Figure 1).

The primary outcome was receipt of an opioid or benzodiazepine prescription at discharge. The secondary outcome was exposure to opioid or benzodiazepine during the hospitalization. "Any exposure" was defined as opioid or benzodiazepine administration on at least one day of hospitalization, and "length of exposure" was defined as the total number of days with an opioid or benzodiazepine administered. Inpatient prescription data were abstracted from the MAR. The included medications are detailed in Supporting Information: Appendix Table 1.

Variables of interest included patient age, sex, body mass index, comorbidities, Charlson comorbidity index, highest level of care during hospitalization, disease severity as indicated by oxygenation requirements, and length of stay. Hospital characteristics were abstracted from the American Hospital Association Annual Survey Database.

Unadjusted comparisons between patients discharged with and without an opioid or benzodiazepine prescription were performed using Student's t test or χ^2 tests. Separate hierarchical logistic regression models examined the relationship between inpatient opioid or benzodiazepine exposure and a discharge prescription for an opioid or benzodiazepine, accounting for the clustering of patients within hospitals. The final parsimonious regression models were selected to include variables that were clinically relevant or statistically significant while the model fit was assessed. Multicollinearity between independent variables was assessed, and variance inflation factors were between 1 and 3.4.

RESULTS

Of 1165 patients hospitalized with COVID-19, 77% ($n = 899$) were opioid- and benzodiazepine-naïve. After excluding 42 (4.7%) patients with mechanical ventilation, a total of 857 patients admitted for the management of COVID-19 from March 6th to November 11th, 2020, were included in the cohort. Positive COVID-19 tests were present among 533 (62.2%) patients, with the rest of the patients identified with clinical documentation or billing codes. The majority of primary diagnoses were infectious (48%) and respiratory (28%) diseases, and secondary diagnoses were respiratory (41%) and infectious (20%) diseases. In this cohort, 443 patients (51.7%) were male, with a mean age of 60 years (SD = 16.1), and the mean length of stay was 4.9 days (SD = 3.8) (Table 1).

During the admission, 186 patients (21.7%) received opioid medications and 113 patients (13.2%) received a benzodiazepine, ranging from 0 to 21 days and 0 to 11 days, respectively (Table 1). In addition, 51 patients received both an opioid and a benzodiazepine during the hospitalization. Opioids were administered to 22.1% (n = 17) of the patients in observation status, 17.9% (n = 76) of patients in step-down units, 17.9% (n = 62) of patients in general care, and 30.1% (n = 31) of patients in intensive care units. Opioid receipt did not vary across oxygen requirements ($p = 0.61$). Similarly, new benzodiazepine exposure did not differ across levels of care ($p = 0.264$), or oxygen requirements ($p = 0.504$).

At discharge, 7.8% (n = 67) of the patients were discharged with an opioid, 2.6% (n = 22) with a benzodiazepine, and 0.5% (n = 4) with both (Appendix Table 2). Of patients discharged with an opioid, 16 patients (24%) did not receive opioids during admission (Appendix Table 3). Of the 22 patients discharged with a benzodiazepine, 8 (36.3%) did not receive benzodiazepines during hospitalization.

TABLE 1 Patient characteristics and comparison of inpatient exposure to an opioid and benzodiazepine prescription

	All patients (*N* = 857) No. of cases (% total)	Opioid prescription during admission (*N* = 186) No. of cases (%)	*p* Value	Benzodiazepine prescription during admission (*N* = 113) No. of cases (%)	*p* Value
Discharge prescription					
Opioid	67 (7.8)	51 (27.4)	<0.001	13 (11.5)	0.117
Benzodiazepine	22 (2.6)	17 (2.5)	0.014	14 (12.4)	<0.001
Age, *mean (SD)*	60 (16.1)	57 (16)	0.009	57 (16.2)	0.07
Sex					
Female	414 (48.3)	89 (47.9)	0.888	55 (48.7)	0.934
Male	443 (51.7)	97 (52.2)		58 (51.3)	
Race					
White	442 (51.6)	98 (52.7)	0.483	70 (62)	0.032
Black	258 (30.1)	50 (26.9)		23 (20.4)	
Others/Unknown	157 (18.3)	38 (20.4)		20 (17.7)	
BMI, *mean (SD)*	31.8 (8.4)	30.5 (7.5)	0.013	30.5 (7.5)	0.062
Charlson CI, *median (range)*	1 (0-6)	1 (0-6)	0.205	1 (0-6)	0.998
Highest level of care					
Observation	77 (9)	17 (9.1)	0.029	8 (7.1)	0.264
General care	424 (49.5)	76 (40.9)		50 (44.3)	
Step-down	253 (29.5)	62 (33.3)		36 (31.9)	
Intensive care unit	103 (12)	31 (16.7)		19 (16.8)	
Any benzodiazepine amount during hospitalization	113 (13.2)	51 (27.4)	<0.001	51 (45.1)	<0.001
Comorbidities					
Past or present smoker	373 (43.5)	83 (44.6)	0.732	64 (56.6)	0.003
Mental disorders	34 (4)	4 (2.2)	0.151	13 (11.5)	<0.001
COPD	116 (13.5)	21 (11.3)	0.312	19 (16.8)	0.274
CKD	189 (22.1)	39 (21)	0.686	13 (11.5)	0.004
Respiratory support					
No supplementary O_2	364 (42.5)	82 (44.1)	0.061	49 (43.4)	0.504
Low-flow NC	422 (49.2)	85 (45.7)		51 (45.1)	
Heated high flow NC	57 (6.7)	12 (6.5)		11 (9.7)	
Noninvasive PPV	14 (1.6)	7 (3.8)		2 (1.8)	
Length of stay, *median (range)*	4 (0-35)	4 (1-24)	0.004	5 (1-35)	0.008
ICU days *median (range)*	0 (0-20)	0 (0-20)	0.015	0 (0-20)	0.003
Hospital characteristics					
Teaching hospital	744 (86.8)	167 (89.8)	0.176	92 (81.4)	0.069
Bed size, *mean (SD)*	422 (10.6)	383.3 (22)	0.153	398 (283.5)	0.375

(Continued)

TABLE 1 (Continued)

	All patients (*N* = 857) No. of cases (% total)	Opioid prescription during admission (*N* = 186) No. of cases (%)	*p* Value	Benzodiazepine prescription during admission (*N* = 113) No. of cases (%)	*p* Value
Ownership					
Not for profit	814 (95)	174 (93.6)	0.311	106 (93.8)	0.538
For profit	43 (5)	31 (4.6)		7 (6.2)	

All statistical tests were 2-sided, and *p*-values less than .05 were significant. Categorical variables (Sex, Race, Highest Level of Care, Any Benzodiazepine amount during hospitalization, Smoker, Mental Disorders, COPD, CKD, Respiratory Support, Teaching Hospital, Hospital Ownership) were analyzed using chi-squared tests. Continuous variables (Age, BMI, Charlson Comorbidity Index, Length of Stay, ICU Days, Bed Size) were analyzed using student's t-test. Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

TABLE 2 Adjusted odds of discharge with an opioid or benzodiazepine prescription

	Discharge with Opioid		Discharge with Benzodiazepine	
	aOR (95%CI)	*p* Value	aOR (95% CI)	*p* Value
Inpatient opioid exposure	4.47 (1.96-10.23)	<0.001	6.35 (1.81-22.28)	0.004
Days with opioid prescription	1.63 per day (1.34-1.98)	<0.001	1.34 per day (1.01-1.77)	0.041
Length of stay	0.75 per day (0.65-0.86)	<0.001	0.95 per day (0.83-1.09)	0.449
Highest level of care (ref: Observation)				
General Care	1.6 (0.54-4.73)	0.399	1.76 (0.2-15.7)	0.614
Step-down	1.22 (0.39-3.8)	0.729	4.49 (0.49-41.3)	0.184
Intensive Care Unit	1.91 (0.47-7.67)	0.364	1.2 (0.09-16.79)	0.893
Charlson Comorbidity Index*	1.23 (0.9-1.69)	0.198	-	-
Teaching hospital*	3.35 (0.78-14.32)	0.104	-	-
Female (ref: Male)*	-	-	9.24 (2.56-33.42)	0.001

*Covariates only included in only one of the multivariable regression models.

After multivariable adjustment, inpatient opioid exposure was associated with receipt of a prescription at discharge (OR 4.47, 95% CI 1.96-10.23) (Table 2). Each additional day of inpatient opioid receipt was associated with higher odds of an opioid prescription at discharge (OR 1.63, 95% CI 1.34-1.98). Inpatient benzodiazepine exposure (OR 6.35, 95% CI 1.81-22.28) and length of exposure (OR 1.34, 95% CI 1.01-1.77) were both associated with an increased odds of a benzodiazepine prescription at discharge (Table 2).

DISCUSSION

Among COVID-19 patients hospitalized from March to November 2020, over 20% of patients were newly exposed to opioids, 13% were newly exposed to benzodiazepines, and 6% were exposed to both during hospitalization. Overall, 8% of patients received a new opioid prescription at discharge, and inpatient opioid exposure was associated with a four-fold higher odds of receiving a discharge prescription. Benzodiazepine exposure during admission was associated with a six-fold higher odds of a discharge prescription.

Opioid administration during hospitalization has been shown to be associated with a discharge prescription. Reported rates of a discharge opioid prescription range from 15% to 19% among opioid-naïve Medicare beneficiaries and up to 29% among all patients of one safety-net hospital.[1,3,10] We identified a slightly lower rate, with 8% of patients receiving a new opioid prescription at discharge. It is possible that clinicians have appropriately reduced prescribing among patients with respiratory illness, particularly in response to initiatives to enhance opioid stewardship. However, 22% of individuals were exposed to opioids during hospitalization. Although the indications

are difficult to discern, there are very few acute or chronic pain conditions where opioids are the first-line treatment.[11,12] Additionally, opioids and benzodiazepines are not recommended for COVID-19 patients due to the risk of respiratory impairment, and respiratory failure is an independent risk factor for opioid-related adverse events.[13–15] Furthermore, any exposure is a risk factor for future use and dependence.[3,5,16] Notably, 24% of patients who received an opioid prescription at discharge did not receive opioids during the hospitalization. Previous work suggests that individuals who do not consume opioids in the 24-48 hours before discharge need few, if any, at discharge.[17] To date, benzodiazepine prescribing for COVID-19 patients has only been described in the context of palliative care.[7,18] In our cohort, 13% of patients were administered a benzodiazepine during hospitalization and 2.6% received a new prescription at discharge. These findings align with other reports of prescribing during COVID-19 care, and contribute a unique assessment across 39 hospitals during an early period of the pandemic.[7,8]

The rate of new opioid or benzodiazepine starts among naïve individuals in this cohort is notable. Opioid alternatives alongside multimodal pain control strategies should be prioritized during hospitalization and opioid weaning should be considered prior to discharge. Patient-centered approaches to limit discharge opioid prescriptions, such as tailoring discharge prescriptions to inpatient requirements, have been shown to effectively control pain and reduce excessive prescribing.[17,19] In addition, screening for risk factors, such as anxiety and depression, that might potentiate prolonged use should be considered.

Our study has several limitations. First, opioid-naïve status was defined using a 30-day opioid-free period, which is less conservative than other definitions.[2] However, many Michigan insurance policies prevent opioid prescriptions for over 30 days, and we expect that this window captures most current users.[20] Additionally, discharge prescriptions are not equivalent to consumption. However, prescription size correlates with use, and the focus of this study was provider prescribing habits.[21] Although the prescription indications are unknown, the majority of primary diagnoses were infectious or respiratory related. Data on procedural interventions in this cohort are unavailable, and we excluded those with a record of mechanical ventilation in our cohort across care settings to capture only nonsurgical patients. Lastly, additional factors that affect the relationship between inpatient and discharge prescribing may be unavailable in this data set.

In this cohort of COVID-19 patients across hospitals in Michigan, new exposure to opioids and/or benzodiazepines is common, and discharge prescriptions are correlated with inpatient administration. Future efforts should aim to ensure that discharge prescriptions adhere to best practices in safe opioid stewardship, and that strong care transitions with consistent follow-up are prioritized.

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CONFLICTS OF INTEREST

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PRIOR PRESENTATIONS

None

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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