Prescribing of Z-Drugs With and Without Opioid Coprescribing to Primary Care Patients in a Large Health Care System From 2019–2020

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Abstract

Objective: This study aimed to characterize Z-drug prescribing with and without opioid coprescribing pre- and post-COVID-19 lockdown in the primary care clinics of a large health care system.

Methods: A retrospective, cross-sectional study was conducted that measured the prevalence of Z-drug prescribing with and without opioids for adults aged ≥18 years that were seen in the primary care clinics of a large health care system in 2019 and 2020. The pre-COVID time period was defined as March 24, 2019–December 31, 2019, and the post-lockdown time period was defined as March 24, 2020–December 31, 2020.

Results: Among 455,537 adult patients, 6,743 (1.48%) were prescribed a Z-drug during the study period. In addition, 1,064 (0.2%) were coprescribed a Z-drug and an opioid at least once, constituting 15.78% of patients receiving a Z-drug prescription. There was no change in the rate of Z-drug prescription post-lockdown (odds ratio [OR] = 0.978, 95% confidence interval [CI] = 0.942–1.010, $P = .233$), though odds of coprescribing decreased (OR = 0.883, 95% CI = 0.789–0.988, $P = .031$). Important correlates of receiving a Z-drug prescription during the study period were older age, White race, and diagnosis of opioid use disorder. Older age and a diagnosis of opioid use disorder were also associated with coprescribing. Receiving a de novo Z-drug prescription post-lockdown was associated with increased age, White race, and diagnosis of bipolar disorder, generalized anxiety disorder, and insomnia.

Conclusions: Rates of Z-drug prescribing were unchanged post-lockdown, while rates of Z-drug with opioid coprescribing decreased. Some patient populations vulnerable to Z-drug adverse effects were at heightened risk of Z-drug prescription, while racial disparities in Z-drug prescribing were observed.

J Clin Psychiatry 2023;84(6):22m14753

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Insomnia is a frequently encountered clinical problem that is often treated pharmacologically, with data from the 2020 National Health Interview Survey indicating 18.4% of American adults used a sleep medication at least once in the past month.[1] Nonbenzodiazepine sedative-hypnotics or "Z-drugs" are primarily used to treat insomnia and were initially marketed as safer alternatives to benzodiazepines for this frequently encountered clinical condition.[2] However, Z-drug safety has been called into question in multiple pharmacovigilance studies due to clinically important adverse effects, including addiction, bradypnea, dependence, dizziness, cortical dysfunction, disruptive sleep-related disorders (parasomnias, sleepwalking, and sleep-driving), euphoria, falls, overdose, and withdrawal.[3–6] Long-term Z-drug prescribing presents the most risk for patients, particularly older adults, due to falls and fractures.[7] Coprescription of Z-drugs with opioids,[8] which sometimes occurs given the complex relationship between pain and sleep, raises additional safety concerns given increased risk of lethal respiratory depression.[9]

Recent studies have highlighted increased psychological distress and sleep problems worldwide during the early COVID-19 pandemic.[10,11] Perhaps, then, it is unsurprising that a 2021 study reported Z-drug prescribing had increased across the US health care system during the early COVID-19 pandemic.[12] Notably, new-onset pain is associated with COVID-19 infection, and the emotional distress inflicted by the pandemic appears to have exacerbated chronic pain for some patients.[13] As a result, it is possible that Z-drug and opioid coprescribing may

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Clinical Points

- From 2019 to 2020, pre- and post-COVID-19 lockdown, the odds of coprescribing of Z-drugs and opioids decreased post-lockdown.
- Patients of increasing age were at higher risk of receiving Z-drug prescriptions with and without opioids and had higher odds of receiving Z-drug prescriptions de novo post-lockdown.
- Non-Whites had decreased odds of receiving Z-drug prescriptions through the period and de novo post-lockdown than Whites.

have increased during the early COVID-19 pandemic, though we are unaware of studies investigating this issue. Overall, opioid analgesic prescribing appears to have dipped during the early months of the pandemic for opioid-naïve patients before rebounding, while remaining steady for patients already prescribed opioids.[14]

Given that most Z-drugs are prescribed by primary care providers[15] and the lack of data on changes in Z-drug prescribing by primary care providers during the early COVID-19 pandemic, as well as a lack of data on changes in Z-drug and opioid coprescribing in any setting during this time frame, we sought to investigate Z-drug prescribing with and without opioid coprescribing in the primary care clinics of a large health care system from 2019 to 2020. Specifically, we aimed to estimate rates of Z-drug prescribing and opioid coprescribing over the entire study period (2019–2020) as well as during each of the periods before and after the beginning of the COVID-19 pandemic. We also sought to examine which patient and clinical characteristics were associated with Z-drug prescribing and opioid coprescribing during the entire study period. Finally, we also wanted to examine which patient and clinical characteristics were associated with de novo Z-drug prescription after the COVID-19 pandemic began.

METHODS

Setting and Study Sample

Cleveland Clinic Healthcare System (CCHS) currently provides primary care services to approximately 1 million patients who are insured via employer-based plans, Medicaid, Medicare, and individual plans. The analytic sample included all adult patients (≥ 18 years) with at least 1 primary care visit at CCHS from January 1, 2019, to December 31, 2020.

Statistical Analysis Definitions

All available prescription Z-drugs (zolpidem, zaleplon, zopiclone, and eszopiclone) were analyzed as a group. Receipt of a Z-drug or opioid prescription was defined as being prescribed a drug from one of these classes for at least 1 day. Coprescribing was defined as receipt of an opioid prescription (hydrocodone, hydromorphone, morphine, oxycodone, and tramadol) within 30 days of a Z-drug prescription. The pre-COVID time period was defined as March 24, 2019–December 31, 2019, and the post-COVID time period was defined as March 24, 2020–December 31, 2020, given the COVID-19 lockdown date of March 24, 2020, in Ohio. For analyses examining prescriptions before and after the beginning of the COVID-19 pandemic, we excluded patient appointments between January 1 and March 23 from each year in order to remove the confounding effects of the interim period of early 2020 when COVID-19 had begun to spread in the United States. Z-drug prescription rates were computed as the number of patients prescribed at least 1 Z-drug during the specified period by a primary care provider divided by the number of patients who had at least 1 primary care visit during the specified period (eg, entire study period, pre-COVID, post-COVID).

Statistical Analysis

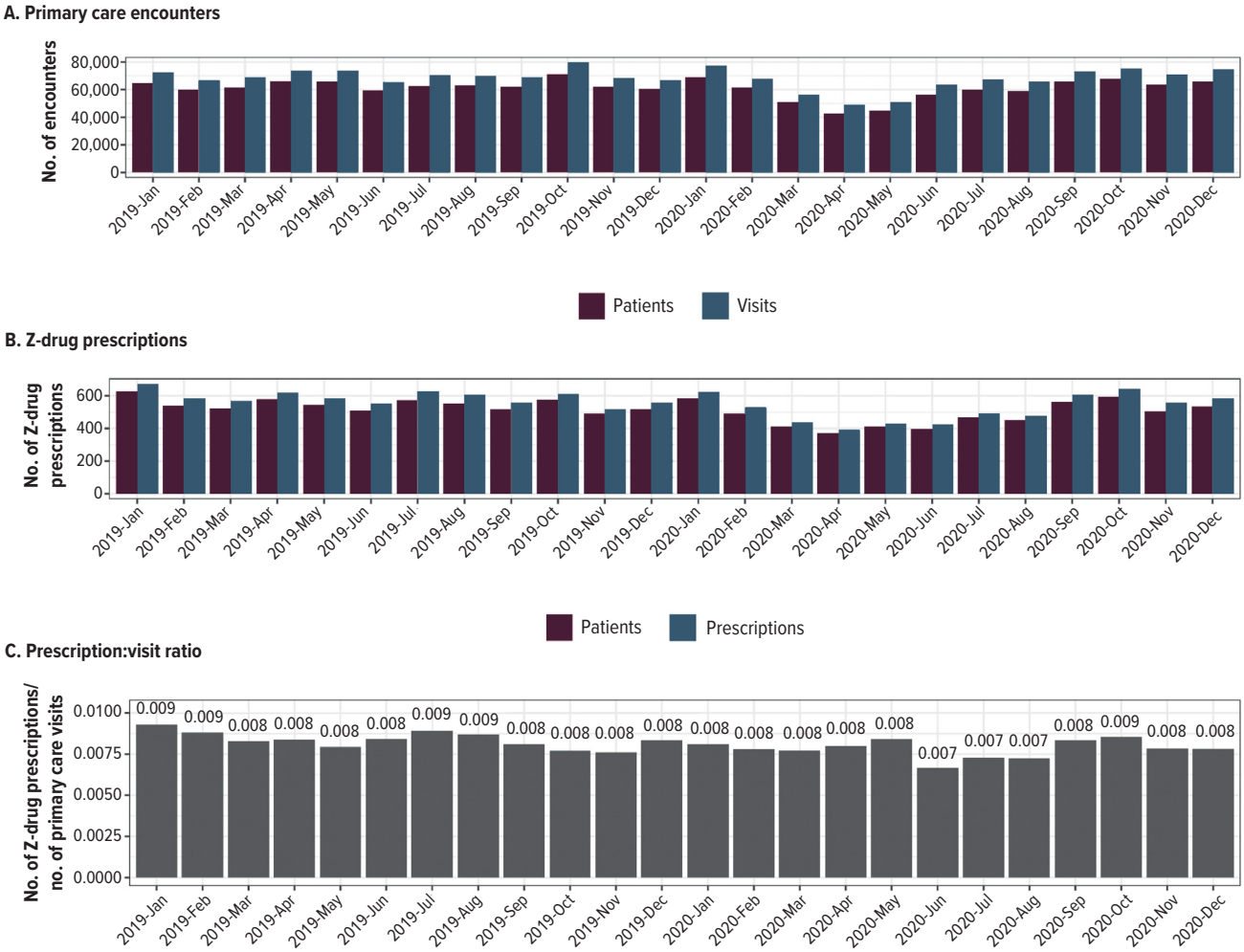
Z-drug prescribing throughout the study period. Using each patient's first visit in the study period, descriptive statistics (eg, mean, standard deviation, frequency, and percent) of patient characteristics were computed for the entire patient sample and stratified by whether patients received at least 1 Z-drug prescription during the study period. Comparisons were made using 2-sample *t* tests for continuous variables and χ^2 or Fisher exact test for categorical variables. Using a multivariable logistic regression model, we also examined factors associated with being prescribed a Z-drug. The dependent variable was an indicator for receiving at least 1 Z-drug prescription during the study period. Covariates were primarily selected based on previous association with sedative-hypnotic prescribing and included patient age,[16] gender,[17] race (White, Black, other [American Indian/Alaska Native, etc]),[17,18] marital status (married/partnered, single, divorced/separated, widowed),[19] insurance status (private/other, Medicaid, Medicare, self-pay),[18] median income by ZIP code of address,[20] categorized number of primary care visits during the study period (1, 2, 3, 4+),[21] and binary indicators for *ICD*-coded insomnia, major depressive disorder, generalized anxiety disorder, bipolar disorder, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, schizophrenia spectrum disorders, and substance use disorders.[22]

Z-drug/opioid coprescribing throughout the study period. We also examined which factors were associated with coprescription of an opioid with a Z-drug during the study period. For this outcome, we also used multivariable logistic regression with the same predictors described above.

Z-drug and Z-drug/opioid coprescribing pre- and post-lockdown. Pre-COVID and post-COVID Z-drug prescription rates were computed. Patient demographics

Figure 1.

Frequency of Primary Care Visits (A) and Z-Drug Prescriptions (B) and Ratio of Z-Drug Prescriptions to Primary Care Visits (C)

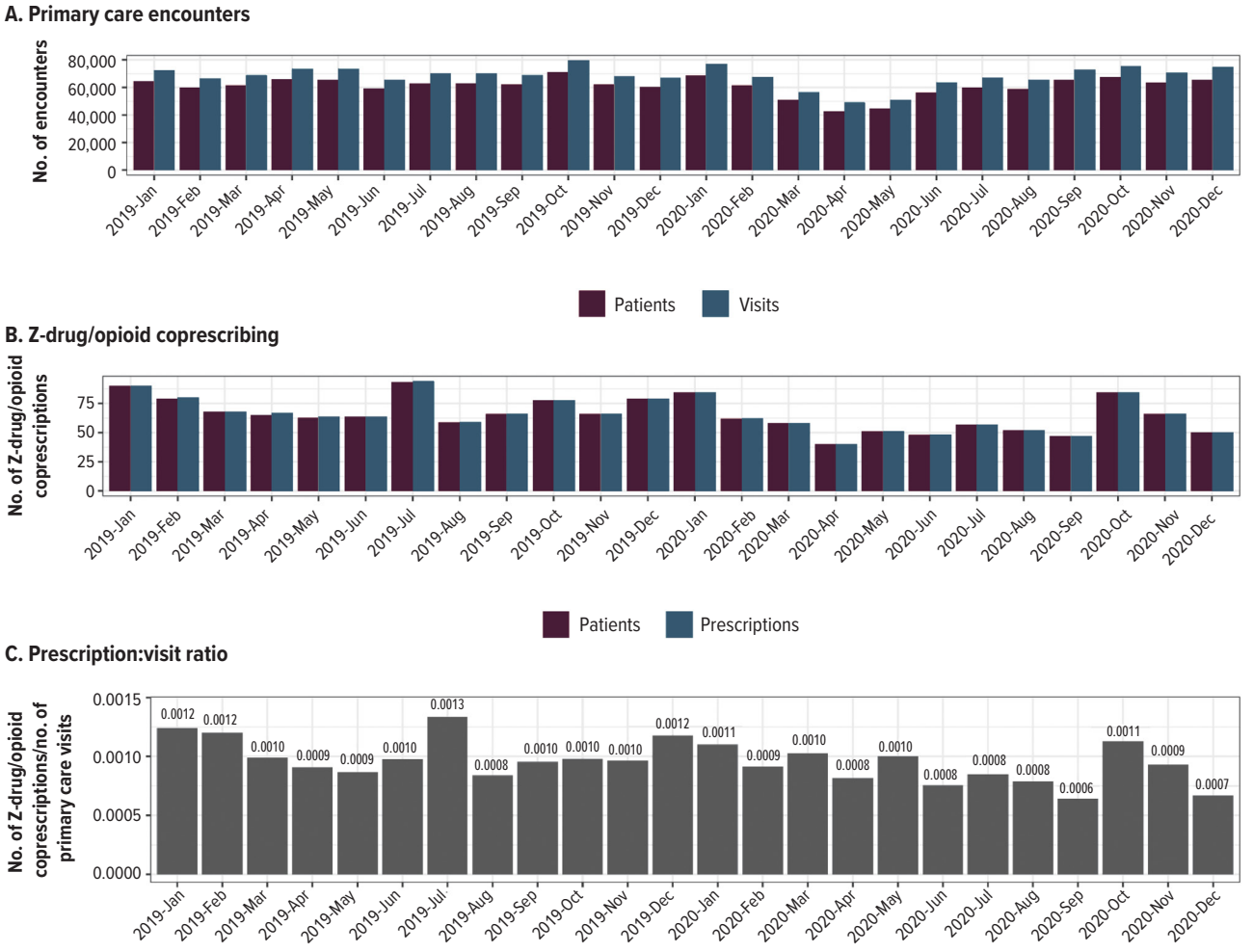


and previous diagnoses in each of these time periods were summarized using descriptive statistics and single-predictor logistic regression models where the dependent variable was time period (post-lockdown vs pre-lockdown). Because some patients had primary care visits in both the pre- and post-lockdown periods, we fit these single-predictor logistic regression models using generalized estimating equations (GEE) to account for repeated measurements. We also computed Z-drug prescription rates for the 2 time periods that accounted for repeated measurements and adjusted for confounding. This was accomplished by fitting a multivariable logistic regression model with GEE where Z-drug prescription (yes vs no) was the dependent variable, time period was the independent variable, and an exchangeable correlation structure was employed. Each of the patient characteristics or previous diagnoses was included as covariates. Unadjusted and covariate-adjusted odds ratios were computed to see whether there was any difference in Z-drug prescription rates pre- and post-lockdown. In addition, we created bar graphs of the number of primary care encounters, the number of Z-drug prescriptions, and the prescription-to-visit ratio by month (Figure 1). Similar analyses were done for coprescription of Z-drug and opioids pre- and post-lockdown (Figure 2).

De novo Z-drug prescribing post-lockdown. Comparisons were also made among patients who were not prescribed a Z-drug before the lockdown (before March 24, 2020) and either did or did not receive at least 1 Z-drug prescription after (between March 24, 2020, and December 31, 2020). Descriptive statistics were used, and comparisons were made using 2-sample *t* tests for continuous variables and χ^2 tests for categorical variables. A multivariable logistic regression model was used to examine which factors were associated with post-lockdown de novo Z-drug prescription, after adjusting for the other covariates.

Figure 2.

Monthly Frequency of Primary Care Visits (A) and Z-Drug/Opioid Coprescriptions (B) and Ratio of Z-Drug/Opioid Coprescriptions to Primary Care Visits (C)



All computations were done in R, version 4.1.0. All tests were 2-sided, and *P* values less than .05 were considered statistically significant. For all logistic regression models, we computed odds ratios, 95% confidence intervals, and *P* values.

Ethics Approval

The CCHS Institutional Review Board reviewed and approved this study.

RESULTS

Between January 1, 2019, and December 31, 2020, 455,537 adult patients had 1,643,473 primary care visits (847,655 visits in 2019; 795,818 visits in 2020). Of those patients, 6,743 (1.48%) were prescribed a Z-drug at some point during the study period. The prevalence of prescription was 1.58% for women (3,945/249,836) and 1.36% for men (2,797/205,646). Among the 6,743 patients prescribed a Z-drug, there were 13,193 Z-drug prescriptions (7,022 prescriptions in 2019; 6,171 prescriptions in 2020). The ratio of prescriptions to primary care visits was 13,193/1,643,473 (0.80%) during the entire study period (7,022/847,655 [0.83%] in 2019; 6,171/795,818 [0.78%] in 2020) (Figure 1). Among the 13,193 Z-drug prescriptions, 11,524 were zolpidem (87.35%), 1,327 were eszopiclone (10.06%), 242 were zaleplon (1.83%), and 100 were zopiclone (0.76%). Of the entire patient sample, 1,064 (0.2%) were coprescribed a Z-drug and an opioid at least once during the study period. This constituted 15.78% of patients prescribed a Z-drug during the study period.

Univariate Analysis of Z-Drug Prescribing Throughout the Study Period

On univariate analysis (Table 1), patients who were prescribed a Z-drug by a primary care provider during the study period were disproportionately older, female,

Table 1.

Patient Characteristics Stratified by Receipt of Z-Drug Prescription During the Study Period[a]

Characteristic	All patients (n = 455,537)	Had Z-drug prescription (n = 6,743)	Did not have Z-drug prescription (n = 448,794)	*P* value
Age, mean (SD), y	52.4 (18.1)	59.7 (14.0)	52.3 (18.1)	<.001
Gender				
Female	249,836 (54.8)	3,945 (58.5)	245,891 (54.8)	<.001
Male	205,646 (45.1)	2,797 (41.5)	202,849 (45.2)	
Nonbinary	12 (0.0)	0 (0.0)	12 (0.0)	
X	14 (0.0)	0 (0.0)	14 (0.0)	
Other	4 (0.0)	0 (0.0)	4 (0.0)	
Unknown	25 (0.0)	1 (0.0)	24 (0.0)	
Race				
White	349,218 (76.7)	5,666 (84.0)	343,552 (76.6)	<.001
Black	55,737 (12.2)	530 (7.9)	55,207 (12.3)	
American Indian/Alaska Native	750 (0.2)	10 (0.1)	740 (0.2)	
Asian	11,950 (2.6)	97 (1.4)	11,853 (2.6)	
Multiracial/Multicultural	15,592 (3.4)	157 (2.3)	15,435 (3.4)	
Hispanic/Latino	3 (0.0)	0 (0.0)	3 (0.0)	
Native Hawaiian/Pacific Islander	5 (0.0)	0 (0.0)	5 (0.0)	
Other	1,320 (0.3)	18 (0.3)	1,302 (0.3)	
Unavailable	7,758 (1.7)	82 (1.2)	7,676 (1.7)	
Declined	6,385 (1.4)	101 (1.5)	6,284 (1.4)	
Unknown	6,819 (1.5)	82 (1.2)	6,737 (1.5)	
Marital status				
Married	241,239 (53.0)	3,912 (58.0)	237,327 (52.9)	<.001
Domestic partner	1,638 (0.4)	39 (0.6)	1,599 (0.4)	
Single	149,280 (32.8)	1,571 (23.3)	147,709 (32.9)	
Divorced	29,804 (6.5)	632 (9.4)	29,172 (6.5)	
Legally separated	2,614 (0.6)	65 (1.0)	2,549 (0.6)	
Widowed	20,909 (4.6)	409 (6.1)	20,500 (4.6)	
Other	543 (0.1)	8 (0.1)	535 (0.1)	
Patient refused	52 (0.0)	2 (0.0)	50 (0.0)	
Unknown	7,171 (1.6)	85 (1.3)	7,086 (1.6)	
Missing	2,287 (0.5)	20 (0.3)	2,267 (0.5)	
Insurance				
Private/other	280,492 (61.6)	3,711 (55.0)	276,781 (61.7)	<.001
Medicare	105,277 (23.1)	2,347 (34.8)	102,930 (22.9)	
Medicaid	50,690 (11.1)	586 (8.7)	50,104 (11.2)	
Self-pay	1,080 (0.2)	3 (0.0)	1,077 (0.2)	
Missing	17,998 (4.0)	96 (1.4)	17,902 (4.0)	
Median income by ZIP code (×$1,000), mean (SD)	55.6 (20.0)	56.5 (20.6)	55.6 (20.0)	<.001
Number of primary care visits				
Mean (SD)	3.6 (3.5)	5.8 (4.7)	3.6 (3.5)	<.001
1	141,039 (31.0)	787 (11.7)	140,252 (31.3)	<.001
2	87,440 (19.2)	811 (12.0)	86,629 (19.3)	
3	60,419 (13.3)	821 (12.2)	59,598 (13.3)	
4+	166,639 (36.6)	4,324 (64.1)	162,315 (36.2)	
Alcohol use disorder	9,866 (2.2)	191 (2.8)	9,675 (2.2)	<.001
Bipolar disorder	7,682 (1.7)	197 (2.9)	7,485 (1.7)	<.001
Cannabis use disorder	3,797 (0.8)	49 (0.7)	3,748 (0.8)	.366
Cocaine/stimulant use disorder	1,831 (0.4)	38 (0.6)	1,793 (0.4)	.044
Generalized anxiety disorder	98,776 (21.7)	2,961 (43.9)	95,815 (21.3)	<.001
Hallucinogen use disorder	73 (0.0)	1 (0.0)	72 (0.0)	1.000
Sedative, hypnotic, or anxiolytic drug use disorder	251 (0.1)	12 (0.2)	239 (0.1)	<.001
Major depressive disorder	67,714 (14.9)	1,865 (27.7)	65,849 (14.7)	<.001
Obsessive-compulsive disorder	1,980 (0.4)	28 (0.4)	1,952 (0.4)	.880
Opioid use disorder	3,435 (0.8)	158 (2.3)	3,277 (0.7)	<.001
Other psychoactive use disorder	3,567 (0.8)	79 (1.2)	3,488 (0.8)	<.001
Panic disorder	7,935 (1.7)	213 (3.2)	7,722 (1.7)	<.001
Posttraumatic stress disorder	7,238 (1.6)	221 (3.3)	7,017 (1.6)	<.001
Schizoaffective disorder	955 (0.2)	13 (0.2)	942 (0.2)	.864
Schizophrenia	1,473 (0.3)	18 (0.3)	1,455 (0.3)	.475
Insomnia	19,078 (4.2)	2,689 (39.9)	16,389 (3.7)	<.001

[a]Data expressed as n (%) unless otherwise noted.

Table 2.

Multivariable Logistic Regression Models for Receipt of Any Z-Drug Prescription (Yes vs No) and Z-Drug/Opioid Coprescription (Yes vs No) During the Study Period

	Any Z-drug prescription		Coprescribed Z-drug and opioid	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age (per 10 years)	1.17 (1.15–1.20)	<.001	1.19 (1.12–1.25)	<.001
Male (reference: female)	1.06 (1.01–1.12)	.032	1.20 (1.05–1.37)	.007
Race (reference: White)				
Black	0.76 (0.69–0.83)	<.001	0.99 (0.81–1.22)	.942
Other	0.75 (0.66–0.86)	<.001	0.75 (0.54–1.04)	.082
Marital status (reference: married/partnered)				
Single	0.88 (0.82–0.94)	<.001	0.88 (0.75–1.04)	.125
Divorced	1.05 (0.96–1.14)	.324	0.97 (0.78–1.20)	.745
Widowed	0.68 (0.61–0.77)	<.001	0.88 (0.69–1.11)	.279
Insurance (reference: private/other)				
Medicaid	0.80 (0.73–0.89)	<.001	1.05 (0.83–1.32)	.689
Medicare	0.89 (0.83–0.96)	.002	1.37 (1.15–1.62)	<.001
Median income by ZIP code (per $10,000)	1.03 (1.02–1.04)	<.001	0.95 (0.91–0.98)	.003
Number of primary care visits (reference: 1)				
2	1.45 (1.30–1.61)	<.001	0.71 (0.51–0.99)	.043
3	1.93 (1.73–2.14)	<.001	1.03 (0.76–1.41)	.835
4+	2.80 (2.57–3.05)	<.001	2.78 (2.25–3.43)	<.001
Alcohol use disorder	0.81 (0.69–0.96)	.014	0.75 (0.53–1.08)	.119
Bipolar disorder	1.23 (1.04–1.44)	.013	1.17 (0.82–1.66)	.378
Cannabis use disorder	0.72 (0.52–0.98)	.037	0.61 (0.31–1.20)	.153
Cocaine/stimulant use disorder	1.01 (0.70–1.47)	.945	1.36 (0.75–2.46)	.312
Generalized anxiety disorder	1.71 (1.61–1.81)	<.001	1.77 (1.53–2.04)	<.001
Sedative, hypnotic, or anxiolytic drug use disorder	0.93 (0.44–1.97)	.851	1.72 (0.60–4.96)	.313
Insomnia	11.76 (11.11–12.45)	<.001	9.37 (8.18–10.73)	<.001
Major depressive disorder	1.04 (0.97–1.11)	.264	1.29 (1.11–1.50)	<.001
Obsessive-compulsive disorder	0.58 (0.38–0.87)	.009	0.13 (0.02–0.96)	.045
Opioid use disorder	1.50 (1.23–1.83)	<.001	3.72 (2.80–4.95)	<.001
Other psychoactive use disorder	1.17 (0.91–1.52)	.221	1.44 (0.92–2.26)	.110
Panic disorder	0.94 (0.81–1.10)	.439	0.90 (0.63–1.29)	.557
Posttraumatic stress disorders	1.17 (1.00–1.36)	.051	1.36 (0.99–1.87)	.057
Schizoaffective disorder	0.77 (0.41–1.44)	.415	1.08 (0.38–3.09)	.880
Schizophrenia	0.66 (0.37–1.17)	.154	1.06 (0.42–2.68)	.904

White, married, divorced, on Medicare, living in ZIP codes with higher median income, having 4 or more primary care visits, and diagnosed with the following: alcohol use disorder, bipolar disorder, cocaine/stimulant use disorder, generalized anxiety disorder, sedative/hypnotic use disorder, major depressive disorder, opioid use disorder, other psychoactive use disorder, panic disorder, posttraumatic stress disorder, and insomnia.

Multivariate Analysis of Z-Drug Prescribing Throughout the Study Period

Multivariable logistic regression (Table 2) revealed that older age, being male (vs female), living in higher income ZIP code, having more primary care visits during the study period, and having bipolar disorder, generalized anxiety disorder, insomnia, and opioid use disorder were each associated with greater odds of Z-drug prescription during the study period. Being Black or other race (vs White), having Medicaid or Medicare (vs private/other insurance), being single or widowed (vs married), and having alcohol use disorder, cannabis use disorder, or obsessive-compulsive disorder were each associated with lower odds of Z-drug prescription during the study period.

Multivariate Analysis of Z-Drug/Opioid Coprescribing Throughout the Study Period

Multivariable logistic regression (Table 2) also showed that older age, being male (vs female), having Medicare (vs private/other insurance), having 4 or more primary care visits (vs 1 visit), and having generalized anxiety disorder, insomnia, major depressive disorder, and opioid use disorder were each associated with greater odds of Z-drug/opioid coprescription during the study period. Living in wealthier ZIP codes, having 2 primary care visits during the study period (vs 1 visit), and having obsessive-compulsive disorder were each associated with lower odds of Z-drug/opioid coprescription during the study period.

Table 3.

Multivariable Logistic Regression Results for Receiving a Z-Drug Prescription De Novo Post-Lockdown (Yes vs No)

	Odds ratio (95% CI)	*P* value
Age (per 10 years)	1.08 (1.04–1.13)	<.001
Male (reference: female)	0.99 (0.89–1.10)	.912
Race (reference: White)		
Black	0.62 (0.51–0.76)	<.001
Other	0.71 (0.56–0.91)	.007
Marital status (reference: married/partnered)		
Single	0.82 (0.72–0.94)	.004
Divorced	0.97 (0.82–1.16)	.757
Widowed	0.74 (0.59–0.92)	.006
Insurance (reference: private/other)		
Medicaid	0.82 (0.67–1.00)	.053
Medicare	1.10 (0.96–1.26)	.187
Median income by ZIP code (per $10,000)	1.04 (1.02–1.07)	.002
Number of primary care visits (reference: 1)		
2	1.15 (1.01–1.31)	.035
3	1.37 (1.17–1.59)	<.001
4+	1.57 (1.37–1.81)	<.001
Alcohol use disorder	0.81 (0.58–1.13)	.212
Bipolar disorder	1.39 (1.03–1.88)	.030
Cannabis use disorder	0.93 (0.53–1.63)	.803
Cocaine/stimulant use disorder	1.33 (0.67–2.67)	.417
Generalized anxiety disorder	1.76 (1.57–1.97)	<.001
Sedative, hypnotic, or anxiolytic drug use disorder	0.58 (0.08–4.21)	.587
Insomnia	8.30 (7.40–9.31)	<.001
Major depressive disorder	0.84 (0.74–0.96)	.011
Obsessive-compulsive disorder	0.77 (0.38–1.56)	.467
Opioid use disorder	0.77 (0.47–1.29)	.325
Other psychoactive use disorder	1.20 (0.72–2.00)	.494
Panic disorder	0.84 (0.62–1.15)	.279
Posttraumatic stress disorder	1.05 (0.77–1.44)	.738
Schizoaffective disorder	0.26 (0.04–1.90)	.183
Schizophrenia	0.95 (0.35–2.61)	.921

Z-Drug and Z-Drug/Opioid Coprescribing Pre- and Post-Lockdown

Pre-lockdown (March 24, 2019–December 31, 2019), 3,690 (1.20%) of the 307,554 patients who had at least 1 primary care visit received at least 1 Z-drug prescription and 512 (0.17%) received a Z-drug/opioid coprescription. This constituted a prevalence of Z-drug/opioid coprescription of 13.88% among patients receiving a Z-drug during that period. Post-lockdown (March 24, 2020–December 31, 2020), 3,500 (1.19%) of the 293,575 patients who had at least 1 primary care visit received at least 1 Z-drug prescription, and 440 (0.15%) received a Z-drug/opioid coprescription. This constituted a prevalence of Z-drug/opioid coprescription of 12.57% among patients receiving a Z-drug during that period. For more detailed information about frequency of Z-drug prescribing and Z-drug/opioid coprescribing during different intervals within the study period, see Supplementary Table 1.

The unadjusted odds ratio for being prescribed a Z-drug post-lockdown versus pre-lockdown was 0.994 (95% CI = 0.948–1.041, *P* = .787). After accounting for correlated responses within patients and adjusting for patient demographics and preexisting disorders using multivariable logistic regression with GEE, there was no significant difference in the odds of being prescribed a Z-drug pre- or post-lockdown (OR = 0.978, 95% CI = 0.942–1.010, *P* = .233).

The unadjusted odds ratio for Z-drug/opioid coprescription post-lockdown versus pre-lockdown was 0.900 (95% CI = 0.792–1.023, *P* = .106). After accounting for correlated responses within patients and adjusting for patient demographics and preexisting disorders using multivariable logistic regression with GEE, the odds of receiving a Z-drug/opioid coprescription were 11.7% lower post-lockdown (OR = 0.883, 95% CI = 0.789–0.988, *P* = .031).

See Supplementary Table 2 for descriptive statistics for patients in pre- and post-lockdown periods. There were small but statistically significant differences for some of the variables.

De Novo Z-Drug Prescribing Post-Lockdown

On univariate analysis, patients prescribed a Z-drug de novo post-lockdown were disproportionately older, White, married, on Medicare, living in wealthier ZIP codes, having more primary care visits, and diagnosed with bipolar disorder, generalized anxiety disorder, major depressive disorder, panic disorder, post-traumatic stress disorder, and insomnia. For further details, see Supplementary Table 3.

Multivariable logistic regression revealed that older age, living in wealthier ZIP codes, having more primary care visits, and being diagnosed with bipolar disorder, generalized anxiety disorder, and insomnia were each associated with greater odds of being prescribed a Z-drug de novo post-lockdown. Being Black or other race (vs White), being single or widowed (vs married), or having major depressive disorder were each associated with lower odds of being prescribed a Z-drug de novo post-lockdown. For further details, see Table 3.

DISCUSSION

We believe this to be the first study evaluating Z-drug prescribing with and without opioid coprescribing exclusively in a US primary care setting during the COVID-19 pandemic. In our primary care sample, 1.48% of patients received a Z-drug prescription during the study period, and the ratio of Z-drug prescriptions to primary care visits was 0.80%. Similar to other recent research,[15] zolpidem was the most commonly prescribed Z-drug, accounting for 87.35% of prescriptions. Consistent with Z-drugs' primary use as sedative-

hypnotics, an insomnia diagnosis conferred the highest odds of receiving a prescription of all factors analyzed (OR = 11.76). Despite a 2021 report of heightened Z-drug prescribing during the early pandemic,[12] we found no statistically significant change in odds of receiving a Z-drug prescription among primary care patients during the first 9 months of pandemic. This difference may have been due to the fact that the other study assessed Z-drug prescribing in a variety of health care settings, while we only examined the primary care setting.

The previously mentioned study[12] also demonstrated a gender disparity in Z-drug prescribing rate for October 2020 (1.46% in women vs 1.00% in men). While we also observed a gender disparity, it was not as pronounced (1.58% for women and 1.36% for men). Of note, we found that men actually had slightly higher odds of receiving a Z-drug prescription during the study period when controlling for other variables (OR = 1.06). This finding contradicts previous studies, which have suggested that benzodiazepines and Z-drugs are more commonly prescribed in females.[12,23] A possible explanation for this difference could be that the previously observed gender disparities were due to confounding factors. Alternatively, our finding may support previous research suggesting a marginal increase in sleep problems in men during the COVID-19 pandemic.[24,25] Consistent with previous findings, we also found that non-White patients were less likely to receive a prescription for a Z-drug during the study period.[26] This observation is particularly unfortunate since Blacks are more likely than Whites to report short sleep duration,[27] with racial discrimination shown to account for 57% of the relationship between race and insomnia severity in Black patients in one study.[28] One likely contributing factor to this treatment disparity is that, despite obtaining less adequate sleep, Black women are less likely to report trouble sleeping to health care providers,[29] indicating a need for proactive screening in this population by clinicians. Importantly, racial bias in the assessment and treatment of pain by health care providers has been repeatedly observed,[30] raising the possibility that a similar bias could exist around insomnia and contribute to this treatment disparity as well.

Consistent with previous literature,[31] we found that age was positively associated with receiving a Z-drug prescription during the study period (OR = 1.17 for every 10-year increase), despite important Z-drug related risks in older patients including cognitive side effects, daytime fatigue, falls, and fractures.[4,32] Strikingly, although all other substance use disorders were either associated with decreased risk of receiving a Z-drug prescription during the study period or had no statistically significant association, opioid use disorder was associated with increased risk (OR = 1.50). This is concerning since patients with opioid use disorder have a high risk of misusing Z-drugs,[33] as well as elevated risk of accidental overdose due to respiratory suppression from Z-drugs and opioids in combination, though not surprising since Z-drug use is known to be higher in patients who misuse opioids.[8]

Notable factors positively associated with receiving a de novo Z-drug prescription post-lockdown were age (OR = 1.08 for every 10-year increase), having bipolar disorder (OR = 1.39), having generalized anxiety disorder (OR = 1.76), and having insomnia (OR = 8.30), while being Black (OR = 0.62) and having major depressive disorder (OR = 0.84) were negatively associated. The association with age may be explained by insomnia secondary to the pandemic's disproportional impact on older adults in terms of mortality and morbidity, public health restrictions, social isolation, economics, and health care access. Multiple studies have shown a rise in depression, anxiety, insomnia, and chronic pain in older adults during the pandemic.[34,35] Prior studies have indicated a pandemic-related rise in insomnia globally as well.[36] The increased risk of Z-drug prescribing in patients with generalized anxiety disorder and bipolar disorder we observed could be secondary to increased susceptibility to stress and higher sleep reactivity in patients with anxiety and mood disorders.[37] However, caution is warranted around this hypothesis since patients with major depressive disorder had lower odds of de novo Z-drug prescription post-lockdown.

We found a high rate of Z-drug/opioid coprescribing during the study period (15.78% of patients prescribed a Z-drug), despite evidence of increased mortality in patients receiving this combination of medications.[38] Notable populations at increased risk of coprescribing included older patients (OR = 1.19 for every 10-year increase in age), Medicare patients (OR = 1.37), and patients with opioid use disorder (OR = 3.72). The association with increased age is troubling for multiple reasons. First, health care providers are reluctant to taper older adults off these medications once initiated because of patient hesitancy, lack of provider proficiency, lack of tapering guidelines, and limited access to nonpharmacological alternatives.[39] Second, deprescribing these drugs in older patients often requires inpatient hospitalizations due to risk and clinical complexity.[40] Third, given their slower metabolism and renal clearance, older adults are more sensitive to these medications' adverse effects,[41] which is a likely contributor to the ongoing rise of older adult overdose rates.[42] Reassuringly, we found a significant decrease in Z-drug/opioid coprescribing post-lockdown (OR = 0.88), possibly due to less frequent de novo opioid prescribing observed nationwide during this period.[14]

Increased odds of Z-drug prescribing with or without opioid coprescribing to groups vulnerable to drug-induced harm in this cohort highlight continued opportunities for clinicians and health care systems to enhance thoughtful prescribing and deprescribing of these medications. Clinicians should regularly conduct a benefit-risk analysis for patients already receiving Z-drugs, particularly in patients coprescribed opioids. If it is determined that the risks outweigh the

benefits, then deprescribing is strongly recommended. Despite its challenges, successful deprescribing of Z-drugs is possible.[43] Effective strategies and tools for deprescribing include increasing physician-patient time, patient buy-in, patient education, multidisciplinary collaboration, effective alternative treatments (pharmacotherapy and psychosocial intervention), clinician training, prescription drug monitoring tools, and protocolized deprescribing guidelines.[44]

Strengths and Limitations

The main strength of this study is its reliance on an electronic medical record from a large health care system that includes Medicaid and Medicare patients, allowing for a large sample size and the ability to gather several important variables to control for confounding. Important limitations include the study's retrospective, cross-sectional, observational design; reliance on billing codes for diagnoses; and lack of information on whether prescriptions were filled or consumed.

CONCLUSION

We believe this to be the first study examining Z-drug prescribing with and without opioid coprescribing exclusively in a US primary care population during the COVID-19 pandemic. We found no increase in the rate of Z-drug prescriptions post-lockdown. The rate of opioid coprescribing was high in patients receiving Z-drugs, though the odds of coprescribing decreased post-lockdown. We found that patients of increasing age and with opioid use disorder, 2 groups vulnerable to adverse effects of Z-drugs and opioids, were at increased risk of receiving Z-drug prescriptions with and without opioids. Increasing age was also associated with higher odds of de novo Z-drug prescription post-lockdown. Importantly, we identified a racial disparity in the form of decreased odds of Z-drug prescribing to non-White patients during the study period, as well as de novo prescribing post-lockdown. This study adds to previous research indicating a need for more thoughtful prescribing of Z-drugs with and without opioid coprescribing, as well as research demonstrating undertreatment of insomnia in non-White patients.

Article Information

Published Online: September 11, 2023. https://doi.org/10.4088/JCP.22m14753

Submitted: December 5, 2022; accepted May 2, 2023.

To Cite: Anand A, Weleff J, Thompson NR, et al. Prescribing of Z-drugs with and without opioid coprescribing to primary care patients in a large health care system from 2019–2020. *J Clin Psychiatry.* 2023;84(6):22m14753.

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Relevant Financial Relationships: Dr Barnett has received stock options from CB Therapeutics as compensation for advisory services. He also receives monetary compensation for editorial work for DynaMed Plus (EBSCO Industries, Inc) and consulting services for Cerebral. No other financial disclosures were reported.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Supplementary Material: Available at Psychiatrist.com.

References

1. Reuben C, Elgaddal N, Black LI. Sleep Medication Use in Adults Aged 18 and Over: United States, 2020. *NCHS Data Brief.* 2023;(462):1–8. Accessed February 16, 2023. https://www.cdc.gov/nchs/data/databriefs/db462.pdf
2. Brandt J, Leong C. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. *Drugs R D.* 2017;17(4):493–507.
3. Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. *Arch Intern Med.* 2009;169(21):1952–1960.
4. Treves N, Perlman A, Kolenberg Geron L, et al. Z-drugs and risk for falls and fractures in older adults-a systematic review and meta-analysis. *Age Ageing.* 2018;47(2):201–208.
5. Schifano F, Chiappini S, Corkery JM, et al. An insight into Z-drug abuse and dependence: an examination of reports to the European Medicines Agency database of suspected adverse drug reactions. *Int J Neuropsychopharmacol.* 2019;22(4):270–277.
6. Szmulewicz A, Bateman BT, Levin R, et al. The risk of overdose with concomitant use of Z-drugs and prescription opioids: a population-based cohort study. *Am J Psychiatry.* 2021;178(7):643–650.
7. Scharner V, Hasieber L, Sönnichsen A, et al. Efficacy and safety of Z-substances in the management of insomnia in older adults: a systematic review for the development of recommendations to reduce potentially inappropriate prescribing. *BMC Geriatr.* 2022;22(1):87.
8. Tubbs AS, Ghani SB, Naps M, et al. Past-year use or misuse of an opioid is associated with use of a sedative-hypnotic medication: a US National Survey on Drug Use and Health (NSDUH) study. *J Clin Sleep Med.* 2022;18(3):809–816.
9. Tardelli VS, Bianco MCM, Prakash R, et al. Overdose deaths involving non-BZD hypnotic/sedatives in the USA: trends analyses. *Lancet Reg Health Am.* 2022;10:100190.
10. Xiong J, Lipsitz O, Nasri F, et al. Impact of COVID-19 pandemic on mental health in the general population: a systematic review. *J Affect Disord.* 2020;277:55–64.
11. Choudhry AA, Shahzeen F, Choudhry SA, et al. Impact of COVID-19 infection on quality of sleep. *Cureus.* 2021;13(9):e18182.
12. Milani SA, Raji MA, Chen L, et al. Trends in the use of benzodiazepines, Z-hypnotics, and serotonergic drugs among us women and men before and during the COVID-19 pandemic. *JAMA Netw Open.* 2021;4(10):e2131012. https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2785392. Accessed August 26, 2022.
13. Murphy MT, Latif U. Pain during COVID-19: a comprehensive review and guide for the interventionalist. *Pain Pract.* 2021;21(1):132–143.
14. Currie JM, Schnell MK, Schwandt H, et al. Prescribing of opioid analgesics and buprenorphine for opioid use disorder during the COVID-19 pandemic. *JAMA Netw Open.* 2021;4(4):e216147.
15. Anderson KE, Basting JL, Gifeisman RI, et al. High prescribing and state-level variation in Z-drug use among Medicare patients. *medRxiv.* Preprint posted online May 10, 2022. doi:10.1101/2022.05.10.22274909 >
16. Cadogan CA, Ryan C, Cahir C, et al. Benzodiazepine and Z-drug prescribing in Ireland: analysis of national prescribing trends from 2005 to 2015. *Br J Clin Pharmacol.* 2018;84(6):1354–1363.
17. Kim HM, Gerlach LB, Van T, et al. Predictors of long-term and high-dose use of zolpidem in veterans. *J Clin Psychiatry.* 2019;80(2):18m12149.
18. Esechie A, Kuo Y-F, Goodwin JS, et al. Trends in prescribing pattern of opioid and benzodiazepine substitutes among Medicare part D beneficiaries from 2013 to 2018: a retrospective study. *BMJ Open.* 2021;11(11):e053487.
19. Mokhar A, Tillenburg N, Dirmaier J, et al. Potentially inappropriate use of benzodiazepines and Z-drugs in the older population-analysis of associations between long-term use and patient-related factors. *PeerJ.* 2018;6(5):e4614.
20. Woods A, Begum M, Gonzalez-Chica D, et al. Long-term benzodiazepines and

z-drug prescribing in Australian general practice between 2011 and 2018: A national study. *Pharmacol Res Perspect*. 2022;10(1):e00896.
21. Landolt S, Rosemann T, Blozik E, et al. Benzodiazepine and Z-drug use in Switzerland: prevalence, prescription patterns and association with adverse healthcare outcomes. *Neuropsychiatr Dis Treat*. 2021;17:1021–1034.
22. Gerlach LB, Maust DT, Leong SH, et al. Factors associated with long-term benzodiazepine use among older adults. *JAMA Intern Med*. 2018;178(11):1560–1562.
23. Soyombo S, Stanbrook R, Aujla H, et al. Socioeconomic status and benzodiazepine and Z-drug prescribing: a cross-sectional study of practice-level data in England. *Fam Pract*. 2020;37(2):194–199.
24. Alimoradi Z, Gozal D, Tsang HWH, et al. Gender-specific estimates of sleep problems during the COVID-19 pandemic: systematic review and meta-analysis. *J Sleep Res*. 2022;31(1):e13432.
25. Salfi F, Lauriola M, Amicucci G, et al. Gender-related time course of sleep disturbances and psychological symptoms during the COVID-19 lockdown: a longitudinal study on the Italian population. *Neurobiol Stress*. 2020;13:100259.
26. Tardelli VS, Fidalgo TM, Martins SS. How do medical and non-medical use of Z-drugs relate to psychological distress and the use of other depressant drugs? *Addict Behav*. 2021;112:106606.
27. Nunes J, Jean-Louis G, Zizi F, et al. Sleep duration among black and white Americans: results of the National Health Interview Survey. *J Natl Med Assoc*. 2008;100(3):317–322.
28. Cheng P, Cuellar R, Johnson DA, et al. Racial discrimination as a mediator of racial disparities in insomnia disorder. *Sleep Health*. 2020;6(5):543–549.
29. Amyx M, Xiong X, Xie Y, et al. Racial/ethnic differences in sleep disorders and reporting of trouble sleeping among women of childbearing age in the United States. *Matern Child Health J*. 2017;21(2):306–314.
30. Hoffman KM, Trawalter S, Axt JR, et al. Racial bias in pain assessment and treatment recommendations, and false beliefs about biological differences between blacks and whites. *Proc Natl Acad Sci U S A*. 2016;113(16):4296–4301.
31. Kaufmann CN, Spira AP, Alexander GC, et al. Trends in prescribing of sedative-hypnotic medications in the USA: 1993–2010. *Pharmacoepidemiol Drug Saf*. 2016;25(6):637–645.
32. Glass J, Lanctôt KL, Herrmann N, et al. Sedative hypnotics in older people with insomnia: meta-analysis of risks and benefits. *BMJ*. 2005;331(7526):1169–1173.
33. Schepis TS, Teter CJ, Simoni-Wastila L, et al. Prescription tranquilizer/sedative misuse prevalence and correlates across age cohorts in the US. *Addict Behav*. 2018;87:24–32.
34. Lebrasseur A, Fortin-Bédard N, Lettre J, et al. Impact of the COVID-19 pandemic on older adults: rapid review. 2021;4(2):e26474.
35. De Pue S, Gillebert C, Dierckx E, et al. The impact of the COVID-19 pandemic on wellbeing and cognitive functioning of older adults. *Sci Rep*. 2021;11(1):4636.
36. Morin CM, Bjorvatn B, Chung F, et al. Insomnia, anxiety, and depression during the COVID-19 pandemic: an international collaborative study. *Sleep Med*. 2021;87:38–45.
37. Kalmbach DA, Anderson JR, Drake CL. The impact of stress on sleep: pathogenic sleep reactivity as a vulnerability to insomnia and circadian disorders. *J Sleep Res*. 2018;27(6):e12710.
38. Linnet K, Thorsteinsdottir HS, Sigurdsson JA, et al. Co-prescribing of opioids and benzodiazepines/Z-drugs associated with all-cause mortality: A population-based longitudinal study in primary care with weak opioids most commonly prescribed. *Front Pharmacol*. 2022;13:932380.
39. Doherty AJ, Boland P, Reed J, et al. Barriers and facilitators to deprescribing in primary care: a systematic review. *BJGP Open*. 2020;4(3):bjgpopen20X101096.
40. Treating Substance Use Disorder in Older Adults: Updated 2020. Substance Abuse and Mental Health Services Administration; 2020. Accessed August 28, 2022. https://pubmed.ncbi.nlm.nih.gov/34106564/
41. Conti EC, Stanley MA, Amspoker AB, et al. Sedative-hypnotic use among older adults participating in anxiety research. *Int J Aging Hum Dev*. 2017;85(1):3–17.
42. Mason M, Soliman R, Kim HS, et al. Disparities by sex and race and ethnicity in death rates due to opioid overdose among adults 55 years or older, 1999 to 2019. *JAMA Netw Open*. 2022;5(1):e2142982.
43. Soni A, Thiyagarajan A, Reeve J. Feasibility and effectiveness of deprescribing benzodiazepines and Z-drugs: systematic review and meta-analysis. *Addiction*. 2023;118(1):7–16.
44. Rasmussen AF, Poulsen SS, Oldenburg LIK, et al. The barriers and facilitators of different stakeholders when deprescribing benzodiazepine receptor agonists in older patients—a systematic review. *Metabolites*. 2021;11(4):254.

The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Prescribing of Z-Drugs With and Without Opioid Co-Prescribing to Primary Care Patients in a Large Health Care System From 2019–2020

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DOI Number: 10.4088/JCP.22m14753

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

DISCLAIMER

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary material for "Prescribing of Z-drugs with and without opioid co-prescribing to primary care patients in a large healthcare system from 2019-2020"

Supplementary Table 1. Z-drug prescribing and Z-drug/opioid co-prescribing during study period sub-intervals*

Time Period	Number Of Patients Seen During Time Period	Prescribed Z-drug	Co-Prescribed Z-drug and Opioid	Co-Prescribing Rate Among Patients Prescribed Z-drug during interval
1/1/2019-3/23/2019	142099	1495 (1.05%)	209 (0.15%)	209/1495 (13.98%)
3/24/2019-12/31/2019 (Pre-lockdown)	307554	3690 (1.20%)	512 (0.17%)	512/3690 (13.88%)
1/1/2020-3/23/2020	142909	1343 (0.94%)	187 (0.13%)	187/1343 (13.92%)
3/24/2020-12/31/2020 (Post-lockdown)	293575	3500 (1.19%)	440 (0.15%)	440/3500 (12.57%)
2019	449653	4450 (0.99%)	650 (0.14%)	650/4450 (14.61%)
2020	436484	4221 (0.97%)	572 (0.13%)	572/4221 (13.55%)
Entire study period (2019-2020)	455537	6743 (1.48%)	1064 (0.23%)	1064/6743 (15.78%)

*Of note, when combining proportions of patients prescribed Z-drugs or co-prescribed Z-drugs and opioids during smaller intervals (such as 3 months or 9 months), these do not sum to the proportions reported for the larger intervals containing them (12 months or 24 months). For example, 13.98% of patients who received a Z-drug prescription from 1/1/2019-3/23/2019 were co-prescribed opioids, while this proportion was 13.88% from 3/24/2019-12/31/2019. However, the total was 14.61% of all patients prescribed a Z-drug in 2019. The reason prescription prevalence can be higher when looking at longer time periods is because the two smaller intervals within a larger interval are not mutually exclusive, and patients have more opportunity to be prescribed and/or co-prescribed medications at least once during a one-year or two-year period than a 3-month or 9-month period.

Supplementary Table 2. Patient characteristics pre-lockdown and post-lockdown*

	Pre-COVID (3/24/2019-12/31/2019)	Post-COVID (3/24/2020-12/31/2020)	Odds Ratio (95% CI)	P-value
N	307554	293575		
Age, mean (SD)	54.3 (17.9)	54.1 (18.0)	0.994 (0.992–0.995)	< 0.001
Gender				
Female	170372 (55.4%)	163833 (55.8%)	Reference	
Male	137161 (44.6%)	129711 (44.2%)	0.983 (0.977–0.990)	< 0.001
Nonbinary	4 (0.0%)	7 (0.0%)	1.535 (0.968–2.434)	0.068
X	6 (0.0%)	10 (0.0%)		
Other	2 (0.0%)	4 (0.0%)		
Unknown	9 (0.0%)	10 (0.0%)		
Race				
White	239064 (77.7%)	227821 (77.6%)	Reference	
Black	37309 (12.1%)	36075 (12.3%)	1.015 (1.005–1.024)	0.003
American Indian/Alaska Native	456 (0.1%)	476 (0.2%)	1.095 (1.007–1.192)	0.034
Asian	7694 (2.5%)	7099 (2.4%)	0.968 (0.948–0.989)	0.003

Multiracial/Multicultural	9560 (3.1%)	9616 (3.3%)	1.055 (1.036–1.076)	< 0.001
Hispanic/Latino	3 (0.0%)	3 (0.0%)	1.010 (0.957–1.066)	0.717
Native Hawaiian/Pacific Islander	3 (0.0%)	3 (0.0%)		
Other	927 (0.3%)	892 (0.3%)		
Unavailable	4466 (1.5%)	4643 (1.6%)	1.091 (1.059–1.123)	< 0.001
Declined	4143 (1.3%)	4063 (1.4%)	1.029 (1.001–1.058)	0.040
Unknown	3929 (1.3%)	2884 (1.0%)	0.770 (0.741–0.800)	< 0.001
Marital Status				
Married	166281 (54.1%)	157529 (53.7%)	Reference	
Domestic Partner	989 (0.3%)	1122 (0.4%)	1.198 (1.134–1.265)	< 0.001
Single	94614 (30.8%)	91229 (31.1%)	1.018 (1.010–1.025)	< 0.001
Divorced	21180 (6.9%)	20530 (7.0%)	1.023 (1.012–1.035)	< 0.001
Legally Separated	1780 (0.6%)	1711 (0.6%)	1.015 (0.974–1.057)	0.481
Widowed	16124 (5.2%)	15358 (5.2%)	1.005 (0.994–1.017)	0.367
Other	320 (0.1%)	361 (0.1%)	1.191 (1.082–1.311)	< 0.001
Patient Refused	35 (0.0%)	34 (0.0%)	1.025 (0.755–1.392)	0.872
Unknown	4928 (1.6%)	4752 (1.6%)	1.018 (0.994–1.043)	0.148
Missing	1303 (0.4%)	949 (0.3%)	0.769 (0.718–0.824)	< 0.001
Insurance				
Private/Other	184266 (59.9%)	173854 (59.2%)	Reference	
Medicare	79047 (25.7%)	77416 (26.4%)	1.038 (1.031–1.045)	< 0.001
Medicaid	32267 (10.5%)	32996 (11.2%)	1.084 (1.072–1.095)	< 0.001
Self-Pay	734 (0.2%)	562 (0.2%)	0.812 (0.754–0.873)	< 0.001
Missing	11240 (3.7%)	8747 (3.0%)	0.825 (0.808–0.842)	< 0.001
Median Income by ZIP Code (x $1,000), mean (SD)	55.5 (19.8)	55.3 (19.8)	0.994 (0.992–0.995)	< 0.001
Number Primary Care Visits				
1	146615 (47.7%)	146505 (49.9%)	Reference	
2	77577 (25.2%)	73147 (24.9%)	0.944 (0.932–0.955)	< 0.001
3	40406 (13.1%)	35907 (12.2%)	0.889 (0.876–0.903)	< 0.001
4+	42956 (14.0%)	38016 (12.9%)	0.886 (0.874–0.898)	< 0.001
Alcohol Use Disorder	7034 (2.3%)	7095 (2.4%)	1.058 (1.039–1.078)	< 0.001
Bipolar Disorder	5547 (1.8%)	5443 (1.9%)	1.029 (1.007–1.050)	0.008
Cannabis Use Disorder	2549 (0.8%)	2585 (0.9%)	1.063 (1.028–1.099)	< 0.001
Cocaine Stimulant Use Disorder	1272 (0.4%)	1294 (0.4%)	1.066 (1.020–1.114)	0.005
Generalized Anxiety Disorder	73483 (23.9%)	73554 (25.1%)	1.065 (1.058–1.072)	< 0.001
Hallucinogen Use Disorder	38 (0.0%)	50 (0.0%)	1.379 (1.023–1.858)	0.035
Sedative, Hypnotic or Anxiolytic Drug Use Disorder	167 (0.1%)	181 (0.1%)	1.136 (1.000–1.290)	0.051
Major Depressive Disorder	51385 (16.7%)	49885 (17.0%)	1.021 (1.013–1.028)	< 0.001

Obsessive Compulsive Disorder	1436 (0.5%)	1408 (0.5%)	1.027 (0.987–1.069)	0.182
Opioid Use Disorder	2613 (0.8%)	2495 (0.8%)	1.000 (0.972–1.029)	0.983
Other Psychoactive Use Disorder	2416 (0.8%)	2435 (0.8%)	1.056 (1.021–1.093)	0.002
Panic Disorder	5981 (1.9%)	5923 (2.0%)	1.038 (1.019–1.058)	< 0.001
Post-Traumatic Stress Disorder	5364 (1.7%)	5476 (1.9%)	1.071 (1.050–1.092)	< 0.001
Schizoaffective Disorder	705 (0.2%)	657 (0.2%)	0.976 (0.920–1.035)	0.423
Schizophrenia	1069 (0.3%)	1013 (0.3%)	0.993 (0.946–1.041)	0.764
Insomnia	15013 (4.9%)	14811 (5.0%)	1.035 (1.024–1.047)	< 0.001

*Odds ratios, 95% confidence intervals, and p-values are from single-predictor logistic regression models where the dependent variable was time period (post-lockdown vs. pre-lockdown) and generalized estimating equations were used to account for repeated measurements among patients who had primary care visits in both the pre-lockdown and post-lockdown periods.

Supplementary Table 3. Comparison of patient demographic and clinical characteristics among patients who were not prescribed a Z-drug pre-COVID (3/24/2019-12/31/2019) and either did or did not start a Z-drug after COVID began (3/24/2020-12/31/2020).

	Had Z-drug Prescription Between 3/24/2020-12/31/2020	**Did Not Have Z-drug Prescription Between 3/24/2020-12/31/2020**	**P-value**
N	1656	285298	
Age, mean (SD)	58.8 (14.5)	54.1 (18.0)	< 0.001
Gender			
Female	986 (59.5%)	159082 (55.8%)	0.161
Male	670 (40.5%)	126186 (44.2%)	
Nonbinary	0 (0.0%)	7 (0.0%)	
X	0 (0.0%)	10 (0.0%)	
Other	0 (0.0%)	3 (0.0%)	
Unknown	0 (0.0%)	10 (0.0%)	
Race			
White	1408 (85.0%)	221038 (77.5%)	0.002
Black	112 (6.8%)	35250 (12.4%)	
American Indian/Alaska Native	5 (0.3%)	461 (0.2%)	
Asian	24 (1.4%)	6977 (2.4%)	
Multiracial/Multicultural	35 (2.1%)	9410 (3.3%)	
Hispanic/Latino	0 (0.0%)	3 (0.0%)	
Native Hawaiian/Pacific Islander	0 (0.0%)	3 (0.0%)	
Other	3 (0.2%)	870 (0.3%)	
Unavailable	33 (2.0%)	4538 (1.6%)	
Declined	23 (1.4%)	3925 (1.4%)	
Unknown	13 (0.8%)	2823 (1.0%)	

Marital Status			
Married	976 (58.9%)	152994 (53.6%)	< 0.001
Domestic Partner	12 (0.7%)	1071 (0.4%)	
Single	373 (22.5%)	88885 (31.2%)	
Divorced	142 (8.6%)	19842 (7.0%)	
Legally Separated	19 (1.1%)	1645 (0.6%)	
Widowed	103 (6.2%)	14907 (5.2%)	
Other	2 (0.1%)	353 (0.1%)	
Patient Refused	0 (0.0%)	32 (0.0%)	
Unknown	24 (1.4%)	4636 (1.6%)	
Missing	5 (0.3%)	933 (0.3%)	
Insurance			
Private/Other	903 (54.5%)	169104 (59.3%)	< 0.001
Medicare	602 (36.4%)	74975 (26.3%)	
Medicaid	133 (8.0%)	32141 (11.3%)	
Self-Pay	1 (0.1%)	545 (0.2%)	
Missing	17 (1.0%)	8533 (3.0%)	
Median Income by ZIP Code (x $1,000), mean (SD)	57.2 (20.7)	55.3 (19.8)	< 0.001
Number of Primary Care Visits			
Mean (SD)	2.5 (2.1)	2.0 (1.6)	< 0.001
1	652 (39.4%)	145169 (50.9%)	< 0.001
2	417 (25.2%)	70992 (24.9%)	
3	258 (15.6%)	34384 (12.1%)	
4+	329 (19.9%)	34753 (12.2%)	
Alcohol Use Disorder	40 (2.4%)	6875 (2.4%)	1.000
Bipolar Disorder	51 (3.1%)	5227 (1.8%)	< 0.001
Cannabis Use Disorder	13 (0.8%)	2520 (0.9%)	0.768
Cocaine Stimulant Use Disorder	10 (0.6%)	1254 (0.4%)	0.412
Generalized Anxiety Disorder	703 (42.5%)	70397 (24.7%)	< 0.001
Hallucinogen Use Disorder	0 (0.0%)	50 (0.0%)	1.000
Sedative, Hypnotic or Anxiolytic Drug Use Disorder	2 (0.1%)	166 (0.1%)	0.253
Major Depressive Disorder	386 (23.3%)	47885 (16.8%)	< 0.001
Obsessive Compulsive Disorder	7 (0.4%)	1370 (0.5%)	0.873
Opioid Use Disorder	19 (1.1%)	2338 (0.8%)	0.181
Other Psychoactive Use Disorder	16 (1.0%)	2352 (0.8%)	0.617
Panic Disorder	46 (2.8%)	5677 (2.0%)	0.028
Post-Traumatic Stress Disorder	48 (2.9%)	5242 (1.8%)	0.002
Schizoaffective Disorder	2 (0.1%)	642 (0.2%)	0.453
Schizophrenia	4 (0.2%)	993 (0.3%)	0.600
Insomnia	532 (32.1%)	12465 (4.4%)	< 0.001