Prevalence and Predictors of Benzodiazepine Monotherapy in Patients With Depression:
A National Cross-Sectional Study

Mate M. Soric, PharmD, BCPS[a,b,*]; Chris Paxos, PharmD, BCPP, BCPS, BCGP[b,c]; Sara E. Dugan, PharmD, BCPP, BCPS[b]; Susan M. Fosnight, RPh, BCPS, BCGP[b,d]; Jodie Z. Turosky, RPh, BCPS[b,e]; Prabodh Sadana, PhD[b]; Jessica B. Emshoff, PharmD, BCPS, BCGP[b,c]; Lukas Everly, PharmD, BCPS[a,b]; Brittany M. Snyder, PharmD, BCPS[a]; Bhavin K. Mistry, PharmD, BCPS[b,d]; Shubha Bhat, PharmD, MS, BCACP[f]; Amy E. Unruh, PhD[g]; and Ismail M. Safi, BA[g]

ABSTRACT

Objective: Depression guidelines discourage benzodiazepine monotherapy and limit use to short-term adjunctive therapy with antidepressants; however, patients with depression continue to receive benzodiazepine monotherapy. The prevalence and predictors of this prescribing pattern have not been described previously and are warranted to assist clinicians in identifying patients at highest risk of receiving benzodiazepine monotherapy.

Methods: A national, cross-sectional analysis of the National Ambulatory Medical Care Survey from 2012 to 2015 was performed for adults treated for depression. Depression was identified using a survey item specifically assessing the presence of depression. Office visits involving patients with bipolar disorder, schizoaffective disorder, or pregnancy were identified by *ICD-9* code or specific survey item and were excluded. The primary endpoint was benzodiazepine monotherapy prescribing rate defined as initiation or continuation of a benzodiazepine in the absence of any antidepressant agent. A multivariate logistic regression model was created to identify variables associated with benzodiazepine monotherapy.

Results: In total, 9,426 unweighted visits were eligible for inclusion. Benzodiazepine monotherapy was identified in 9.3% of patients treated for depression (95% CI, 8.2%–10.6%). Predictors of benzodiazepine monotherapy included age of 45–64 years (OR = 1.39; 95% CI, 1.01–1.91), epilepsy-related office visit (OR = 5.34; 95% CI, 1.39–20.44), anxiety-related office visit (OR = 1.67; 95% CI, 1.23–2.27), underlying pulmonary disease (OR = 1.43; 95% CI, 1.09–1.87), and concomitant opiate prescribing (OR = 2.86; 95% CI, 2.01–4.06). Psychiatrists were less likely to prescribe benzodiazepine monotherapy than were other providers (OR = 0.42; 95% CI, 0.29–0.61).

Conclusions: Benzodiazepine monotherapy is utilized in nearly 1 in 10 patients treated for depression. Adults aged 45 to 65 years, patients prescribed opioids, patients seen by primary care providers, and those with underlying anxiety, epilepsy, or pulmonary disorders are at highest risk.

J Clin Psychiatry 2019;80(4):18m12588

To cite: Soric MM, Paxos C, Dugan SE, et al. Prevalence and predictors of benzodiazepine monotherapy in patients with depression: a national cross-sectional study. *J Clin Psychiatry.* 2019;80(4):18m12588.

To share: https://doi.org/10.4088/JCP.18m12588

[a]Department of Pharmacy, University Hospitals Geauga Medical Center, Chardon, Ohio

[b]Department of Pharmacy Practice, Northeast Ohio Medical University College of Pharmacy, Rootstown, Ohio

[c]Department of Pharmacy, Cleveland Clinic Akron General, Akron, Ohio

[d]Department of Pharmacy, SUMMA Akron City Hospital, Akron, Ohio

[e]Department of Pharmacy, St Vincent Charity Medical Center, Cleveland, Ohio

[f]Department of Pharmacy, Boston Medical Center, Boston, Massachusetts

[g]Northeast Ohio Medical University College of Pharmacy, Rootstown, Ohio

**Corresponding author:* Mate M. Soric, PharmD, BCPS, 4209 State Rte 44, PO Box 95, Rootstown, OH 44272 (msoric@neomed.edu).

Major depressive disorder (MDD) affects over 300 million individuals globally and is the leading cause of disability worldwide.[1] It is characterized by symptoms such as depressed mood and anhedonia that last for at least 2 weeks and result in impairment in work, school, or other areas of functioning.[2] In the United States, 16.2 million adults (6.7%) experienced at least 1 major depressive episode in the past year.[3] According to 2017 data from the National Institute of Mental Health,[4] rates of major depressive episodes are higher in women (8.7%) than in men (5.3%) and highest (13.1%) in the young adult population between 18 and 25 years of age. The financial impact of MDD in the United States is estimated to be approximately $210 billion as a result of direct medical costs, absenteeism, presenteeism, and costs related to suicide.[5] Adults experiencing a major depressive episode within the last year report receiving some form of treatment in 51.9% of cases.[6] Antidepressants are one of the most commonly prescribed medication classes in the United States. Nearly 13% of individuals over the age of 12 years, approximately 1 in 8 Americans, are prescribed an antidepressant medication.[7]

The use of antidepressants for the treatment of MDD is broadly supported by practice guidelines.[8–11] In general, either antidepressant therapy or psychotherapy is recommended for patients with mild-to-moderate MDD, whereas antidepressant therapy or the combination of antidepressants and psychotherapy is recommended for severe MDD.[8,9] Guidelines also support the use of antidepressants for cases of mild MDD, particularly for patients with a personal preference for antidepressant therapy, history of prior antidepressant response, or lack of response to psychotherapy.[10,11] First-line pharmacotherapeutic options for MDD include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion.[8–11] Vortioxetine is recognized as a first-line treatment option by more recent practice guidelines.[10,11] On the other hand, trials have assessed the efficacy

Clinical Points

- Benzodiazepine monotherapy is not recommended by any major depressive disorder guidelines, but data to quantify this prescribing pattern do not exist.
- Benzodiazepine monotherapy is utilized in nearly 1 in 10 office visits involving patients treated for depression. Psychiatrists are significantly less likely to utilize benzodiazepine monotherapy compared to practitioners in other specialties.
- Concomitant opioid prescribing increased the likelihood of benzodiazepine monotherapy utilization.

of benzodiazepines as antidepressants with conflicting results, with most conducted more than 20 years ago. A systematic review and meta-analysis[8] of 22 trials comparing benzodiazepines to placebo or tricyclic antidepressants found no difference in response, very likely due to small sample sizes, variability in methods for measuring response, and short treatment durations. Whereas practice guidelines consider antidepressants and psychotherapy as primary treatment options, they either do not mention or fail to endorse benzodiazepine monotherapy for the treatment of MDD.[9–12] Practice guidelines from the American Psychiatric Association[9] state that benzodiazepines can be used as adjuncts to antidepressant therapy for patients with MDD with comorbid anxiety or insomnia; however, they assert that benzodiazepines are not antidepressants and should not be the sole treatment for patients with MDD. The Canadian Network for Mood and Anxiety Treatments practice guidelines[11,12] provide a narrow use for benzodiazepines, suggesting their use for patients with catatonic features.

Existing evidence suggests the use of benzodiazepines in MDD places patients at considerable risk for adverse effects and poor outcomes. Benzodiazepines have been shown to prolong time to remission from MDD, worsen depressive symptoms, and carry a risk for dependence, delirium, and respiratory depression, especially with concomitant opioids or in the presence of sleep apnea.[13–21] Observational trials have identified an association between benzodiazepine use and suicide attempts.[22–24] Additionally, an association with falls and fractures has been reported in older patients.[25–29]

Regardless of recommendations from current practice guidelines, data evaluating the use of benzodiazepines in patients with depressive disorders are conflicting. A cross-sectional trial[15] of 326 patients with MDD found the prevalence of benzodiazepine prescribing to be 25% and more likely in patients with a number of factors, including comorbid panic disorder. A cross-sectional study[30] evaluating prescribing patterns in 1,484 patients diagnosed with MDD without anxiety found 14% were prescribed benzodiazepines. A retrospective cohort trial[31] conducted in Japan identified 7,338 patients with newly diagnosed nonpsychotic MDD. Only 2.2% of patients had a mixed anxiety and depressive disorder; however, the percentage of patients treated with benzodiazepine monotherapy was 13.5%. Lastly, an epidemiologic study[32] conducted in China with 1,192 patients with MDD found that 4.4% received benzodiazepines without an antidepressant. However, the aforementioned trials were single-center studies, evaluated a limited range of physician specialties, or were conducted outside of the United States, very likely leading to varying benzodiazepine monotherapy utilization rates.

Given the lack of support for using benzodiazepines as monotherapy for the management of MDD, the increased risk of adverse events, and existing data that fail to evaluate patients across the United States, the purpose of this study is to evaluate the prevalence of benzodiazepine monotherapy in patients with a depressive disorder diagnosis. The study also seeks to identify patient- and provider-level predictors for receiving benzodiazepine monotherapy in the presence of MDD.

METHODS

Data collected via the National Ambulatory Medical Care Survey (NAMCS) were used to analyze a nationally representative population in the outpatient setting (data available at https://www.cdc.gov/nchs/ahcd/index.htm). The NAMCS is a probability sample survey conducted annually to collect national data from non-federal, office-based providers and community health centers. This survey is administered by the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) for the duration of 1 randomly selected week per year. Over the course of the surveyed week, a provider or office staff member completes a patient record form that includes details regarding patient care activities (including diagnoses, medication therapy initiated or continued, geographic location, and prescriber specialty) along with information on patient demographics. A total of 8,189 providers were included in the sample during the study period of 2012–2015, representing a response rate of 54.7%. The information collected at each office visit was weighted by NCHS using a process that adjusts for survey nonresponse using factors including time of year, geographic location, and urban or rural designation. This weighting generates an unbiased national estimate of non-federal outpatient visit characteristics. Additional details regarding the methods employed in the NAMCS are outlined elsewhere.[33]

To assess the prescribing patterns of benzodiazepine monotherapy in the presence of MDD, encounters involving patients aged 18 years and older receiving benzodiazepine monotherapy, antidepressant treatment, or psychotherapy were included. Patients with MDD were identified via a specific survey item that collects data regarding the presence of depression, regardless of the reason for the office visit. Patients receiving psychotherapy in addition to a benzodiazepine were not considered benzodiazepine monotherapy users. This analysis excluded encounters involving patients with a diagnosis of bipolar disorder or schizoaffective disorder identified using *International Classification of Disease, 9th Edition, Clinical Modification* (*ICD-9-CM*) codes, treatment with lithium, or pregnancy. Lastly, certain benzodiazepines have narrow indications and are not utilized routinely in

Table 1. Population Demographics

Characteristic	Unweighted Value (9,426 visits), n (%)	Value Weighted per Year (180,002,000 visits), n (%)
Patient Characteristics		
Sex		
Female	6,645 (70.5)	126,117,000 (70.1)
Age, y		
18–24	468 (5.0)	9,375,000 (5.2)
25–44	2,276 (24.1)	42,639,000 (23.7)
45–64	4,152 (44.0)	78,962,000 (43.9)
≥65	2,530 (26.8)	49,045,000 (27.2)
Primary payer type		
Medicare	2,732 (29.0)	54,395,000 (30.2)
Medicaid	847 (9.0)	15,906,000 (8.8)
Private	4,269 (45.3)	82,065,000 (45.6)
Other or unknown	1,578 (16.7)	27,655,000 (15.4)
Race and ethnicity		
White, non-Hispanic	8,091 (85.8)	145,919,000 (81.1)
Black, non-Hispanic	487 (5.2)	13,994,000 (7.8)
Hispanic	584 (6.2)	15,366,000 (8.5)
Other or multiracial	264 (2.8)	4,742,000 (2.6)
Comorbidities		
Anxiety	1,728 (18.3)	38,356,000 (21.3)
Insomnia	264 (2.8)	6,632,000 (3.7)
Posttraumatic stress disorder	196 (2.1)	3,184,000 (1.8)
Epilepsy	67 (0.7)	896,000 (0.5)
Multiple sclerosis	50 (0.5)	697,000 (0.4)
Substance use disorder	420 (4.5)	8,681,000 (4.8)
Chronic kidney disease	214 (2.3)	6,679,000 (3.7)
Pulmonary disease	1,516 (16.1)	26,639,000 (14.8)
Obesity	1,179 (12.5)	22,498,000 (12.5)
Total no. of chronic conditions		
1	3,439 (36.5)	61,677,000 (34.3)
2	2,092 (22.2)	41,482,000 (23.0)
3	1,606 (17.0)	30,517,000 (17.0)
≥4	2,289 (24.3)	46,345,000 (25.7)
New patient	1,207 (12.8)	21,406,000 (11.9)
Concomitant opioid prescribing	2,074 (22.0)	38,726,000 (21.5)
Visit year		
2012	3,085 (32.7)	35,819,000 (19.9)
2013	2,514 (26.7)	41,421,000 (23.0)
2014	2,468 (26.2)	47,074,000 (26.1)
2015	1,359 (14.4)	55,707,000 (30.9)
Provider Characteristics		
Physician provider	8,955 (95.0)	173,470,000 (96.4)
Provider specialty		
Primary care	3,737 (39.6)	86,939,000 (48.3)
Psychiatry	2,527 (26.8)	45,893,000 (25.5)
Neurology	368 (3.9)	3,821,000 (2.1)
Other specialists	2,794 (29.6)	43,368,000 (24.1)
Region		
Northeast	1,202 (12.8)	35,625,000 (19.8)
Midwest	2,912 (30.9)	42,576,000 (23.7)
South	2,895 (30.7)	59,766,000 (33.2)
West	2,417 (25.6)	42,055,000 (23.4)
Rural setting	1,224 (13.0)	17,104,000 (9.5)
Depression screening performed	1,091 (11.6)	27,676,000 (15.4)
Time spent with patient, min		
≤15	3,378 (35.8)	65,498,000 (36.4)
16–30	4,132 (43.8)	79,738,000 (44.3)
≥31	1,916 (20.3)	34,785,000(19.3)

the treatment of psychiatric disorders. Patients receiving these agents, including clobazam, midazolam, and rectal diazepam, were excluded.

The primary outcome was prevalence of benzodiazepine monotherapy use among patients treated for MDD. The secondary outcome was the association between patient and provider characteristics and benzodiazepine monotherapy. Patient demographics assessed included age, sex, race/ethnicity, payer type, and number of chronic conditions. Diagnoses of anxiety, posttraumatic stress disorder (PTSD), insomnia, substance use disorder (including either alcohol or other substances), epilepsy, obesity, chronic kidney disease, pulmonary disease (including chronic obstructive pulmonary disease, asthma, or obstructive sleep apnea), and multiple sclerosis were also assessed. Provider characteristics included geographic location, urban versus rural setting, primary care versus specialist visit, physician versus nonphysician provider, visit year, number of prior clinic visits, and time spent with patient during the visit. Concomitant opioid prescribing or completion of a depression screen was also evaluated. All variables were identified a priori, and, since the study utilized publicly available, de-identified data, it was granted exempt status from the Case Western Reserve University Institutional Review Board.

Per CDC requirements, all analyses were performed on weighted data. Variables with >30% relative standard error or based on fewer than 30 unweighted observations were deemed unreliable and removed from the analysis. Statistical analysis was performed using IBM SPSS (version 25, IBM, Chicago, Illinois) complex sample procedures based on the hierarchical, clustered design of the NAMCS data. Frequency tables were created to screen all categorical variables for sufficient cell counts and to determine utilization rates. Estimates of rates for baseline characteristics and benzodiazepine utilization were calculated as the percentage of all office visits for patients >18 years of age receiving treatment for MDD over the entire study period (2012–2015). Complex-samples multivariable regression was utilized to identify potential predictors of benzodiazepine monotherapy in patients treated for MDD. Total number of medications prescribed was included in the model as a covariate. All variables were included in the initial model, and a backward elimination approach was utilized to remove variables with a P value >.2.

For study years 2012–2013, the NAMCS collected information on up to 10 medications per office visit. For visits involving patients taking >10 medications, benzodiazepine monotherapy may be underrepresented if the agents were not documented in the patient's top 10 medications. A sensitivity analysis was conducted on patients taking fewer than 10 medications to ensure the results were not significantly affected.

RESULTS

A total of 9,426 patients (representing the unweighted total number of visits) treated for MDD met inclusion criteria. This total represents 180,002,000 office visits nationally. The patient population was 70.1% female, had a mean age of 53.7 years, was 81.1% non-Hispanic white, and was taking a mean of 6.3 medications. Table 1 further describes the population utilized in the study. Of the unweighted encounters, 932 patients were treated with benzodiazepine

Figure 1. Benzodiazepine Monotherapy Utilization Rate, 2012–2015

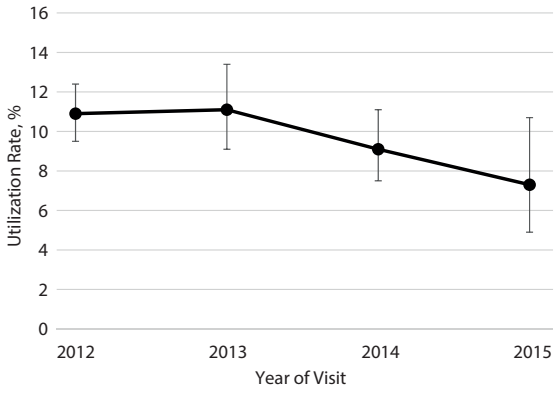

Table 2. Predictors of Benzodiazepine Monotherapy Utilization in Patients With Depression

Characteristic	Benzodiazepine Monotherapy Use, %	Odds Ratio (95% CI)
Age, y		
18–24	5.5	0.82 (0.46–1.49)
25–44	8.1	Referent
45–64	10.3	1.39 (1.01–1.91)
≥65	9.6	1.27 (0.84–1.90)
Primary payer type		
Private	8.2	Referent
Medicare	10.8	1.40 (1.01–1.94)
Medicaid	11.7	1.39 (0.95–2.04)
Other or unknown	8.6	1.24 (0.86–1.77)
Anxiety		
No	9.0	Referent
Yes	10.5	1.67 (1.23–2.27)
Epilepsy		
No	9.2	Referent
Yes	32.3	5.34 (1.39–20.44)
Pulmonary disease		
No	8.9	Referent
Yes	12.0	1.43 (1.09–1.87)
Substance use disorder		
No	9.3	Referent
Yes	9.4	0.67 (0.40–1.12)
Depression screening performed		
No	10.0	Referent
Yes	5.9	0.68 (0.46–1.00)
Concomitant opioid prescribing		
No	7.3	Referent
Yes	16.9	2.86 (2.01–4.06)
Provider specialty		
Primary care	10.0	Referent
Psychiatry	4.4	0.42 (0.29–0.61)
Neurology	14.0	0.90 (0.53–1.55)
Other specialists	12.9	1.36 (1.02–1.81)
Region		
Midwest	8.0	Referent
Northeast	9.0	1.24 (0.85–1.81)
South	11.7	1.54 (1.14–2.08)
West	7.7	0.94 (0.65–1.36)

monotherapy (representing 16,824,000 visits nationally), resulting in a prevalence of benzodiazepine monotherapy of 9.3% (95% CI, 8.2%–10.6%). The most commonly prescribed benzodiazepine monotherapies were alprazolam (42.1%), lorazepam (27.7%), clonazepam (20.3%), and diazepam (13.8%). The rate of prescribing for antipsychotic medications was low and did not vary significantly based on presence or absence of benzodiazepine monotherapy (9.4% of patients received atypical antipsychotics and 0.5% of patients received typical antipsychotics). Benzodiazepine monotherapy prescribing did not change significantly over the study period compared to baseline (see Figure 1).

For the secondary outcome, all variables met the requisite sample size for inclusion in the final model; however, multiple sclerosis and PTSD-related office visits had a relative standard error > 30% and were removed from the multivariate logistic regression analysis. After backward elimination of variables with $P > .2$, the final regression model included age, payer type, depression screening, geographic location, concomitant opioid prescribing, provider specialty, and diagnoses of epilepsy, anxiety, pulmonary disease, or substance use disorder (see Table 2). The model accounted for between 4.3% (Cox and Snell R^2) and 9.3% (Nagelkerke R^2) of the variance in benzodiazepine monotherapy utilization.

In the final model, the adjusted odds ratio (OR) for benzodiazepine monotherapy prescribing was significantly increased for the following predictors: age 45–64 years (OR = 1.39; 95% CI, 1.01–1.91, compared to age 25–44 years), Medicare (OR = 1.40; 95% CI, 1.01–1.94, compared to private insurance), epilepsy (OR = 5.34; 95% CI, 1.39–20.44), anxiety (OR = 1.67; 95% CI, 1.23–2.27), pulmonary disease (OR = 1.43; 95% CI, 1.09–1.87), other specialist (OR = 1.36; 95% CI, 1.02–1.81, compared to primary care providers), visits in the southern United States (OR = 1.54; 95% CI, 1.14–2.08, compared to the Midwest), and being prescribed concomitant opioids (OR = 2.86; 95% CI, 2.01–4.06).

In contrast, the likelihood of benzodiazepine monotherapy was significantly decreased in patients completing a depression screen (OR = 0.68; 95% CI, 0.46–1.00) and those seen by psychiatrists (OR = 0.42; 95% CI, 0.29–0.61, compared to primary care providers). Of note, the following variables had no association with benzodiazepine monotherapy prescribing: sex, race/ethnicity, history of substance use disorder, chronic kidney disease, being seen by neurology specialists, and total number of chronic conditions. The sensitivity analysis of patients taking fewer than 10 medications did not demonstrate significantly different results compared to the full analysis.

DISCUSSION

The results reveal that approximately 1 in 10 patients (9.3%) treated for MDD is prescribed benzodiazepine monotherapy. A number of variables that would ideally be associated with less benzodiazepine monotherapy were, instead, found to have no association or were associated with increased likelihood of utilization. Benzodiazepines carry a US Food and Drug Administration black box warning related to concomitant prescribing with opioid therapy. Rather than finding a negative association, our data reveal a significant increase in benzodiazepine monotherapy

prescribing in patients receiving opioids. Conditions such as chronic kidney disease, pulmonary disease, and substance use disorder also carry cautions related to benzodiazepine use, and our data revealed either no impact of these variables (in the case of chronic kidney disease and substance use disorder) or an increased likelihood of receiving benzodiazepine monotherapy (in the case of underlying pulmonary disease). Concerns about fall risk or worsening cognition in the elderly did not lead to fewer benzodiazepine orders than for younger adults.

Other predictors did demonstrate a logical connection to benzodiazepine monotherapy. For example, patients with a concurrent diagnosis of epilepsy were more likely to receive benzodiazepine monotherapy when compared to those without. This was expected given that benzodiazepines are commonly used to treat seizure activity and prescribers may be hesitant to utilize antidepressants due to a perceived risk of seizure threshold reduction. This hesitancy has been previously documented, as 52% of surveyed primary care physicians and 10% of neurologists reported that the main barrier related to providing treatment for MDD in epileptic patients is a concern for increased seizure frequency.[34] The use of SSRIs and SNRIs is generally considered safe, as clinically relevant decreases in seizure threshold are not typically associated with these antidepressants.[35] Patients with a reported diagnosis of anxiety were also more likely to receive benzodiazepine monotherapy, very likely stemming from the common use of benzodiazepines in these conditions. However, it should be noted that in the presence of underlying MDD, anxiety and insomnia should be primarily treated with other pharmacologic options.

Office visits involving depression screenings or psychiatrists were associated with less benzodiazepine monotherapy. Potential strategies to further decrease benzodiazepine monotherapy in the presence of MDD include improving screening for depression among providers or encouraging referral to psychiatrists when possible. Additional factors associated with a higher likelihood of receiving benzodiazepine monotherapy included those residing in the southern United States, Medicare beneficiaries, and patients receiving care from other specialists (not including psychiatrists or neurologists). These associations emphasize the need for targeted educational interventions involving both patients and prescribers regarding the utilization of more appropriate treatment strategies based on region, payer type, and provider specialty.

The prevalence of benzodiazepine monotherapy in this analysis is similar to that (10%) in prior studies that have assessed overall benzodiazepine use in patients with MDD.[36–38] However, it should be noted that this analysis specifically assessed the use of benzodiazepines as monotherapy, whereas previous studies included concomitant use of antidepressants and other medications. These findings highlight the ongoing prevalence of benzodiazepine use in the absence of proper first-line MDD therapy.

Previous studies have determined benzodiazepine prescribing to be more prevalent in elderly, female, Medicare, and Medicaid populations. Furthermore, benzodiazepines were more likely to be prescribed to patients using opioids, alcohol, or tobacco; by non-psychiatrist providers; and to patients with diagnoses of substance use disorders, MDD, anxiety, osteoporosis, chronic obstructive pulmonary disease, sleep apnea, or asthma.[15,36,39–41] This cohort identified some similar predictors. Interestingly, variables such as sex and substance use disorder were not significant predictors. These differences may be explained given that the NAMCS database is a large data set that is nationally representative and includes a diverse patient and provider population in contrast to the previous studies. Additionally, a diagnosis of epilepsy and geographic region were significant predictors of benzodiazepine monotherapy prescribing that have not been previously identified in the literature.

This study has a number of strengths. Utilizing the NAMCS database generated a large sample size. Weighting of the 9,426 office visits included in our study resulted in a population of over 180 million representative encounters. The data encompass a wide range of providers, provider settings, and patient characteristics, including age, race, ethnicity, geographic location, socioeconomic status, and insurance coverage. To accurately capture the prescribing trends of benzodiazepine monotherapy in patients with MDD, the study excluded patients with conditions for which benzodiazepine monotherapy is appropriate and those that can confound the findings. These included patients with bipolar disorder, schizophrenia, manic disorders, or schizoaffective disorders, thus allowing for a reliable cohort of patients with MDD in which benzodiazepine monotherapy was very likely guideline discordant.

There are a number of important limitations that need to be considered with respect to this study. Firstly, the cross-sectional design makes it impossible to assess the duration of benzodiazepine monotherapy in this patient population. It is likely that some proportion of patients receiving monotherapy with benzodiazepines took them for a short time, limiting the negative effects of these agents. However, it could be argued that any duration of benzodiazepine monotherapy in a patient with otherwise untreated MDD has the potential to cause harm. In previous studies of patients on benzodiazepine therapy,[36] the proportion of patients receiving long-term (≥ 120 days) therapy ranged from 14.7% in young adults to 31.4% in the elderly, and the mean duration of therapy was 224.9–245.4 days. Secondly, utilizing NAMCS data limits the study to only the variables present in the survey. As data on the type of depressive disorder, doses of medications, and complete past medical history are not collected, it is not possible to include these factors in the study design. The omission of these factors may have contributed to the low R^2 values identified in the current model. Future studies will need to identify other variables not included in our model that can further explain the variability observed in benzodiazepine monotherapy prescribing in the presence of MDD. Lastly, a number of conditions of interest (schizophrenia, bipolar

disorder, anxiety, insomnia, PTSD, and multiple sclerosis) were identified using *ICD-9-CM* codes related to the office visit. This method may have led to the omission of patients with a history of these conditions if the current office visit was for another disease state.

CONCLUSION

For patients treated for MDD, benzodiazepine monotherapy very likely continues to be utilized in a guideline-discordant manner. Rates of benzodiazepine monotherapy were similar to overall benzodiazepine prescribing rates in this patient population, suggesting that a diagnosis of MDD does not necessarily decrease the likelihood of receiving benzodiazepine monotherapy compared to the general population. On the basis of this study, educational or technological interventions to minimize benzodiazepine monotherapy utilization should be implemented to raise the awareness of the impact of this treatment modality on patients with MDD.

Submitted: September 24, 2018; accepted January 2, 2019.

Published online: May 21, 2019.

Potential conflicts of interest: The authors have no potential or actual conflicts of interest to disclose.

Funding/support: None

Previous presentation: Poster presentation at the American College of Clinical Pharmacy Global Conference on Clinical Pharmacy; October 22, 2018; Seattle, Washington.

REFERENCES

1. World Health Organization. Depression and other common mental disorders: global health estimates. 2017. WHO website. www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/. Accessed June 8, 2018.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fifth Edition. Arlington, VA: American Psychiatric Publishing; 2013.
3. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. SAMHSA website. https://www.samhsa.gov/data. 2017.
4. National Institute of Mental Health. Major depression. NIH website. www.nimh.nih.gov/health/statistics/major-depression.shtml. Accessed June 8, 2018.
5. Greenberg PE, Fournier AA, Sisitsky T, et al. The economic burden of adults with major depressive disorder in the United States (2005 and 2010). *J Clin Psychiatry*. 2015;76(2):155–162.
6. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of adult *DSM-5* major depressive disorder and its specifiers in the United States. *JAMA Psychiatry*. 2018;75(4):336–346.
7. Pratt LA, Brody DJ, Gu Q. *Antidepressant Use Among Persons Aged 12 and Over: United States, 2011–2014. NCHS Data Brief, No 283*. Hyattsville, MD: National Center for Health Statistics; 2017.
8. Benasi G, Guidi J, Offidani E, et al. Benzodiazepines as a monotherapy in depressive disorders: a systematic review. *Psychother Psychosom*. 2018;87(2):65–74.
9. American Psychiatric Association. *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*. 3rd ed. Arlington, VA: American Psychiatric Association; 2010.
10. Veterans Health Administration and Department of Defense. *VA/DoD Practice Guideline for the Management of Major Depressive Disorder, Version 3.0*. Washington, DC: Veterans Health Administration and the Department of Defense; 2016.
11. Kennedy SH, Lam RW, McIntyre RS, et al; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder, section 3: pharmacological treatments. *Can J Psychiatry*. 2016;61(9):540–560.
12. Parikh SV, Quilty LC, Ravitz P, et al; CANMAT Depression Work Group. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: section 2. psychological treatments. *Can J Psychiatry*. 2016;61(9):524–539.
13. Steffens DC, McQuoid DR. Impact of symptoms of generalized anxiety disorder on the course of late-life depression. *Am J Geriatr Psychiatry*. 2005;13(1):40–47.
14. Patten SB, Williams JV, Love EJ. Self-reported depressive symptoms following treatment with corticosteroids and sedative-hypnotics. *Int J Psychiatry Med*. 1996;26(1):15–24.
15. Rizvi SJ, Sproule BA, Gallaugher L, et al. Correlates of benzodiazepine use in major depressive disorder: the effect of anhedonia. *J Affect Disord*. 2015;187:101–105.
16. Ait-Daoud N, Hamby AS, Sharma S, et al. A review of alprazolam use, misuse, and withdrawal. *J Addict Med*. 2018;12(1):4–10.
17. Tan KR, Rudolph U, Lüscher C. Hooked on benzodiazepines: GABAA receptor subtypes and addiction. *Trends Neurosci*. 2011;34(4):188–197.
18. Pisani MA, Murphy TE, Araujo KL, et al. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med*. 2009;37(1):177–183.
19. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65(1):34–41.
20. Torrance N, Mansoor R, Wang H, et al. Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study. *Br J Anaesth*. 2018;120(6):1345–1355.
21. Seda G, Tsai S, Lee-Chiong T. Medication effects on sleep and breathing. *Clin Chest Med*. 2014;35(3):557–569.
22. Dodds TJ. Prescribed benzodiazepines and suicide risk: a review of the literature. *Prim Care Companion CNS Disord*. 2017;19(2):e1–e6.
23. Neutel CI, Patten SB. Risk of suicide attempts after benzodiazepine and/or antidepressant use. *Ann Epidemiol*. 1997;7(8):568–574.
24. Carlsten A, Waern M, Holmgren P, et al. The role of benzodiazepines in elderly suicides. *Scand J Public Health*. 2003;31(3):224–228.
25. Bloch F, Thibaud M, Dugué B, et al. Psychotropic drugs and falls in the elderly people: updated literature review and meta-analysis. *J Aging Health*. 2011;23(2):329–346.
26. 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.
27. Berdot S, Bertrand M, Dartigues JF, et al. Inappropriate medication use and risk of falls: a prospective study in a large community-dwelling elderly cohort. *BMC Geriatr*. 2009;9(1):30.
28. Pariente A, Dartigues JF, Benichou J, et al. Benzodiazepines and injurious falls in community dwelling elders. *Drugs Aging*. 2008;25(1):61–70.
29. Bolton JM, Morin SN, Majumdar SR, et al. Association of mental disorders and related medication use with risk for major osteoporotic fractures. *JAMA Psychiatry*. 2017;74(6):641–648.
30. Brieler JA, Scherrer JF, Salas J. Differences in prescribing patterns for anxiety and depression between General Internal Medicine and Family Medicine. *J Affect Disord*. 2015;172:153–158.
31. Onishi Y, Hinotsu S, Furukawa TA, et al. Psychotropic prescription patterns among patients diagnosed with depressive disorder based on claims database in Japan. *Clin Drug Investig*. 2013;33(8):597–605.
32. Li YH, Xiang YT, Su YA, et al. Long-term benzodiazepine use in patients with major depressive disorder in China. *Perspect Psychiatr Care*. 2014;50(3):149–154.
33. National Ambulatory Medical Care Survey public-use files and documentation 2018. CDC website. https://www.cdc.gov/nchs/data_access/ftp_data.htm. Accessed September 7, 2018.
34. Cotterman-Hart S. Depression in epilepsy: why aren't we treating? *Epilepsy Behav*. 2010;19(3):419–421.
35. Johannessen Landmark C, Henning O, Johannessen SI. Proconvulsant effects of antidepressants: what is the current evidence? *Epilepsy Behav*. 2016;61:287–291.
36. Olfson M, King M, Schoenbaum M. Benzodiazepine use in the United States. *JAMA Psychiatry*. 2015;72(2):136–142.
37. Olfson M, Marcus SC, Druss B, et al. National trends in the outpatient treatment of depression. *JAMA*. 2002;287(2):203–209.
38. Bushnell GA, Stürmer T, Gaynes BN, et al. Simultaneous antidepressant and benzodiazepine new use and subsequent long-term benzodiazepine use in adults with depression, United States, 2001-2014. *JAMA Psychiatry*. 2017;74(7):747–755.
39. Kroll DS, Nieva HR, Barsky AJ, et al. Benzodiazepines are prescribed more frequently to patients already at risk for benzodiazepine-related adverse events in primary care. *J Gen Intern Med*. 2016;31(9):1027–1034.
40. Sonnenberg CM, Bierman EJ, Deeg DJ, et al. Ten-year trends in benzodiazepine use in the Dutch population. *Soc Psychiatry Psychiatr Epidemiol*. 2012;47(2):293–301.
41. Hausken AM, Furu K, Skurtveit S, et al. Starting insomnia treatment: the use of benzodiazepines versus z-hypnotics: a prescription database study of predictors. *Eur J Clin Pharmacol*. 2009;65(3):295–301.