Drug and Alcohol Dependence Reports 15 (2025) 100325

Contents lists available at ScienceDirect

Drug and Alcohol Dependence Reports

journal homepage: www.elsevier.com/locate/dadr

Influence of SSRI and SNRI co-prescription on benzodiazepine prescription trajectories

Kerry L. Kinney [a,1,*], Eliseu da Cruz Moreira-Junior [b,1], Laís F. Berro [b], Matthew C. Morris [b,c], James K. Rowlett [b]

[a] Osher Center for Integrative Health, Department of Physical Medicine & Rehabilitation, Vanderbilt University Medical Center, 3401 West End Ave, Nashville, TN 37203, USA
[b] Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, 2500 N State St, Jackson, MS 39216, USA
[c] Department of Anesthesiology, Vanderbilt University Medical Center, 1211 Medical Center Drive, Nashville, TN 37232, USA

HIGHLIGHTS

- SSRI or SNRI co-prescription is linked to longer benzodiazepine treatment duration.
- SSRI or SNRI co-prescription is associated with greater maximum benzodiazepine dose.
- Younger age and non-Black race were associated with higher benzodiazepine dose.
- Anxiety disorder diagnosis was associated with greater benzodiazepine dose.

ARTICLE INFO

Keywords:
Benzodiazepine
Selective serotonin reuptake inhibitor
Serotonin and norepinephrine reuptake inhibitor
Prescription
Prescribing practices

ABSTRACT

Purpose: This study examined whether co-prescription of selective serotonin reuptake inhibitors (SSRIs) or serotonin or norepinephrine reuptake inhibitors (SNRI)s with benzodiazepines is associated with differences in benzodiazepine prescriptions both within individual patients over time and between patients.
Methods: We analyzed deidentified electronic health records of patients prescribed a benzodiazepine between 2020 and 2022 ($N = 847$). Patients were categorized into three groups: those co-prescribed an SSRI, those co-prescribed an SNRI, and those not co-prescribed an SSRI or SNRI.
Results: Individuals co-prescribed an SSRI (M=6.63) or an SNRI (M=8.31) had more benzodiazepine prescription encounters than those who were not co-prescribed an SSRI/SNRI (M=5.08). Individuals co-prescribed an SSRI or SNRI also received a higher maximum benzodiazepine dosage than those who were not co-prescribed an SSRI/SNRI (SSRI M=2.41; SNRI M=2.30; No SSRI/SNRI M=1.91 diazepam milligram equivalent defined daily doses). Multilevel models indicated the SSRI co-prescription group received a higher initial benzodiazepine dosage (b=0.394), but showed no significant change in benzodiazepine dosage over time. When controlling for demographic and clinical correlates of benzodiazepine prescriptions, those who were not co-prescribed an SSRI showed an increase in benzodiazepine dose over time (b=0.075). Multilevel models revealed no relationship between SNRI co-prescription and starting benzodiazepine dosage or change in benzodiazepine dosage over time. An anxiety disorder diagnosis, younger age, and non-Black/African American race were associated with higher benzodiazepine dose.
Conclusions: Individuals who are co-prescribed an SSRI/SNRI may be vulnerable to longer treatment durations and higher prescribed doses of benzodiazepines, raising concerns about risk for dependence among individuals receiving combined benzodiazepine and SSRI/SNRI treatment.

* Correspondence to: 2301 Vanderbilt Place, Nashville, TN 37240, USA.
E-mail address: kerry.l.kinney@vumc.org (K.L. Kinney).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.dadr.2025.100325
Received 11 October 2024; Received in revised form 7 March 2025; Accepted 14 March 2025
Available online 18 March 2025

1. Introduction

Since their discovery in the early 1960s, benzodiazepines have been prescribed widely as therapeutic tools because of their anxiolytic, sedative, and anticonvulsant properties (Calcaterra and Barrow, 2014; Maust et al., 2019; Wick, 2013). Despite their clinical utility, benzodiazepines are associated with risk of adverse effects, including psychomotor impairment, cognitive decline, falls, accidents, and substance use disorders, and chronic use can lead to physical dependence or the development of a use disorder (Guina and Merrill, 2018; Lader, 2011; Licata and Rowlett, 2008; Uzun et al., 2010; Vgontzas et al., 1995). Moreover, as drug overdoses have surged in recent decades, benzodiazepines remain the second most common prescription medication involved in overdose deaths (NIDA, 2024). Benzodiazepines are often prescribed in combination with selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), but it remains unclear how SSRI/SNRI co-prescription affects benzodiazepine use trajectories, which could affect patients' risk for adverse outcomes (Bushnell et al., 2021, 2017). The present study examines how co-prescribed SSRIs or SNRIs with benzodiazepines relate to variation in benzodiazepine treatment.

Pre-clinical (Bagdy et al., 2001; Griebel, 1995) and clinical (Gorman et al., 1987; Grillon et al., 2007) research indicates acute administration of SSRIs is associated with an anxiogenic effect. Consequently, reuptake inhibitors and benzodiazepines are commonly co-prescribed, especially during the first weeks of SSRI treatment (Bushnell et al., 2021, 2017). Some evidence supports this combination approach, particularly in individuals with comorbid depression and anxiety; it can mitigate the transient increase in anxiety symptoms and sleep disturbance associated with early SSRI/SNRI treatment (Dunlop and Davis, 2008). Furthermore, compared to SSRI/SNRI monotherapy, SSRI/SNRI and benzodiazepine co-prescription may improve anxiety and depression symptoms more rapidly, reduce co-occurring sleep disruption, and reduce antidepressant treatment drop-out (Dunlop and Davis, 2008; Smith et al., 1998; Furukawa et al., 2001, but see Wu et al., 2012; Altmann et al., 2020). Preclinical evidence suggesting benzodiazepine treatment attenuated the acute anxiogenic effects of SSRIs in animals supports this practice (e.g., Birkett et al., 2011). However, some research suggests the benefits of co-prescribing a benzodiazepine with an SSRI are short-lived (Furukawa et al., 2001; Pollack et al., 2003).

Preliminary research suggests that co-prescription of benzodiazepines and selective reuptake inhibitors may carry increased risk compared to benzodiazepines alone. One study found that co-prescription of SSRIs and benzodiazepines might be associated with longer-term use of benzodiazepines (Bushnell et al., 2017), thereby increasing risk for dependence. For example, patients who are co-prescribed an SSRI and a benzodiazepine are more likely to continue taking the benzodiazepine after 6 months compared to those who are co-prescribed a benzodiazepine with another antidepressant (mirtazapine; Hashimoto et al., 2016). Because SSRIs and SNRIs have overlapping mechanisms of action, it is possible that SNRI co-prescription has a similar relationship with benzodiazepine prescription duration, but to our knowledge, this question remains unexamined. There is growing concern that benzodiazepine dependence may develop in the context of long-term benzodiazepine use, even in the absence of a benzodiazepine use disorder or dose escalation and among those taking benzodiazepines as prescribed (Peng et al., 2022a). Therefore, it is important to clarify the relationship between the co-prescription of an SSRI/SNRI and benzodiazepine treatment duration.

Preliminary evidence also suggests that, compared to individuals prescribed a benzodiazepine without an antidepressant, individuals co-prescribed an antidepressant are at greater risk of benzodiazepine dose escalation (Mori et al., 2023; Soumerai et al., 2003). Soumerai and colleagues (2003) found that patients co-prescribed a benzodiazepine and antidepressant were more than three times as likely to escalate to a high benzodiazepine dosage compared to those prescribed a benzodiazepine without an antidepressant. However, the authors examined the effect of all antidepressants, rather than limiting the analysis to SSRIs/SNRIs. Additional studies are needed to understand the impact of SSRIs/SNRIs on benzodiazepine treatment. Moreover, Mori and colleagues (2023) found that, in a sample of individuals with an anxiety disorder who were prescribed a benzodiazepine at an outpatient psychiatric clinic in Japan, those who were co-prescribed an SSRI exhibited a larger increase in benzodiazepine dosage over two years compared to those who were not. The potential association between SSRI co-prescription and increasing benzodiazepine dosage is concerning, as higher benzodiazepine dose can increase risk for physical dependence, benzodiazepine use disorder, and other negative outcomes, such as accidents and falls (Brandt and Leong, 2017; Lader, 2014; Peng et al., 2022b; Skinner et al., 2017).

The present study investigated benzodiazepine prescription patterns, combined or not with SSRI and SNRI prescriptions, using data from a research data warehouse at an academic medical center in the Southeastern United States. We conducted a within- and between-person investigation of the relationship between the co-prescription of SSRIs or SNRIs and benzodiazepines over time. We aimed to determine whether:

1. the duration or maximum dosage of benzodiazepine treatment differed between the SSRI/SNRI groups and the non-SSRI/SNRI group.
2. the starting benzodiazepine dosage differed between the SSRI/SNRI and the non-SSRI/SNRI groups.
3. the benzodiazepine dosage trajectories over time differed between individuals in the SSRI/SNRI and the non-SSRI/SNRI groups
4. any identified relationship between SSRI/SNRI exposure and starting benzodiazepine dose or benzodiazepine trajectory persists when controlling for established demographic and clinical correlates of benzodiazepine prescriptions to control for potential confounders and enhance the validity of our findings.

2. Methods

2.1. Data source

We retrospectively analyzed electronic health record data obtained from a research data warehouse at an academic medical center (University of Mississippi Medical Center, 2020). The data warehouse compiles data from the electronic records system, Epic, based on encounters at the institution's hospitals and clinics. All 18 HIPAA identifiers have been removed from the dataset, all encounters are date-shifted, and the researchers have no means to re-identify the data. Thus, this dataset meets the standard in §164.514(a) of the HIPAA Privacy Rule. The deidentified data is no longer protected by the Privacy Rule because it does not fall within the definition of Protected Health Information. Research using deidentified data that cannot be re-identified is not considered human subjects research and is, therefore, not subject to Institutional Review Board approval.

This study included data from encounters in the following specialties, which have previously been linked to high rates of benzodiazepine visits: family medicine, outpatient psychiatry, geriatric medicine, neurology, obstetrics, and/or gynecology (Agarwal and Landon, 2019). Encounters and prescriptions from other specialties were excluded. Only patients who were prescribed a benzodiazepine at an encounter in one or more of the included specialties occurring between January 1, 2020 and December 31, 2022 were included in the final analyses. Patients who were prescribed a benzodiazepine in the previous year (between January 1, 2019 and December 31, 2019) and patients who did not have data available on benzodiazepine prescription status in 2019 were excluded from the final analyses to limit confounding factors (see Fig. 1 for a diagram of included patients and encounters). Research suggests benzodiazepines are cleared from the body within weeks to a month

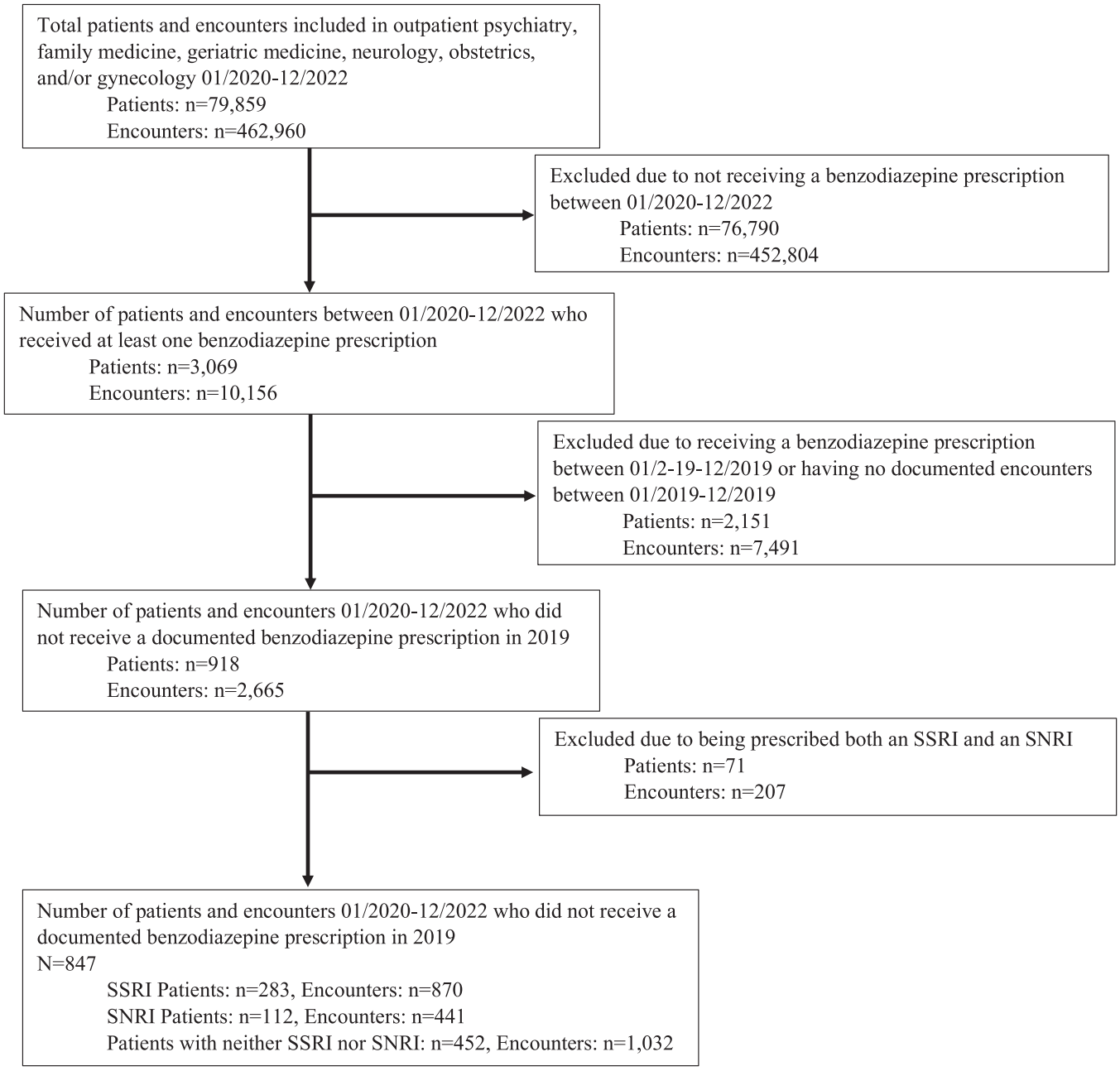

Fig. 1. Encounter flow diagram.

following discontinuation, though higher doses can extend the window of detection (Substance Abuse and Mental Health Services Administration, 2012); a one-year washout period was chosen to limit the contribution of any potential prior benzodiazepine exposure to the present findings. No other exclusion criteria were applied.

2.2. Analytic approach

We used the Statistical Package for the Social Sciences (SPSS; Chicago, IL version 28.0) for data management and descriptive analyses. Patients prescribed a benzodiazepine were divided into three groups: those that received an SSRI but no SNRI (SSRI group), those that received an SNRI but no SSRI (SNRI group), and those that received neither an SSRI nor an SNRI (No SNRI/SSRI group). Comparisons between the groups on demographic characteristics were made using independent t-tests or Chi-square analysis, as appropriate (see Table 1).

2.2.1. Variable definitions

Full information on the creation and definition of all study variables can be found in the Supplementary Material. Variables of primary interest to the study are described below.

2.2.1.1. Encounter dosage. We converted the benzodiazepine dose at each encounter for each patient to the diazepam milligram equivalent defined daily doses (DMEDDD) to permit examination of all benzodiazepine agents prescribed to patients in the present sample. DMEDDD represents the number of diazepam defined daily doses that would be equal to the dosage prescribed of the original drug at the encounter (Brandt et al., 2018).

2.2.1.2. Maximum dosage. For each patient, the "Maximum Dosage" was determined by identifying the highest dosage prescribed at any benzodiazepine prescription encounter (i.e., the patient's maximum

Table 1
Descriptive and clinical characteristics for patients who were prescribed an SSRI or SNRI with a benzodiazepine prescription ("SSRI" and "SNRI" groups, respectively) at any point during the time frame of interest, and those who were not prescribed an SSRI or SNRI ("No SSRI/SNRI" group).

	Mean (*SD*) or *n* (%)			Group Comparison Between SSRI and No SSRI/SNRI		Group Comparison Between SNRI and No SSRI/SNRI	
	SSRI (*n*= 283)	SNRI (*n*= 112)	No SSRI/SNRI (*n* = 452)	*t or* χ^2	*p*	*t or* χ^2	*p*
Sociodemographic Variable							
Age (years)	47.53 (16.67)	49.13 (14.02)	49.48 (18.55)	1.47	.14	0.22	.83
Female	229 (80.92 %)	89 (79.46 %)	333 (73.67 %)	5.08 *	.02	1.60	.21
Race							
Black/African American	110 (38.87 %)	43 (38.39 %)	209 (46.24 %)	4.48	.11	2.24	.33
White/Caucasian	163 (57.60 %)	69 (61.61 %)	233 (51.55 %)				
Other	10 (3.53 %)	3 (2.68 %)	10 (2.21 %)				
Has Insurance	219 (77.39 %)	88 (78.57 %)	347 (76.77 %)	0.04	.85	0.17	.68
Diagnostic Status							
Anxiety Disorder	249 (87.99 %)	99 (88.39 %)	254 (56.19 %)	81.43 * **	< .001	39.74 * **	< .001
Mood Disorder	215 (75.97 %)	75 (66.96 %)	120 (26.55 %)	171.38 * **	< .001	64.82 * **	< .001
Sleep Disorder	115 (40.64 %)	40 (35.71 %)	100 (22.12 %)	28.82 * **	< .001	8.88 * *	.003
Seizure Disorder	24 (8.48 %)	14 (12.50 %)	92 (20.35 %)	18.46 * **	< .001	3.63	.06

Note. SSRI=Prescribed an SSRI at any encounter between January 1, 2020 and December 31, 2022; SNRI=Prescribed an SNRI at any encounter between January 1, 2020 and December 31, 2022; No SSRI/SNRI=Not prescribed an SSRI or an SNRI at any encounter between January 1, 2020 and December 31, 2022; DMEDDD=diazepam milligram equivalent defined daily doses.
* **$p < .001$; * $p < .01$; *$p < .05$

Encounter Dosage).

2.2.1.3. Total benzodiazepine prescriptions. For each patient, we determined the number of benzodiazepine prescription events, including refills, as a proxy of benzodiazepine treatment duration. Days' supply was unavailable in this dataset.

2.2.1.4. Benzodiazepine encounter index. "Benzodiazepine Encounter Index" indicates the count of encounters a patient had at any of the departments of interest since January 1, 2020 where they were prescribed a benzodiazepine, adjusted so that the intercept reflects the first encounter at which a benzodiazepine was prescribed (e.g., 0 indicates patient's first benzodiazepine prescription encounter in the time frame, 1 indicates patient's second benzodiazepine prescription encounter, etc.). Benzodiazepine Encounter Index was entered as an independent variable in the multilevel models (see below for further detail) to examine discrete dates a given patient received benzodiazepine prescriptions.

2.2.1.5. Diagnoses. Dichotomous variables indicated whether a patient was diagnosed with anxiety, sleep, mood, or seizure disorders at a given encounter.

2.2.2. Objective 1 analysis

To determine whether the duration of benzodiazepine treatment or maximum benzodiazepine dosage differed in the SSRI/SNRI groups compared to the non-SSRI/SNRI group, we conducted independent samples t-tests.

2.2.3. Objectives 2–4 analysis

Multilevel models (MLMs) were specified using Hierarchical Linear Models (HLM v. 8) to examine within-individual changes in benzodiazepine dosage across encounters (level 1) and between-patient differences in benzodiazepine dosage (level 2) (Raudenbush et al., 2019). MLMs permit examination of nested data; we examined benzodiazepine prescription events over time within patients (Nezlek, 2012; Peugh, 2010). This accounts for nonindependent observations, given each patient may have multiple benzodiazepine prescription events. MLM analyses proceeded in three steps. Model 1 ("Base Model") examined the relationship between SSRI co-prescription and starting benzodiazepine dosage (intercept) and linear change in benzodiazepine over time (slope) (Objectives 2–3). Model 2 ("Demographic Model") examined the relationship between SSRI co-prescription and several demographic factors (i.e., Age, Sex, Race, and Insurance status) and benzodiazepine dosage (Objective 4). Model 3 ("Diagnosis Model") included all independent variables from Model 2, as well as diagnostic status for Anxiety, Mood, Sleep, and Seizure disorders (Objective 4). The same analyses were repeated to investigate the relationship between SNRI co-prescription and benzodiazepine dosage. The full model, including all independent variables, is presented in the Supplementary Material.

Missing data were handled using maximum-likelihood estimation; the model used all available data, even if some patients were missing some level 1 data points, to estimate the parameters (Nezlek, 2012). For the MLMs, simple slope analysis was used to probe significant interactions (Preacher et al., 2006). To account for multiple hypothesis tests, we used the Benjamini-Hochberg false discovery rate correction to control for Type I errors by adjusting the p-value based on the number of significant results in a family of tests (Benjamini & Hochberg, 1995).

3. Results

3.1. Patient characteristics

Demographic characteristics are presented in Table 1 separately for patients in the SSRI (n = 283), SNRI (n = 112), and No SSRI/SNRI (n = 452) groups. Most patients were female, and a greater percentage of patients in the SSRI group were female compared to the No SSRI/SNRI group. Across groups, the patients on average were in their late forties. Patients primarily identified as White/Caucasian and had medical insurance. Other than percentage of females per group differing between the SSRI and No SSRI/SNRI groups, no other demographic variables significantly differed between the No SSRI/SNRI group and the other two groups.

3.2. Objective 1

Fig. 2 displays the average number of benzodiazepine prescriptions (a) and average maximum benzodiazepine dosage (b) by group. Patients in the SSRI group were prescribed benzodiazepines for a greater duration (M=6.63 prescriptions, SD=7.79) than patients in the No SSRI/SNRI group (M=5.08 prescriptions, SD=6.89; t=2.73, $p = .007$, d=.21). The SSRI group also received a significantly greater maximum benzodiazepine dosage (M=2.41 DMEDDD, SD=2.63) than the No SSRI/SNRI group (M=1.91 DMEDDD, SD=2.26; $t = 2.75$, $p = .006$), d= .21.

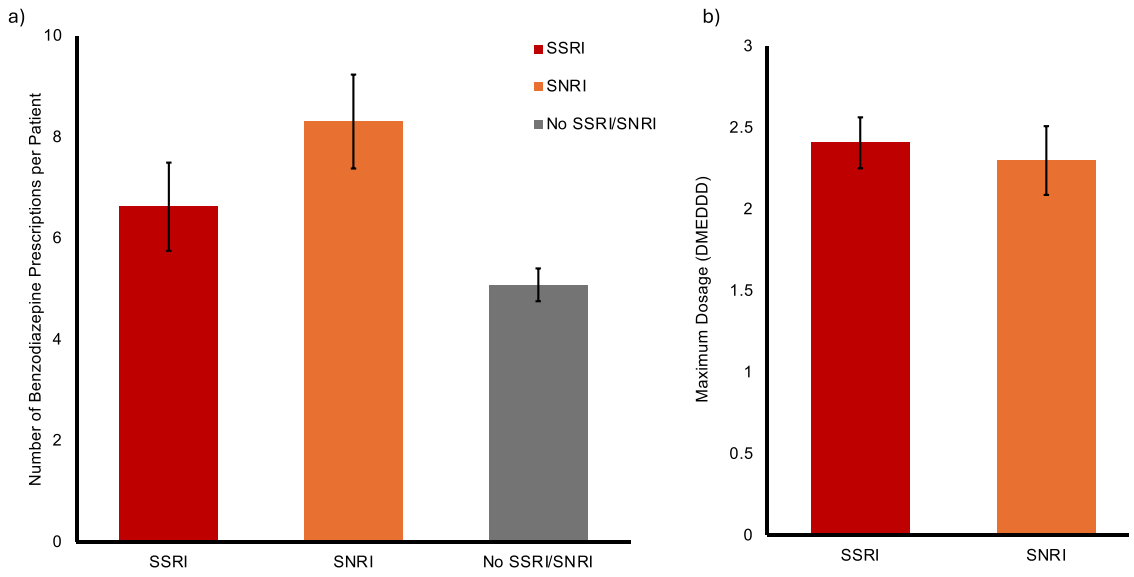

Fig. 2. a) Number of benzodiazepine prescriptions, including refills, for patients prescribed a selective serotonin reuptake inhibitor (SSRI) plus a benzodiazepine ("SSRI" group), prescribed a serotonin and norepinephrine reuptake inhibitor (SNRI) plus a benzodiazepine ("SNRI" group), or benzodiazepine alone ("No SSRI/SNRI" group). b) Maximum benzodiazepine dosage for patients in the SSRI, SNRI, or no SSRI/SNRI group. Maximum dose is expressed as the diazepam milligram equivalent defined daily doses (DMEDDD) + SEM. Data were analyzed with independent t-tests.

Patients in the SNRI group were prescribed benzodiazepines for a greater duration (M=8.31 prescriptions, SD=9.83) than patients in the No SSRI/SNRI group ($t = 3.28$, $p < .001$, d=.43). The SNRI group also received a significantly greater maximum benzodiazepine dosage (M=2.30 DMEDDD, SD=2.24) than the No SSRI/SNRI group ($t = 1.65$, $p = .049$, d=.17).

3.3. Objectives 2–4: multilevel model analysis

3.3.1. SSRI Model 1

Full results of the SSRI MLM analyses are presented in Table 2. Model 1 revealed a significant, positive within-person slope (b=0.082, SE=0.025, $p = .007$), suggesting that, on average, benzodiazepine dosage increased across an individual's encounters. SSRI co-prescription was associated with a significantly higher benzodiazepine starting dosage than the no SSRI/SNRI group (b=0.394, SE=0.145, $p = .007$), meaning on average, a patient's starting benzodiazepine dosage was 0.394 DMEDDD higher if they were prescribed an SSRI compared to patients who were not prescribed an SSRI. The relationship between SSRI co-prescription status and the linear change in benzodiazepine dosage over time approached significance (b=-0.111, SE=0.057, $p = .052$).

3.3.2. SSRI Model 2

Model 2 revealed that patients who were younger (b=-0.008, SE=0.003, $p = .007$) and who identified as Black (b=-0.350, SE=0.134, $p = .009$) had a lower benzodiazepine dosage. The association between SSRI co-prescription and starting benzodiazepine dosage (b=0.362, SE=0.148, $p = .015$) remained significant. Benzodiazepine dosage increased significantly over time (slope) (b=0.079, SE=0.025, $p = .002$) across groups. The relationship between SSRI co-prescription status and change in benzodiazepine dosage over time was not significant (b=-

Table 2
Multilevel Model Analysis of Benzodiazepine Dose at Each Encounter: SSRI Models.

	Base Model for Benzodiazepine Dose		Demographic-Adjusted Model for Benzodiazepine Dose		Diagnosis-Adjusted Model for Benzodiazepine Dose	
Independent Variables	*b (SE)*	*p*	*b (SE)*	*p*	*b (SE)*	*p*
Level 1 (within person)						
Benzodiazepine Encounter Index	0.082 (0.025)* *	.001	0.079 (0.025)* *	.002	0.075 (0.024)* *	.002
Anxiety Disorder					0.373 (0.110)* *	.001
Sleep Disorder					−0.064 (0.162)	.69
Mood Disorder					0.226 (0.162)	.07
Seizure Disorder					0.258 (0.171)	.13
Level 2 (between person)						
Intercept	1.618 (0.081)* **	< .001	2.098 (0.236)* **	< .001	1.88 (0.229)* **	< .001
SSRI	0.394 (0.145)* *	.01	0.362 (0.148)*	.01	0.220 (0.156)	.16
SSRI x Encounter Index	−0.111 (0.057)	.05	−0.108 (0.057)	.06	−0.108 (0.055)*	.049
Age			−0.008 (0.003)* *	.01	−0.008 (0.003)* *	.01
Sex			−0.201 (0.149)	.18	−0.276 (0.147)	.06
Black Race			−0.350 (0.134)* *	.01	−0.301 (0.130)*	.02
Other Race			0.424 (0.402)	.29	0.321 (0.398)	.42
Insurance Status			−0.234 (0.172)	.18	−0.222 (0.170)	.19

Note. Encounter Number=Count of encounters a patient had at any of the departments of interest in the study timeframe; Anxiety Disorder=Whether an anxiety disorder was included in the encounter diagnoses; Sleep Disorder=Whether a sleep disorder was included in the encounter diagnoses; Mood Disorder=Whether a mood disorder was included in the encounter diagnoses; Seizure Disorder=Whether a seizure disorder was included in the encounter diagnoses; SSRI=Whether a patient was prescribed an SSRI at any encounter in the study timeframe.
* **$p < .001$; * *$p < .01$; *$p < .05$.

0.108, *SE*=0.057, $p = .056$).

3.3.3. SSRI Model 3

Model 3 revealed an anxiety disorder diagnosis was associated with higher benzodiazepine dosage (*b*=0.373, *SE*=0.110, $p = .001$). No other diagnoses had a significant relationship with benzodiazepine dosage. The relationship between SSRI co-prescription and starting benzodiazepine dosage was no longer significant (*b*=0.220, *SE*=0.156, $p = .159$). However, the relationship between SSRI co-prescription and the linear change in benzodiazepine dosage over time was significant (*b*=-0.208, *SE*=0.055, $p = .049$). Follow-up simple slope analysis revealed there was a significant increase in benzodiazepine dose over time in the No SSRI/SNRI group (*b*=0.075, $t = 3.167$, $p = .002$) but not in the SSRI group (*b*=-0.033, $t = -0.668$, $p = .504$) (Fig. 3).

3.3.4. SNRI Model 1

Full results of the SNRI MLM are presented in Table 3. Model 1 revealed a significant increase in benzodiazepine dosage over time (*b*=0.070, *SE*=0.024, $p = .004$) across groups. SNRI co-prescription was not associated with starting benzodiazepine dosage (*b*=0.101, *SE*=0.183, $p = .579$) or linear change in benzodiazepine dosage over time (*b*=0.057, *SE*=0.053, $p = .278$).

3.3.5. SNRI Model 2

Model 2 revealed individuals with insurance had a lower starting benzodiazepine dosage (*b*=-0.510, *SE*=0.219, $p = .020$) than those who were uninsured. The effects of age (*b*=-0.007, *SE*=0.004, $p = .056$) and Black race (*b*=-0.297, *SE*=0.155, $p = .055$) approached significance. No other effects were significant ($p \geq .136$).

3.3.6. SNRI Model 3

Model 3 revealed anxiety disorder (*b*=0.339, *SE*=0.107, $p = .002$) and mood disorder diagnosis (*b*=0.401, *SE*=0.158, $p = .011$) were associated with higher benzodiazepine dosage. Individuals who were older (*b*=-0.008, *SE*=-.004, $p = .047$) and insured (*b*=-0.507, *SE*=0.216, $p = .019$) had lower benzodiazepine dosage. No other effects were significant ($p \geq .117$).

4. Discussion

This retrospective analysis of electronic health records found that patients prescribed a benzodiazepine and an SSRI or SNRI received benzodiazepine prescriptions for a greater duration and at a higher maximum benzodiazepine dose than patients who were prescribed neither an SSRI nor an SNRI. Additionally, patients co-prescribed an SSRI had higher initial benzodiazepine doses, which remained stable over time, whereas patients without an SSRI started at lower benzodiazepine doses but experienced benzodiazepine dose increases. There was no relationship between SNRI co-prescription status and benzodiazepine dose changes over time. Moreover, patients who were assigned an anxiety disorder diagnosis at a given encounter received a higher benzodiazepine dose at that encounter, irrespective of SSRI/SNRI prescription status, whereas younger patients were prescribed higher doses than older patients.

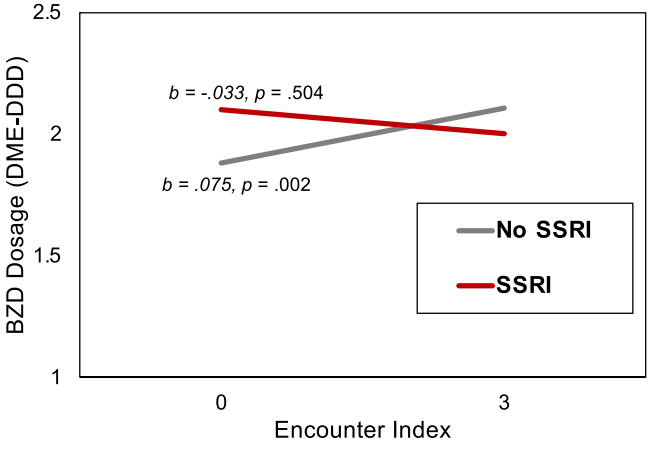

Fig. 3. This figure illustrates a simple slope analysis of benzodiazepine (BZD) dosage (expressed as diazepam milligram equivalent defined daily dose, DMEDDD) across encounters in individuals prescribed a selective serotonin reuptake inhibitor (SSRI and individuals who were not prescribed an SSRI or SNRI.

Our findings suggest that individuals co-prescribed an SSRI or an SNRI may experience longer benzodiazepine treatment durations and higher prescribed benzodiazepine doses. The reasons underlying this prescription pattern remain unclear, but these findings align with prior research showing that co-prescribing benzodiazepines and SSRIs might be associated with longer-term benzodiazepine use (Bushnell et al., 2017; Hashimoto et al., 2016). Co-administering some SSRIs (e.g., fluvoxamine, fluoxetine) may increase benzodiazepine plasma concentrations by inhibiting enzymes responsible for the drugs' metabolism (e.g., alprazolam, diazepam, bromazepam; Fleishaker and Hulst, 1994; Lemberger et al., 1988; Suzuki et al., 2003). However, increased exposure levels would suggest that clinicians use a lower, rather than higher, benzodiazepine dose. It is possible that higher plasma concentrations in individuals co-prescribed an SSRI with a benzodiazepine could result in greater levels of dependence, thereby motivating patients to continue requesting benzodiazepine prescriptions from their provider. Additionally, individuals with comorbid depression and anxiety often show more severe, chronic symptoms (e.g., Dunlop and Davis, 2008; Sareen et al., 2005; Stein, 2001), possibly necessitating higher starting doses and longer treatment duration to achieve efficacy. Further research is needed to explicate the mechanism(s) by which SSRI/SNRI co-prescription is associated with increased dose and duration of benzodiazepine treatment.

To examine within- and between-person associations with benzodiazepine dosage over time, multilevel model (MLM) analyses were performed. The MLM analysis revealed that for SSRIs, the starting benzodiazepine dosage was 0.394 DMEDDD higher for patients prescribed the combination compared to the group who was not prescribed an SSRI, but they showed no change in dose across encounters. In contrast, patients prescribed benzodiazepines without an SSRI had a lower starting dosage but showed a significant increase in dose over time. This pattern was not observed for SNRI co-prescription. Our results contrast with Mori and colleagues' (2023) findings, which showed that, in a sample of individuals with an anxiety disorder, benzodiazepine doses increased modestly over a two-year period when co-prescribed with SSRIs but decreased over time in the no SSRI group. Mori and colleagues' study (2023) took place over a longer time period (2 years after initial encounter) and in a different country (Japan). Therefore, differences in the timeframe and cultural or healthcare factors cannot be ruled out as contributing factors to the discrepant findings.

For patients receiving benzodiazepines alone, the observed dose escalation contrasts with literature showing this phenomenon is rare, even in the context of long-term use (Soumerai et al., 2003; Tvete et al., 2013; Veronese et al., 2007; Willems et al., 2013), although dose escalation is sometimes found (Alessi-Severini et al., 2016; Rosenqvist et al., 2023; Van Hulten et al., 2003). Dose escalation is often associated with misuse and the development of use disorders. However, it is unknown whether the dose escalation in this study was patient- or provider-driven.

Anxiety disorder diagnosis and younger age were associated with higher benzodiazepine doses at a given encounter, while identifying as Black/African American was associated with lower benzodiazepine dosage. The relationship between anxiety disorder diagnosis and higher dosage is in line with current practice guidelines, which suggest utilizing a higher benzodiazepine dosage for anxiety disorders compared to other

Table 3
Multilevel Model Analysis of Benzodiazepine Dose at Each Encounter: SNRI Models.

Independent Variables	Base Model for Benzodiazepine Dose *b (SE)*	*p*	Demographic-Adjusted Model for Benzodiazepine Dose *b (SE)*	*p*	Diagnosis-Adjusted Model for Benzodiazepine Dose *b (SE)*	*p*
Level 1 (within person)						
Benzodiazepine Encounter Index	0.070 (0.024)* **	.004	0.068 (0.024)* *	.01	0.066 (0.023)* *	.01
Anxiety Disorder					0.339 (0.107)* *	.002
Sleep Disorder					0.090 (0.129)	.49
Mood Disorder					0.401 (0.158)*	.01
Seizure Disorder					0.091 (0.335)	.79
Level 2 (between person)						
Intercept	1.611 (0.079)* **	< .001	2.242 (0.259)* **	< .001	2.006 (0.252) * **	.01
SNRI	0.101 (0.183)	.58	0.090 (0.188)	.63	−0.126 (0.211)	.55
SNRI x Encounter Index	0.057 (0.053)	.28	0.057 (0.052)	.27	0.062 (0.052)	.23
Age			−0.007 (0.004)	.06	−0.008 (0.004)	.05
Sex			−0.171 (0.151)	.26	−0.236 (0.151)	.12
Black Race			−0.297 (0.155)	.06	−0.208 (0.154)	.18
Other Race			0.912 (0.611)	.14	0.751 (0.619)	.23
Insurance Status			−0.510 (0.219)*	.02	−0.507 (0.216)*	.02

Note. Encounter Number=Count of encounters a patient had at any of the departments of interest in the study timeframe; Anxiety Disorder=Whether an anxiety disorder was included in the encounter diagnoses; Sleep Disorder=Whether a sleep disorder was included in the encounter diagnoses; Mood Disorder=Whether a mood disorder was included in the encounter diagnoses; Seizure Disorder=Whether a seizure disorder was included in the encounter diagnoses; SNRI=Whether a patient was prescribed an SNRI at any encounter in the study timeframe.
* $^{**}p < .001$; * $^{*}p < .01$; $^{*}p < .05$.

indications (Bounds and Nelson, 2023). Moreover, when including diagnostic status in the model, the association between SSRI co-prescription and starting benzodiazepine dosage was no longer significant, suggesting this finding may have been driven by diagnostic status, rather than SSRI co-prescription per se. It should be noted that only 34 patients who were co-prescribed an SSRI were not diagnosed with an anxiety disorder; thus, further research is needed to parse the relationship between SSRI co-prescription, anxiety disorder diagnosis, and starting benzodiazepine dosage. The finding that younger patients were more likely to receive higher doses is also in line with practice guidelines, which suggest using lower doses in older adults, given they are more sensitive to and less able to effectively metabolize benzodiazepines (American Geriatrics Society Beers Criteria Update Expert Panel, 2023). The finding that patients who identify as Black/African American receive lower starting benzodiazepine dosages extends prior research, which has demonstrated that Black or African American patients are less likely to be prescribed benzodiazepines compared to other racial/ethnic groups (Cook et al., 2018; Dore et al., 2023; Hall et al., 2010; Ribas Roca et al., 2023). Our study adds to this area of investigation by showing evidence of racial disparities in benzodiazepine dosage. Standardized screening and prescription practices may be useful in reducing these prescription disparities.

A clear concern regarding extended benzodiazepine prescription duration at higher doses in patients co-prescribed SSRI/SNRIs is the possibility of developing physical dependence. Chronic daily benzodiazepine use, even at low doses, can lead to dependence, resulting in withdrawal syndrome upon cessation (Authier et al., 2009; Edinoff et al., 2021; Mintzer et al., 1999; Mintzer and Griffiths, 2005). There is growing recognition that physiological dependence is likely prevalent in individuals who use benzodiazepines long-term, even in the absence of misuse or dose escalation (Peng et al., 2022a). The prescription durations observed in this study were long enough to result in physical dependence (Mintzer and Griffiths, 2005). Moreover, higher or escalating doses are associated with more severe withdrawal symptoms (Landry et al., 1992; Seivewright and Dougal, 1993). Although a trend of increasing dose was not observed for patients co-prescribed an SSRI, the higher starting and maximum benzodiazepine dose in the SSRI group is clearly of concern.

The observed dose escalation in the non-SSRI/SNRI group warrants further investigation. Dose escalation can signal risk for physical dependence (Landry et al., 1992; Seivewright and Dougal, 1993). However, this group's lower starting and maximum benzodiazepine doses and shorter benzodiazepine treatment duration might suggest lower risk for dependence. This could reflect cautious prescribing by providers aiming for minimal effective doses for each patient. Alternatively, this group may have less severe symptoms. Further research is needed to understand how patient characteristics and other factors influence the relationship between SSRI/SNRI co-prescription and benzodiazepine dose, duration, and risks.

Our results should be considered in light of several limitations. First, the SSRI/SNRI and benzodiazepine prescriptions occurred in the same window, preventing conclusions regarding the directionality of their associations. It is possible that longer benzodiazepine prescription duration could increase the likelihood of a subsequent SSRI prescription or vice-versa. Second, we did not examine the effect of the dosage, timing, or duration of the SSRI/SNRI prescriptions, which could influence the observed differences if pharmacodynamic interactions are involved. Future research should examine whether these factors relate to baseline benzodiazepine dosage and change in benzodiazepine dosage over time. Similarly, we did not examine whether the relationship between SSRI/SNRI co-prescription and benzodiazepine dose and duration differed depending on the type of SSRI, SNRI, and/or benzodiazepine. Although the mechanisms of action are similar within a drug class, the specific drugs differ in their half-lives, potency, and interactions with other drugs (Marken and Munro, 2000; Strawn and Stimpfl, 2023). Additionally, the extent to which patients filled their prescriptions and used their medications as prescribed remains unknown, since no analysis of drug levels was available for these patients. Finally, while the models adjusted for psychiatric diagnoses which could influence time, dose, and duration of medication treatment, we did not examine symptom severity, which could help explain some of the present findings. It is possible that more severe symptoms leads to both co-prescription of an SSRI/SNRI and a benzodiazepine and higher maximum benzodiazepine dosage and treatment duration. Indeed, some guidelines recommend adjusting benzodiazepine treatment based on symptom severity (Kaplan and DuPont, 2005). Finally, we used a cohort study design; random assignment is needed to draw causal inferences regarding the link between SSRI/SNRI co-prescriptions and benzodiazepine dosage and treatment duration. Future research should utilize a randomized controlled trial to examine the relationship between SSRI/SNRI co-prescription and benzodiazepine dosage and treatment duration while accounting for symptom severity.

In conclusion, we found that for patients in an academic medical center, SSRIs or SNRIs were often co-prescribed with benzodiazepines. Patients prescribed either combination were prescribed benzodiazepines for longer durations and at higher maximum doses than those prescribed a benzodiazepine alone. Higher benzodiazepine doses were associated with patients who were younger, identified as a race other than Black/African American, and had an anxiety disorder. The benzodiazepine prescription durations were long enough to invoke concerns regarding developing physical dependence, a phenomenon associated with increased risk of a substance use disorder. The extent to which co-prescription of SSRIs/SNRIs with benzodiazepines is a risk factor for dependence and substance use disorder involving a benzodiazepine awaits further scrutiny.

Contributors

KLK and ECM designed the study and drafted the manuscript in consultation with LFB and JKR. KLK conducted the analyses in consultation with MCM. MCM contributed to the selection of analytic approaches and interpretation of the results. All authors provided feedback on the manuscript and approved the final version.

Funding

This work was supported, in part, by grants from the National Institutes of Health (K01MD020122 [KLK], T32MH018921 [KLK], R00DA049886 [LFB], R01MD016838 [MCM], R01DA011792 [JKR], R01DA043204 [JKR]). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

CRediT authorship contribution statement

Berro Laís: Writing – review & editing, Writing – original draft, Conceptualization. **da Cruz Moreira-Junior Eliseu:** Writing – review & editing, Writing – original draft, Conceptualization. **Kinney Kerry:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Rowlett James:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Morris Matthew:** Writing – review & editing, Supervision, Formal analysis.

Declaration of Competing Interest

The authors have no relevant financial or non-financial interests to disclose.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dadr.2025.100325.

Data Availability

The data underlying the results presented in the study are available from the University of Mississippi Medical Center's (UMMC) Center for **Informatics** and Analytics: Center for Informatics and Analytics, University of Mississippi Medical Center, 350 W. Woodrow Wilson Ave. Suite 2500 Jackson, MS 39213 cia@umc.eduUMMC's Center for Informatics and Analytics enables collaborative use of information, enhances the existing centralized Enterprise Data Warehouse (EDW) to promote collaboration among investigators, increases analytic capabilities, and manages data in a variety of formats and across platforms. The Center's Honest Broker process provides de-identified data sets, limited data sets, and data sets containing protected health information (PHI) with proper approval and authorizations under the guidance of the EDW Governance Committee. The authors were approved to use the data from the EDW by the Institutional Review Board and the Center for Informatics and Analytics.

References

Agarwal, S.D., Landon, B.E., 2019. Patterns in outpatient benzodiazepine prescribing in the United States. JAMA Netw. Open 2, e187399. https://doi.org/10.1001/jamanetworkopen.2018.7399.

Alessi-Severini, S., Bolton, J.M., Enns, M.W., Dahl, M.E., Chateau, D., Collins, D.M., Sareen, J., 2016. Sustained use of benzodiazepines and escalation to high doses in a Canadian population. Psychiatr. Serv. 67, 1012–1018.

Altmann, H., Stahl, S.T., Gebara, M.A., Lenze, E.J., Mulsant, B.H., Blumberger, D.M., Reynolds III, C.F., Karp, J.F., 2020. Coprescribed benzodiazepines in older adults receiving antidepressants for anxiety and depressive disorders: association with treatment outcomes. J. Clin. Psychiatry 81, 1851.

American Geriatrics Society Beers Criteria Update Expert Panel, 2023. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J. Am. Geriatr. Soc. 71, 2052–2081.

Authier, N., Balayssac, D., Sautereau, M., Zangarelli, A., Courty, P., Somogyi, A.A., Vennat, B., Llorca, P.-M., Eschalier, A., 2009. Benzodiazepine dependence: focus on withdrawal syndrome. Annales Pharmaceutiques Francaises. Elsevier, pp. 408–413.

Bagdy, G., Graf, M., Anheuer, Z.E., Modos, E.A., Kantor, S., 2001. Anxiety-like effects induced by acute fluoxetine, sertraline or m-CPP treatment are reversed by pretreatment with the 5-HT2C receptor antagonist SB-242084 but not the 5-HT1A receptor antagonist WAY-100635. Int. J. Neuropsychopharmacol. 4, 399–408.

Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. stat. soc.: ser. B (Methodol.) 57, 289–300.

Birkett, M.A., Shinday, N.M., Kessler, E.J., Meyer, J.S., Ritchie, S., Rowlett, J.K., 2011. Acute anxiogenic-like effects of selective serotonin reuptake inhibitors are attenuated by the benzodiazepine diazepam in BALB/c mice. Pharmacol. Biochem. Behav. 98, 544–551.

Bounds, C.G., Nelson, V.L., 2023. Benzodiazepines. StatPearls [Internet]. StatPearls Publishing.

Brandt, J., Leong, C., 2017. Benzodiazepines and Z-drugs: an updated review of major adverse outcomes reported on in epidemiologic research. Drugs RD 17, 493–507.

Brandt, J., Alkabanni, W., Alessi-Severini, S., Leong, C., 2018. Translating benzodiazepine utilization data into meaningful population exposure: integration of two metrics for improved reporting. Clin. Drug Investig. 38, 565–572.

Bushnell, G.A., Stürmer, T., Gaynes, B.N., Pate, V., Miller, M., 2017. Simultaneous antidepressant and benzodiazepine new use and subsequent long-term benzodiazepine use in adults with depression, United States, 2001-2014. JAMA 74, 747–755.

Bushnell, G.A., Rynn, M.A., Crystal, S., Gerhard, T., Olfson, M., 2021. Simultaneous benzodiazepine and SSRI initiation in young people with anxiety disorders. J. Clin. Psychiatry 82, 37519.

Calcaterra, N.E., Barrow, J.C., 2014. Classics in chemical neuroscience: diazepam (valium). ACS Chem. Neurosci. 5, 253–260.

Cook, B., Creedon, T., Wang, Y., Lu, C., Carson, N., Jules, P., Lee, E., Alegría, M., 2018. Examining racial/ethnic differences in patterns of benzodiazepine prescription and misuse. Drug Alcohol Depend. 187, 29–34.

Dore, S., Weleff, J., Anand, A., Thompson, N.R., Barnett, B.S., 2023. Race, economic status, and disparities in the receipt of benzodiazepine prescriptions in a large primary care sample. Gen. Hosp. Psychiatry.

Dunlop, B.W., Davis, P.G., 2008. Combination treatment with benzodiazepines and SSRIs for comorbid anxiety and depression: a review. Prim. Care Companion J. Clin. Psychiatry 10, 222–228.

Edinoff, A.N., Nix, C.A., Hollier, J., Sagrera, C.E., Delacroix, B.M., Abubakar, T., Cornett, E.M., Kaye, A.M., Kaye, A.D., 2021. Benzodiazepines: uses, dangers, and clinical considerations. Neurol. Int. 13, 594–607.

Fleishaker, J.C., Hulst, L.K., 1994. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. Eur. J. Clin. Pharmacol. 46, 35–39.

Furukawa, T.A., Streiner, D.L., Young, L.T., 2001. Is antidepressant–benzodiazepine combination therapy clinically more useful?: a meta-analytic study. J. Affect. Disord. 65, 173–177.

Gorman, J.M., Liebowitz, M.R., Fyer, A.J., Goetz, D., Campeas, R.B., Fyer, M.R., Davies, S.O., Klein, D.F., 1987. An open trial of fluoxetine in the treatment of panic attacks. J. Clin. Psychopharmacol. 7, 329–331.

Griebel, G., 1995. 5-Hydroxytryptamine-interacting drugs in animal models of anxiety disorders: more than 30 years of research. Pharmacol. Ther. 65, 319–395.

Grillon, C., Levenson, J., Pine, D.S., 2007. A single dose of the selective serotonin reuptake inhibitor citalopram exacerbates anxiety in humans: a fear-potentiated startle study. Neuropsychopharmacology 32, 225–231.

Guina, J., Merrill, B., 2018. Benzodiazepines I: upping the care on downers: the evidence of risks, benefits and alternatives. J. Clin. Med. 7, 17.

Hall, S.A., Chiu, G.R., Kaufman, D.W., Kelly, J.P., Link, C.L., Kupelian, V., McKinlay, J.B., 2010. General exposures to prescription medications by race/ethnicity in a population-based sample: results from the Boston Area Community Health Survey. Pharmacoepidemiol. Drug Saf. 19, 384–392.

Hashimoto, T., Shiina, A., Hasegawa, T., Kimura, H., Oda, Y., Niitsu, T., Ishikawa, M., Tachibana, M., Muneoka, K., Matsuki, S., 2016. Effect of mirtazapine versus selective serotonin reuptake inhibitors on benzodiazepine use in patients with major depressive disorder: a pragmatic, multicenter, open-label, randomized, active-controlled, 24-week trial. Ann. Gen. Psychiatry 15, 1–15.

Kaplan, E.M., DuPont, R.L., 2005. Benzodiazepines and anxiety disorders: a review for the practicing physician. Curr. Med. Res. Opin. 21, 941–950.
Lader, M., 2011. Benzodiazepines revisited—will we ever learn? Addiction 106, 2086–2109.
Lader, M., 2014. Benzodiazepine harm: how can it be reduced? Br. J. Clin. Pharmacol. 77, 295–301.
Landry, M.J., Smith, D.E., McDuff, D.R., Baughman, O.L., 1992. Benzodiazepine dependence and withdrawal: identification and medical management. J. Am. Board Fam. Pract. 5, 167–175.
Lemberger, L., Rowe, H., Bosomworth, J.C., Tenbarge, J.B., Bergstrom, R.F., 1988. The effect of fluoxetine on the pharmacokinetics and psychomotor responses of diazepam. Clin. Pharmacol. Ther. 43, 412–419.
Licata, S.C., Rowlett, J.K., 2008. Abuse and dependence liability of benzodiazepine-type drugs: GABAA receptor modulation and beyond. Pharmacol. Biochem. Behav. 90, 74–89.
Marken, P.A., Munro, J.S., 2000. Selecting a selective serotonin reuptake inhibitor: clinically important distinguishing features. Prim. care Companion J. Clin. Psychiatry 2, 205.
Maust, D.T., Lin, L.A., Blow, F.C., 2019. Benzodiazepine use and misuse among adults in the United States. Psychiatr. Serv. 70, 97–106.
Mintzer, M.Z., Griffiths, R.R., 2005. Flumazenil-precipitated withdrawal in healthy volunteers following repeated diazepam exposure. Psychopharmacology 178, 259–267.
Mintzer, M.Z., Stoller, K.B., Griffiths, R.R., 1999. A controlled study of flumazenil-precipitated withdrawal in chronic low-dose benzodiazepine users. Psychopharmacology 147, 200–209.
Mori, K., Kodaka, F., Yamamoto, A., Yamazaki, R., Ishii, J., Yamadera, W., Miyata, H., Shigeta, M., 2023. Characteristics of patients with anxiety disorder without selective serotonin reuptake inhibitor prescription over a two-year period of pharmacotherapy. Neuropsychopharmacol. Rep. 44, 67–72.
Nezlek, J.B., 2012. Multilevel modeling for psychologists.
NIDA, 2024. Drug Overdose Deaths: Facts and Figures.
Peng, L., Meeks, T.W., Blazes, C.K., 2022a. Complex persistent benzodiazepine dependence—when benzodiazepine deprescribing goes awry. JAMA Psychiatry 79, 639–640.
Peng, L., Morford, K.L., Levander, X.A., 2022b. Benzodiazepines and related sedatives. Med. Clin. 106, 113–129.
Peugh, J.L., 2010. A practical guide to multilevel modeling. J. Sch. Psychol. 48, 85–112.
Pollack, M.H., Simon, N.M., Worthington, J.J., Doyle, A.L., Peters, P., Toshkov, F., Otto, M.W., 2003. Combined paroxetine and clonazepam treatment strategies compared to paroxetine monotherapy for panic disorder. J. Psychopharmacol. 17, 276–282.
Preacher, K.J., Curran, P.J., Bauer, D.J., 2006. Computational tools for probing interactions in multiple linear regression, multilevel modeling, and latent curve analysis. J. Educ. Behav. Stat. 31, 437–448.
Raudenbush, S.W., Bryk, A.S., Cheong, Y.K., Congdon, R.T., Toit, M., 2019. HLM 8: Linear and nonlinear modeling. Scientific Software International. Inc, Skokie, IL.
Ribas Roca, J., Everett, T., Dongarwar, D., Salihu, H.M., 2023. Racial-ethnic disparities in benzodiazepine prescriptions for anxiety in US Emergency Departments. J. Racial Ethn. Health Disparities 10, 334–342.
Rosenqvist, T.W., Wium-Andersen, M.K., Wium-Andersen, I.K., Jørgensen, M.B., Osler, M., 2023. Long-term use of benzodiazepines and benzodiazepine-related drugs: a register-based danish cohort study on determinants and risk of dose escalation. Am. J. Psychiatry 20230075 (appi. ajp).
Sareen, J., Cox, B.J., Afifi, T.O., De Graaf, R., Asmundson, G.J., Ten Have, M., Stein, M.B., 2005. Anxiety disorders and risk for suicidal ideation and suicide attempts: a population-based longitudinal study of adults. Arch. Gen. Psychiatry 62, 1249–1257.
Seivewright, N., Dougal, W., 1993. Withdrawal symptoms from high dose benzodiazepines in poly drug users. Drug Alcohol Depend. 32, 15–23.
Skinner, B.W., Johnston, E.V., Saum, L.M., 2017. Benzodiazepine initiation and dose escalation: a risk factor for inpatient falls. Ann. Pharmacother. 51, 281–285.
Smith, W.T., Londborg, P.D., Glaudin, V., Painter, J.R., 1998. Short-term augmentation of fluoxetine with clonazepam in the treatment of depression: a double-blind study. Am. J. Psychiatry 155, 1339–1345.
Soumerai, S.B., Simoni-Wastila, L., Singer, C., Mah, C., Gao, X., Salzman, C., Ross-Degnan, D., 2003. Lack of relationship between long-term use of benzodiazepines and escalation to high dosages. Psychiatr. Serv. 54, 1006–1011.
Stein, D.J., 2001. Comorbidity in generalized anxiety disorder: impact and implications. J. Clin. Psychiatry 62, 29–36.
Strawn, J.R., Stimpfl, J., 2023. Optimizing benzodiazepine treatment of anxiety disorders: Understanding the pharmacology of these agents can help guide medication selection and dosing. Curr. Psychiatry 22.
Substance Abuse and Mental Health Services Administration, 2012. Clinical Drug Testing in Primary Care, 32. Technical Assistance Publication (TAP), pp. 12–4668 (HHS Publication No. (SMA)).
Suzuki, Y., Shioiri, T., Muratake, T., Kawashima, Y., Sato, S., Hagiwara, M., Inoue, Y., Shimoda, K., Someya, T., 2003. Effects of concomitant fluvoxamine on the metabolism of alprazolam in Japanese psychiatric patients: interaction with CYP2C19 mutated alleles. Eur. J. Clin. Pharmacol. 58, 829–833.
Tvete, I.F., Bjørner, T., Aursnes, I.A., Skomedal, T., 2013. A 3-year survey quantifying the risk of dose escalation of benzodiazepines and congeners to identify risk factors to aid doctors to more rationale prescribing. BMJ Open 3, e003296.
University of Mississippi Medical Center, C. for I. and A., 2020. Patient Cohort Explorer (PCE). https://doi.org/10.6084/m9.figshare.12252737.v2
Uzun, S., Kozumplik, O., Jakovljević, M., Sedić, B., 2010. Side effects of treatment with benzodiazepines. Psychiatr. Danub. 22, 90–93.
Van Hulten, R., Teeuw, K.B., Bakker, A., Leufkens, H.G., 2003. Initial 3-month usage characteristics predict long-term use of benzodiazepines: an 8-year follow-up. Eur. J. Clin. Pharmacol. 58, 689–694.
Veronese, A., Garatti, M., Cipriani, A., Barbui, C., 2007. Benzodiazepine use in the real world of psychiatric practice: low-dose, long-term drug taking and low rates of treatment discontinuation. Eur. J. Clin. Pharmacol. 63, 867–873.
Vgontzas, A.N., Kales, A., Bixler, E.O., 1995. Benzodiazepine side effects: role of pharmacokinetics and pharmacodynamics. Pharmacology 51, 205–223.
Wick, J., 2013. The history of benzodiazepines. Consult. Pharm. ® 28, 538–548.
Willems, I.A., Gorgels, W.J., Oude Voshaar, R.C., Mulder, J., Lucassen, P.L., 2013. Tolerance to benzodiazepines among long-term users in primary care. Fam. Pract. 30, 404–410.
Wu, C.-H., Farley, J.F., Gaynes, B.N., 2012. Evaluating the association of initial benzodiazepine use and antidepressant adherence among adults with anxiety disorders. J. Exp. Clin. Med. 4, 338–344.