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Conflict of interest

Dr. Bobo reports no competing interests in the past three years.

Dr. Reilly-Harrington receives royalties from Oxford University Press, the American Psychological Association, and New Harbinger. She serves as a consultant for United Biosource Corporation and was a shareholder in Concordant Rater Systems.

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Complexity of illness and adjunctive benzodiazepine use in outpatients with bipolar I or II disorder: results from the Bipolar CHOICE study

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Abstract

Benzodiazepines are widely prescribed for patients with bipolar disorders in clinical practice, but very little is known about the subtypes of patients with bipolar disorder or aspects of bipolar illness that contribute most to benzodiazepine use. We examined the prevalence of and factors associated with benzodiazepine use among 482 patients with bipolar I or II disorder enrolled in the Bipolar CHOICE study. Eighty-one subjects were prescribed benzodiazepines at study entry and were considered benzodiazepine users. Stepwise logistic regression was used to model baseline benzodiazepine use vs. non-use, using entry and exit criteria of $p < 0.1$. In bivariate analyses, benzodiazepine users were prescribed a significantly higher number of other psychotropic medications and were more likely to be prescribed lamotrigine or antidepressants as compared with benzodiazepine non-users. Benzodiazepine users were more likely to have a diagnosis of bipolar I disorder and comorbid anxiety disorder, but not comorbid alcohol or substance use disorders. Benzodiazepine users also had experienced more anxiety and depressive symptoms and suicidality, but not irritability or manic symptoms, than did benzodiazepine non-users. In the multivariate model, anxiety symptom level (regardless of diagnosis), lamotrigine use, number of concomitant psychotropic medications, college education, and high household income predicted benzodiazepine use. Benzodiazepine use in patients with bipolar disorders is associated with greater illness complexity as indicated by a higher number of concomitant psychotropic medications and higher anxiety symptom burden, regardless of a comorbid anxiety disorder diagnosis. Demographic factors were also important determinants of benzodiazepine use, which may be related to access to care and insurance coverage for benzodiazeines.

Introduction

Benzodiazepines are widely prescribed for patients with bipolar disorders.[1,2] However, the risk of abuse associated with these agents may be particularly worrisome in this population[3] and the use of benzodiazepines during longer-term treatment of patients with bipolar disorders is not well-established based on large controlled trials conducted outside of acute settings. Benzodiazepine users in the Systematic Treatment Enhancement Program for Bipolar Disorders (STEP-BD) were at greater risk of a mood episode recurrence during follow-up than participants who were not taking benzodiazepines at the time of symptom remission.[4] However, this may have resulted from the channeling of benzodiazepines to more clinically complex or difficult-to-treat patients. Prior studies of benzodiazepine use in patients with bipolar disorder were largely descriptive in nature,[1–3,5–7] or were not specifically intended to identify aspects of bipolar illness complexity (comorbid diagnoses, symptoms, severity, and other illness characteristics) associated with benzodiazepine use.[4,8,9] This study examined patient- and illness-related factors associated with benzodiazepine use among patients with bipolar I or II disorder enrolled in the Bipolar CHOICE study.

Methods

The Bipolar CHOICE study was a multi-site (Supplemental Table A), parallel-group, randomized trial designed to compare the effectiveness of quetiapine and lithium along with other medications (adjunctive personalized treatment) in outpatients with bipolar I or II disorder over 6 months. Bipolar CHOICE design and methods were published elsewhere.[10] This report focuses on the predictors of benzodiazepine use among Bipolar CHOICE participants at study entry. As such, it is representative of choices of practitioners in local communities of the 11 study sites. The study protocol was approved by the Institutional Review Boards of the 11 study sites. Written informed consent was obtained for all subjects.

Outpatients (ages 18–68 years) meeting DSM-IV-TR criteria for bipolar I or II disorder (confirmed using the Extended Mini-International Neuropsychiatric Interview [E-MINI][11]) who were at least mildly symptomatic (CGI-BP ≥3) and required a change in medication treatment were enrolled between 9/20/2010 and 9/29/2013. Eligible subjects were randomized to receive quetiapine (≥ 100 mg/day) or lithium (dosed to achieve a blood level of 0.6–1.2 meq/L). Participants in both study arms also received adjunctive personalized treatment, which consisted of any adjunctive treatment besides antipsychotics in the lithium group and any adjunctive treatment besides lithium or other antipsychotics in the quetiapine group. This could include benzodiazepines, mood stabilizers (other than lithium), non-benzodiazepine soporific medications, and antidepressants, but not antipsychotics, as deemed necessary by study clinicians.

Data on the use of benzodiazepines (Supplemental Table B) and other prescribed medications were collected by trained clinical research coordinators using standardized forms. Patients who were taking benzodiazepines at baseline (scheduled or as-needed) were considered benzodiazepine users. Remaining subjects were considered benzodiazepine non-users. We did not classify nonbenzodiazepine hypnotics (zolpidem, etc.) as benzodiazepines, as they are chemically distinct from classical benzodiazepines and bind preferentially to ω_1 benzodiazepine recognition sites located within the GABA-A receptor complex.[12] The total number of concomitant non-benzodiazepine psychotropic drugs and use of complex polypharmacy (defined as concomitant use of 4 or more non-benzodiazepine psychotropic medications) were determined for each participant.

Trained clinical research coordinators also collected clinical and demographic data, and assessed current general medical conditions and psychiatric diagnoses, using standardized forms. Clinical data included the number of depressive and manic episodes (lifetime and within the prior year), time spent depressed or manic in the prior year, polarity of the index mood episode, predominant mood polarity (lifetime and within the prior year), lifetime psychiatric comorbidity history, lifetime psychiatric hospitalization history, and lifetime history of psychotic illness features. Comorbid psychiatric and substance use diagnoses were confirmed using the E-MINI. Clinical signs and symptoms at baseline (prior to randomization) were determined by trained raters using the Bipolar Inventory of Symptoms Scale (BISS), which assesses a broad spectrum of clinical signs and symptoms that collapse into mania, psychosis, depression, anxiety, and irritability factors.[13] The BISS also includes a single item (item 4) assessing level of suicidal thinking. Suicide item scores were grouped into three strata (none, slight or mild, moderate or severe).

Summary statistics used to compare benzodiazepine users and non-users are presented as means (SD) or medians (inter-quartile range) for continuous measures, and as proportions for categorical variables. Univariate comparisons between benzodiazepine users and non-users at baseline were conducted for categorical variables using chi-square tests, and for continuous variables using two-sample t-tests. Stepwise logistic regression was used to model baseline benzodiazepine use vs. non-use. We considered any variable with $p<0.10$ (based on univariate analyses) for entry into our model and used entry and exit criteria of $p<0.10$ in the stepwise algorithm. We did not specifically analyze the use of lithium, valproate, carbamazepine, other anticonvulsants, or specific antipsychotics because use prevalences at baseline were too low (<10%). To improve stability of calculations, BISS domain scores were rescaled from 0 to 40. A two-tailed significance threshold of $p<0.05$ was used. Given the exploratory nature of this project, no adjustments for multiple testing were performed.

Results

A total of 482 subjects were enrolled in Bipolar CHOICE. The mean age among Bipolar CHOICE participants was 38.9 ± 12.1 years; 58.7% of participants were female, 72.2% were Caucasian, and 68.3% had a diagnosis of bipolar I disorder. The majority of subjects had a high school (or higher) level of education (82.9%), were unemployed or disabled (53.0%), were in a currently bipolar depressed phase of illness (55.8%), and had a comorbid anxiety disorder (57.5%) or a lifetime history of substance use disorder diagnosis (61.4%). Approximately one-quarter of Bipolar CHOICE subjects had a history of psychotic mood episodes (24.3%). Only 16 subjects (3.3%) were taking complex pharmacotherapy regimens consisting of 4 or more psychotropic medications (not counting benzodiazepines) at baseline.

Baseline characteristics of benzodiazepine users and non-users are shown in Table 1. Of the 482 bipolar CHOICE enrollees, 81 (16.8%) were prescribed benzodiazepines at baseline. Benzodiazepine users were prescribed a marginally but statistically significantly higher number of concomitant psychotropic medications, and were significantly more likely to be prescribed lamotrigine or antidepressants as compared with benzodiazepine non-users. A higher proportion of benzodiazepine users than non-users took complex pharmacotherapy regimens (≥4 non-benzodiazepine psychotropics), but these differences occurred at the level of statistical trend.

A significantly greater proportion of benzodiazepine users had a diagnosis of bipolar I disorder and a comorbid anxiety disorder, but not a comorbid substance use disorder (Table 1). Benzodiazepine users had a significantly higher mean score for the BISS anxiety and depression factors than did benzodiazepine non-users, but not BISS total or other BISS factors. A higher proportion of benzodiazepine users were in the highest stratum for household income (> $75,000/year) and suicidal ideation (moderate or severe). Benzodiazepine use also varied at the trend level according to race (higher among Caucasians), education level (higher with college or higher level of education), history of psychotic features (lower among those with past psychotic illness features), and baseline antipsychotic use (higher among antipsychotic users). There were no statistically significant or trend-level differences in sex, marital status, employment status, age at the first bipolar mood episode, number of lifetime mood episodes, mood polarity at baseline or at the index mood episode, or history of psychiatric hospitalization between benzodiazepine users and non-users.

Multivariable models using stepwise logistic regression included covariates from univariate analyses with entry and exit criteria of $p < 0.1$. Of these, BISS anxiety factor score, lamotrigine use, number of concomitant psychotropic medications, education level, and household income remained statistically significant (Table 2). In general, being in the highest income group (≥$75K/year) and having a college degree were associated with higher odds of being a benzodiazepine user, as compared with other strata within each category (Supplemental Table C). Although the mean BISS depression factor score was significantly higher for benzodiazepine users than non-users, it did not explain enough additional variability to be included in the multivariable model based on the stepwise variable selection algorithm.

Our primary analyses included benzodiazepines classified as anxiolytics and those classified as sedatives. The latter sub-category included only 5 temazepam users. Our findings were unchanged after conducting a sensitivity analysis that excluded these 5 patients (data not shown).

Discussion

This study identified patterns and predictors of benzodiazepine use at baseline in a large, well-characterized cohort of outpatients with bipolar I or II disorder who participated in the Bipolar CHOICE comparative effectiveness trial. This report extends previous findings by showing that greater anxiety symptom burden and other indicators of bipolar illness complexity, regardless of comorbid anxiety disorder diagnosis, is associated with benzodiazepine use in bipolar disorder patients, whereas residual manic symptoms, irritability, and comorbid substance abuse or dependence are not. Although between-group differences in depression symptoms were statistically significant in bivariate analyses, this effect was no longer apparent in multivariable analyses.

Comorbid anxiety disorders have been reported with high frequency in large observational studies of bipolar disorder patients and in the STEP-BD study.[14,15] Anxiety symptoms are also highly prevalent in bipolar I or II disorder patients lacking a full syndromal comorbid anxiety disorder diagnosis.[16] Anxiety symptoms, in addition to anxiety disorder comorbidity, are important markers of greater bipolar illness complexity given higher risk of suicidal ideation and attempts, substance use, mood cyclicity, and poorer response to lithium in patients with bipolar disorder.[17] The established effectiveness of benzodiazepines for treating some anxiety disorders may have driven the substantial rate of benzodiazepine use in Bipolar CHOICE sample and other bipolar disorder cohorts[4,5,18] despite a lack of clear evidence from large controlled trials supporting this practice outside of acute settings. On the other hand, there are few well-supported pharmacotherapies for managing comorbid anxiety symptoms or disorders that persist in bipolar patients spite of treatment with mood stabilizing drugs.[19] Our results highlight the need for additional investigation and consensus regarding optimal approaches for managing anxiety disorders or symptoms in bipolar disorder patients.

Benzodiazepine use in our study was associated with other indices of greater bipolar disorder complexity. Prior research has linked use of polypharmacotherapeutic regimens consisting of large numbers of concomitantly prescribed psychotropic drugs with higher depressive symptom burden, psychiatric comorbidity, and treatment resistance in patients with bipolar disorder.[20,21] In our study benzodiazepine users were taking significantly higher numbers of non-benzodiazepine psychotropic medications than benzodiazepine non-users, but these differences were small. While a higher proportion of benzodiazepine users were taking complex polypharmacy regimens (consisting of ≥4 non-benzodiazepine psychotropic drugs taken concomitantly), overall rates were relatively low and between-group differences existed only at the trend level. Still, these differences suggest that benzodiazepines were used in more clinically complex, severely ill or difficult-to-treat patients. This point is strengthened by a significantly greater proportion of benzodiazepine users in our study who reported moderate or severe levels of suicidal thinking, as compared with non-users. Higher risk of suicide has been consistently linked with indicators of bipolar disorder complexity including comorbid psychiatric and substance use disorders.[22] Others have shown an association between benzodiazepine use and self-reported history of suicidal behavior[23] and deliberate self-poisoning,[24] but a direct causal relationship between benzodiazepine use and suicidality has not been established. Comorbid substance use diagnoses, another marker of clinical complexity,[25] did not significantly influence benzodiazepine use in our cohort even though comorbid substance use would be expected to dissuade clinicians from using these medications. Reasons for lack of significant differences in rates of substance use disorder comorbidity are difficult to determine, but may be related to low substance use disorder detection rates before study entry. Our results may also reflect clinician judgment that the use of benzodiazepines in a given patient with comorbid substance use disorder(s) was justified, for example, based on clinically significant residual symptoms--such as insomnia, anxiety, or irritability—that persist in spite of the use of foundational bipolar disorder pharmacotherapies.

Some benzodiazepines have been associated with acute antimanic effects.[26] Neither manic nor irritability symptoms were associated with benzodiazepine use in this study; and while bipolar I disorder subtype was significantly associated in univariate analyses, bipolar subtype was not a significant independent predictor of benzodiazepine use in our multivariable regression analysis. Our results are consistent with those of the STEP-BD cohort. Benzodiazepine use did not vary by bipolar disorder subtype among the first 500 STEP-BD participants; however, this was a largely descriptive report, and only a limited number of potential predictors of benzodiazepine use were considered.[5] Perlis and colleagues reported no significant differences in bipolar subtype conditional on benzodiazepine use in a larger sample of 1,365 STEP-BD participants who achieved 8 weeks of symptomatic recovery.[4] Our findings are in accord with those of STEP-BD despite differences in patient samples and study methods. Moreover, residual manic symptoms leading to adjunctive benzodiazepine use might be expected to occur more commonly in patients with bipolar I disorder; however, consistent with our results, Perlis et al. did not find significantly higher irritability or manic symptom burden among benzodiazepine users versus non-users.[4]

Lamotrigine use was also a significant independent predictor of benzodiazepine use, even after accounting for the effects of complex polypharmacy. A recent factor analytic study of Hamilton Depression Rating Scale (HDRS)-derived symptom domains identified depressive cognitions and psychomotor slowing, but not anxiety, as being most responsive to lamotrigine,[27] and adjunctive olanzapine was superior to lamotrigine for reducing anxiety symptoms in a 12-week randomized trial of lithium-treated patients with bipolar I or II disorder and a comorbid anxiety disorder.[28] We could not demonstrate whether inadequate control of anxiety and/or greater depressive symptom burden (which could lead to increased lamotrigine use) drove benzodiazepine use among lamotrigine-treated patients in our cohort. The former seems unlikely, given that lamotrigine use remained a significant predictor of benzodiazepine use after adjusting for baseline BISS anxiety subscale scores.

High income and educational levels were both associated with benzodiazepine use. Specific reasons for these findings are not immediately clear. The ability to pay costs of benzodiazepine treatment may provide part of the answer, given exclusion of benzodiazepine coverage by Medicare Part D and only limited coverage of benzodiazepines by some state Medicaid programs.[29] These programs were intended, in part, to increase patient safety by limiting inappropriate or problematic benzodiazepine use. Though well-intended, such programs may disproportionately reduce both problematic and non-problematic use of benzodiazepines among lower-income patients.[30]

Strengths of our study include investigation of a large number of predictor variables for benzodiazepine use in a large, well-characterized cohort of patients with bipolar I or II disorder, which included a wide range of associated signs and symptoms such as anxiety and irritability, and proxy indicators of manic and depressive symptom burden in the year prior to study entry. There are also limitations to consider. Our cohort, although substantial, may have been too small to detect subtle but important predictors of benzodiazepine use, particularly in small subsets of patients. For instance, only a limited number of patients were taking foundational mood stabilizers at baseline, which did not allow use of these medicines as predictor variables in our analyses. We did not collect data on the intended indications for benzodiazepines, thus precluding direct analysis of an important prescriber-level variable.

Additionally, we did not collect data on other factors that may have influenced prescribing decisions, such as individual prescriber or patient preferences, patients' experiences with medications prior to study entry, and insurance status. Our suicidality measure, a score on item 4 of the BISS, is relatively simple in comparison with other suicide measures that consider past suicidal behaviors and level of suicidal intent. This study employed a cross-sectional rather than longitudinal design. And finally, the cohort consisted of voluntary participants in a randomized effectiveness trial who sought treatment at academic medical centers, which limits its representativeness in spite of the minimal exclusion criteria.

In summary, our results show that higher anxiety symptom level, higher number of non-benzodiazepine psychotropic medications, lamotrigine use, college education, and high household income were significant and independent predictors of benzodiazepine use in Bipolar CHOICE participants with bipolar I or II disorder. Anxiety symptom burden predicted benzodiazepine use regardless of a comorbid anxiety disorder diagnosis, thus highlighting the need for additional studies and consensus regarding best practices for treating comorbid anxiety in bipolar disorder patients. A potential relationship between benzodiazepine use and suicide risk among bipolar disorder patients warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Clark RE, Xie H, Brunette MF. Benzodiazepine prescription practices and substance abuse in persons with severe mental illness. J Clin Psychiatry. 2004;65:151–155. [PubMed: 15003066]
2. Baldessarini RJ, Leahy L, Arcona S, et al. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatr Serv. 2007;58:85–91. [PubMed: 17215417]
3. Brunette MF, Noordsy DL, Xie H, et al. Benzodiazepine use and abuse among patients with severe mental illness and co-occurring substance use disorders. Psychiatr Serv. 2003;54:1395–1401. [PubMed: 14557527]
4. Perlis RH, Ostacher MJ, Miklowitz DJ, et al. Benzodiazepine use and risk of recurrence in bipolar disorder: a STEP-BD report. J Clin Psychiatry. 2010;71:194–200. [PubMed: 20193647]
5. Ghaemi SN, Hsu DJ, Thase ME, et al. Pharmacological treatment patterns at study entry for the first 500 STEP-BD participants. Psychiatr Serv. 2006;57:660–665. [PubMed: 16675760]
6. Levine J, Chengappa KN, Brar JS, et al. Psychotropic drug prescription patterns among patients with bipolar I disorder. Bipolar Disord. 2000;2:120–130. [PubMed: 11252651]
7. Kassam A, Patten SB. Hypnotic use in a population-based sample of over thirty-five thousand interviewed Canadians. Popul Health Metr. 2006;4:15. [PubMed: 17125509]
8. Simon NM, Otto MW, Weiss RD, et al. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. J Clin Psychopharmacol. 2004;24:512–520. [PubMed: 15349007]
9. Lin SC, Chen CC, Chen YH, et al. Benzodiazepine prescription among patients with severe mental illness and co-occurring alcohol abuse/dependence in Taiwan. Hum Psychopharmacol. 2011;26:201–207. [PubMed: 21671270]

10. Nierenberg AA, Sylvia LG, Leon AC, et al. Clinical and Health Outcomes Initiative in Comparative Effectiveness for Bipolar Disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. Clin Trials. 2014;11:114–127. [PubMed: 24346608]
11. Sheehan DV, Lecrubier Y, Sheehan KJ, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59 Suppl 20:22–33.
12. Terzano MG, Rossi M, Palomba V, et al. New drugs for insomnia: comparative tolerability of zopiclone, zolpidem and zaleplon. Drug Saf. 2003;26:261–282. [PubMed: 12608888]
13. Thompson PM, Gonzalez JM, Singh V, et al. Principal domains of behavioral psychopathology identified by the Bipolar Inventory of Signs and Symptoms Scale (BISS). Psychiatry Res. 2010;175:221–226. [PubMed: 20022384]
14. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord. 2002;68:1–23. [PubMed: 11869778]
15. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2004;161:2222–2229. [PubMed: 15569893]
16. Rakofsky JJ, Dunlop BW. Treating nonspecific anxiety and anxiety disorders in patients with bipolar disorder: a review. J Clin Psychiatry. 2011;72:81–90. [PubMed: 21208580]
17. Goldberg D, Fawcett J. The importance of anxiety in both major depression and bipolar disorder. Depress Anxiety. 2012;29:471–478. [PubMed: 22553107]
18. Baldessarini R, Henk H, Sklar A, et al. Psychotropic medications for patients with bipolar disorder in the United States: polytherapy and adherence. Psychiatr Serv. 2008;59:1175–1183. [PubMed: 18832504]
19. Schaffer A, McIntosh D, Rector NA, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. Ann Clin Psychiatry. 2012;24:6–22. [PubMed: 22303519]
20. Frye MA, Ketter TA, Leverich GS, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. J Clin Psychiatry. 2000;61:9–15.
21. Goldberg JF, Brooks JO, Kurita K, et al. Depressive illness burden associated with complex polypharmacy in patients with bipolar disorder: findings from the STEP-BD. J Clin Psychiatry. 2009;70:155–162. [PubMed: 19210946]
22. Treuer T, Tohen M. Predicting the course and outcome of bipolar disorder: a review. Eur Psychiatry 2010;25:328–333. [PubMed: 20444581]
23. Bellivier F, Yon L, Luquiens A, et al. Suicidal attempts in bipolar disorder: results from an observational study (EMBLEM). Bipolar Disord. 2011;13:377–386. [PubMed: 21843277]
24. Shih HI, Lin MC, Lin CC, et al. Benzodiazepine therapy in psychiatric outpatinets is associated with deliberate self-poisoning events at emergency departments-a population-based nested case-control study. Psychopharmacology (Berl). 2013;229:665–671. [PubMed: 23657424]
25. Fossey MD, Otto MW, Yates WR, et al. Validity of the distinction between primary and secondary substance use disorder in patients with bipolar disorder: data from the first 1000 STEP-BD participants. Am J Addict. 2006;15:138–143. [PubMed: 16595351]
26. Chouinard G The use of benzodiazepines in the treatment of manic-depressive illness. J Clin Psychiatry. 1988;49 Suppl:15–20. [PubMed: 2903143]
27. Mitchell PB, Hadzi-Pavlovic D, Evoniuk G, et al. A factor analytic study in bipolar depression, and response to lamotrigine. CNS Spectr. 2013;18:214–224. [PubMed: 23702258]
28. Maina G, Albert U, Rosso G, et al. Olanzapine or lamotrigine addition to lithium in remitted bipolar disorder patients with anxiety disorder comorbidity: a randomized, single-blind, pilot study. J Clin Psychiatry. 2008;69:609–616. [PubMed: 18294024]
29. Briesacher BA, Soumerai SB, Firld TS, et al. Medicare part D's exclusion of benzodiazepines and fracture risk in nursing homes. Arch Intern Med 2010;170:693–698. [PubMed: 20421554]

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30. Ross-Degnan D, Simoni-Wastila L, Brown JS, et al. A controlled study of the effects of state surveillance on indicators of problematic and non-problematic benzodiazepine use in a Medicaid population. Int J Psychiatry Med. 2004;34:103–123. [PubMed: 15387395]

Table 1.

Baseline characteristics of benzodiazepine users and non-users

	Benzodiazepine user	**Benzodiazepine non-user**	
Variable	**Mean ± SD**	**Mean ± SD**	**p-value**[a]
Age, yrs.	40.6 ± 12.2	38.5 ± 12.1	0.17
Hospitalizations, n	1.6 ± 2.7	1.6 ± 4.2	0.99
No. psychotropic medications	**1.5 ± 1.2**	**0.8 ± 1.1**	**<0.001**
BISS total and factor scores[b]			
Total	59.2 ± 19.8	55.5 ± 18.6	0.10
Mania	8.5 ± 5.8	9.3 ± 6.5	0.31
Psychosis	2.7 ± 3.9	2.9 ± 4.7	0.81
Depression	**19.4 ± 7.7**	**17.2 ± 7.2**	**0.014**
Anxiety	**19.3 ± 8.4**	**15.2 ± 8.4**	**<.0001**
Irritability	17.3 ± 9.1	16.6	0.54
No. lifetime episodes, depression	36.7 ± 37.6	40.0 ± 42.0	0.51
No. lifetime episodes, mania	31.6 ± 36.8	39.0 ± 49.4	0.13
Variable	**%**	**%**	**p-value**[c]
Female sex	64.2	57.6	0.11
Caucasian race	80.2	70.6	0.08
Married or cohabitating	38.3	29.7	0.11
Education level			0.06
≥ College graduate	43.2	29.4	
High school diploma	46.9	52.1	
< High school	9.9	18.5	
Employed or student	42.0	46.1	0.25
Household income			**0.03**
<$25,000	49.4	52.6	
$25,000–49,999	13.6	19.9	
$50,000–74,999	9.9	13.1	
≥ $75,000	27.2	14.4	
Bipolar disorder subtype			**0.04**
Bipolar I disorder	77.8	66.3	
Bipolar II disorder	22.2	33.7	
History of psychiatric hospitalization	51.3	45.9	0.38
History of psychotic features	16.0	25.9	0.06
Comorbid anxiety disorder[d]	69.1	55.1	0.02
Comorbid substance use disorder (lifetime)[e]	58.0	62.1	0.49
Moderate-severe suicidal ideation	13.6	5.7	**0.02**

	Benzodiazepine user	Benzodiazepine non-user	
Variable	**Mean ± SD**	**Mean ± SD**	**p-value[a]**
Antidepressant use	**33.3**	**16.0**	**<.001**
Antipsychotic use	19.8	12.0	0.06
Lamotrigine use	**29.6**	**9.5**	**<.001**
Complex polypharmacy[r]	6.2	2.7	0.12

[a]Results are based on 2-sample t-tests.

[b]Bipolar Inventory of Signs and Symptoms (BISS) scale domain scores (irritability, psychosis) were re-scaled from 0 to 40.

[c]Results are based on chi-square test.

[d]Includes patients with any of the following current psychiatric diagnoses: panic disorder, agoraphobia (without panic), social phobia, and generalized anxiety disorder.

[e]Includes patients with alcohol, other substance use disorders, or both.

[f]Defined as the concomitant use of 4 or more psychotropic medications.

Table 2.

Multivariate comparisons of benzodiazepine users and non-users

	Estimate	Standard error	Wald chi-square	DF	p-value
BISS anxiety factor score	**0.08**	**0.02**	**20.34**	**1**	**<.0001**
Lamotrigine use	**0.88**	**0.36**	**7.77**	**1**	**.018**
No. psychotropic medications	**0.38**	**0.12**	**9.85**	**1**	**.002**
Education level	**…**	**…**	10.30	5	.07
< High school	−0.56	0.66	0.72	1	NS
High school diploma or GED	−0.39	0.35	1.28	1	NS
Some college (at least 1 year)	0.31	0.27	1.36	1	NS
College degree	**0.81**	**0.28**	**8.36**	**1**	**.004**
Graduate/professional degree	0.12	0.45	0.07	1	NS
Household income	**…**	**…**	**9.34**	**3**	**.025**
$50,000-$74,999	−0.36	0.34	1.11	1	NS
$25,000-$49,999	−0.55	0.30	3.40	1	NS
≤$24,999	0.19	0.22	0.72	1	NS

BISS = Bipolar Inventory of Signs and Symptoms.