Benzodiazepine Use and Risk of Recurrence in Bipolar Disorder: A STEP-BD Report

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Objective: Benzodiazepines are widely prescribed to patients with bipolar disorder, but their impact on relapse and recurrence has not been examined.

Method: We examined prospective data from a cohort of *DSM-IV* bipolar I and II patients who achieved remission during evidence-guided naturalistic treatment in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study (conducted in the United States between 1999 and 2005). Risk for recurrence among individuals who did or did not receive benzodiazepine treatment was examined using survival analysis. Cox regression was used to adjust for clinical and sociodemographic covariates. Propensity score analysis was used in a confirmatory analysis to address the possible impact of confounding variables.

Results: Of 1,365 subjects, 349 (25.6%) were prescribed a benzodiazepine at time of remission from a mood episode. After adjusting for potential confounding variables, the hazard ratio for mood episode recurrence among benzodiazepine-treated patients was 1.21 (95% CI, 1.01–1.45). The effects of benzodiazepine treatment on relapse remained significant after excluding relapses occurring within 90 days of recovery, or stratifying the sample by propensity score, a summary measure of likelihood of receiving benzodiazepine treatment. In an independent cohort of 721 subjects already in remission at study entry, effects of similar magnitude were observed.

Conclusion: Benzodiazepine use may be associated with greater risk for recurrence of a mood episode among patients with bipolar I and II disorder. The prescribing of benzodiazepines, at a minimum, appears to be a marker for a more severe course of illness.

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Despite concerns about substance abuse comorbidity,[1] benzodiazepines are widely prescribed for patients with bipolar I and II disorder,[1,2] driven in part by the high prevalence of anxiety disorders and insomnia in these patients.[3,4] One study[1] found a 5-year prevalence of benzodiazepine use among bipolar patients ranging from 58%–75%. The management of anxiety symptoms in bipolar disorder is not well studied,[5,6] although benzodiazepines have demonstrated efficacy in primary anxiety disorders such as panic disorder.[7]

Benzodiazepines have also demonstrated efficacy in small studies for the acute management of mania,[8–11] and one case series reported some benefit in maintenance treatment,[12] but their impact on long-term outcomes in bipolar disorder is unknown. One study in 70 patients[13] suggested benzodiazepine-treated patients remained in follow-up treatment longer than non–benzodiazepine-treated patients, though that study did not consider clinical confounders. Conversely, a chart review of 15 patients suggested no benefit.[14] Given the potential negative consequences of benzodiazepine use, including exacerbation of substance use disorders,[1] disruption of sleep/wake cycles,[15] or exacerbation of cognitive dysfunction,[16–19] the paucity of long-term study is particularly notable.

We investigated the impact of prescribed benzodiazepines on outcomes in a large cohort of bipolar I and II patients participating in the multicenter Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) cohort study. Clinicians in this study were trained in model practice procedures, including guideline-based care and evidence-based practice, but could prescribe any medication felt to be clinically appropriate, including benzodiazepines. While only a randomized, double-blind trial can directly address the risk or benefit of benzodiazepines, the detailed phenotyping and follow-up in the STEP-BD study provided a unique opportunity to estimate recurrence risk associated with benzodiazepine use after controlling for a variety of confounding variables.

For Clinical Use

- Patients with bipolar disorder who require treatment with benzodiazepines may be at particularly high risk for recurrence of a mood episode.
- Rather than indicating a direct effect of benzodiazepines on outcome, the need for benzodiazepine treatment may simply be a marker for more severe illness.

METHOD

Study overview

STEP-BD was a multicenter "effectiveness" study conducted in the United States between 1999 and 2005 that evaluated prospective outcomes among individuals with bipolar disorder. Methods for the STEP-BD study as a whole are detailed elsewhere and primary analyses of recurrence risk have been previously described.[20,21]

Participants

Study participation was offered to all bipolar patients seeking outpatient treatment at one of the participating study sites. Entry criteria included meeting *DSM-IV* criteria for bipolar disorder I, II, or not otherwise specified (NOS); cyclothymia; or schizoaffective disorder bipolar type and ability to provide informed consent. For individuals age 15–17, written assent was also required from a parent or guardian. Hospitalized individuals were eligible to enter following discharge.

Assessments

Bipolar diagnosis was determined using mood and psychosis modules from the Structured Clinical Interview for *DSM-IV* as incorporated in the Affective Disorders Evaluation (ADE)[20] and confirmed by a second clinical rater using the Mini International Neuropsychiatric Interview (MINI).[22] Comorbid Axis I diagnoses were also determined using the MINI. At each visit, clinicians assigned current mood status based upon the clinical monitoring form,[23] which assesses *DSM-IV* criteria for depressive, manic, hypomanic, or mixed states in the prior 14 days. Each criterion is scored on a 0–2 scale, in which 1 represents "threshold" by *DSM-IV* mood episode criteria; fractional scores are used to indicate subthreshold symptoms. For example, a patient with insomnia less than half the time would receive a "0.5" rather than a "1" on the sleep item. The Clinical Global Impressions-Severity of Illness (CGI-S) scale,[24] a 7-point scale between 1 (not symptomatic) and 7 (among the most severely ill) was also completed by the study clinician at each visit.

Additional details of patient retrospective course on entering STEP-BD were collected by the clinician on the ADE, including proportion of time in the preceding year with depressive, manic, and anxious symptoms as well as number of episodes of each type. A CGI assessment of overall bipolar disorder severity at study entry was also completed.

Intervention

Study clinicians in STEP-BD were trained to use model practice procedures, which included published pharmacotherapy guidelines,[20] but they could prescribe any treatment that they felt to be indicated. Elsewhere, we have reported high concordance between treatment selection and guideline recommendations, indicating that patients received standard-of-care treatment when entering STEP-BD.[25]

Outcomes

Because STEP-BD was intended to mimic clinical practice, participants were seen as frequently as clinically indicated. Clinical mood state at each episode was established using the clinical monitoring form,[20] which determines whether individual *DSM* criteria for a mood episode are met at each visit as well as proportion of time in the preceding 2 weeks with significant mood and anxiety symptoms. Primary outcome definitions were those specified for the STEP-BD study, selected for consistency with the National Institute of Mental Health Collaborative Study of Depression[26–28] as well as the McLean First Episode Study.[29] Recovery was defined as 2 or fewer syndromal features of a mood episode for at least 8 weeks, while recurrence was defined as meeting full *DSM* criteria for a mood episode on any single subsequent visit. The presence of subsyndromal mood symptoms during follow-up was not considered a recurrence.

Statistical Analysis

The present report is based upon all subjects entering STEP-BD with a diagnosis of bipolar I or II disorder. Subjects with bipolar disorder NOS, schizoaffective disorder, bipolar type, or cyclothymia represented less than 9% of the total STEP-BD sample (357/4,107) and were excluded from this analysis because of the heterogeneity in those diagnoses and difficulty in considering their course in episodic terms. The primary at-risk cohort consisted of individuals who (1) were in a mood episode or who were recovering from a mood episode but were not yet euthymic for ≥ 8 weeks at entry into STEP-BD and (2) subsequently achieved 8 continuous weeks of recovery (n = 1,365). An independent confirmatory cohort was defined as individuals who were euthymic at entry into STEP-BD (n = 721).

We compared sociodemographic and clinical features for individuals receiving or not receiving benzodiazepine treatment on a standing or as-needed basis after they had achieved 8 weeks of euthymia following a mood episode (the primary at-risk cohort). Because of the large number

Table 1. Dichotomous Sociodemographic and Clinical Features of Bipolar I and II Patients (N = 1,365) Who Achieved 8 Weeks of Recovery in STEP-BD and Did (+) or Did Not (–) Receive Benzodiazepine Treatment

	Benzodiazepine (–) (n = 1,016)		Benzodiazepine (+) (n = 349)		Full Cohort (N = 1,365)			
Characteristic	n	%	n	%	N	%	OR	95% CI
Male	464	45.7	112	32.1	576	42.2	0.56*	0.44–0.73
Caucasian	915	90.1	325	93.1	1,240	90.8	1.49*	0.94–2.37
Married[a]	358	36.4	142	42.4	500	37.9	1.28*	1.00–1.66
Bipolar I	708	69.7	245	70.2	953	69.8	1.02	0.79–1.34
Anxiety disorder, current	344	33.9	154	44.1	498	36.5	1.54*	1.20–1.98
Anxiety disorder, past	524	51.6	220	63.0	744	54.5	1.60*	1.25–2.06
Alcohol use disorder, current	128	12.6	38	10.9	166	12.2	0.85	0.58–1.25
Alcohol use disorder, past	431	42.4	155	44.4	586	42.9	1.08	0.85–1.39
Other drug use disorder, current	76	7.5	30	8.6	106	7.8	1.16	0.75–1.81
Other drug use disorder, past	283	27.9	98	28.1	381	27.9	1.01	0.77–1.33
Rapid cycling, lifetime	715	70.4	260	74.5	975	71.4	1.23	0.93–1.62
Rapid cycling, past year	493	48.5	168	48.1	661	48.4	0.98	0.77–1.26
History of suicide attempt[a]	350	35.3	137	40.2	487	36.5	1.23*	0.96–1.59
History of psychosis[a]	403	40.9	128	38.3	531	40.3	0.90	0.70–1.16
Current smoking, any	243	23.9	92	26.4	335	24.5	1.14	0.86–1.50
Current alcohol use, any	283	27.9	86	24.6	369	27.0	0.85	0.64–1.12
Treatment								
Lithium	391	38.5	113	32.4	504	36.9	0.77*	0.59–0.99
Valproate	348	34.3	117	33.5	465	34.1	0.97	0.75–1.25
Atypical antipsychotic	375	36.9	149	42.7	524	38.4	1.27*	0.99–1.63
Antidepressant	462	45.5	200	57.3	662	48.5	1.61*	1.26–2.06
Lamotrigine	295	29.0	124	35.5	419	30.7	1.35*	1.04–1.74
Other anticonvulsant	119	11.7	57	16.3	176	12.9	1.47*	1.04–2.07
Trazodone	42	4.1	29	8.3	71	5.2	2.10*	1.29–3.43

[a]Data are not available for marital status (n = 46 subjects), history of suicide attempt (n = 32), and history of psychosis (n = 46).
*$P < .05$ for association with benzodiazepine use; these variables are also indicated in boldface.
†$.05 < P < .1$ for association with benzodiazepine use (no such variables in Table 1).
Abbreviations: CI = confidence interval, OR = odds ratio for receiving benzodiazepine treatment.

Table 2. Continuous/Ordinal Sociodemographic and Clinical Features of Bipolar I and II Patients (N = 1,365) Who Achieved 8 Weeks of Recovery in STEP-BD and Did (+) or Did Not (–) Receive Benzodiazepine Treatment

	Benzodiazepine (–)			Benzodiazepine (+)			Total				
Characteristic	n	Mean	SD	n	Mean	SD	N	Mean	SD	OR	95% CI
Age at entry	1,016	39.1	12.8	349	41.9	11.7	1,365	39.8	12.6	1.018*	1.008–1.028
Age at onset	1,004	16.7	8.5	340	16.6	8.3	1,344	16.7	8.4	0.999	0.984–1.013
Days depressed, past year	989	45.2	28.1	339	48.2	27.9	1,328	45.9	28.1	1.004*	0.999–1.008
Days anxious, past year	976	33.6	32.8	338	41.9	33.3	1,314	35.7	33.2	1.007*	1.004–1.011
Days elevated, past year	981	21.1	21.7	337	18.6	19.1	1,318	20.5	21.1	0.994*	0.988–1.000
Days irritable, past year	980	32.1	29.7	338	34.4	28.8	1,318	32.7	29.5	1.003	0.998–1.007
% time depressed, past 2 wk	1,012	12.2	21.7	349	15.1	23.3	1,361	12.9	22.1	1.006*	1.000–1.011
% time anxious, past 2 wk	1,012	15.6	28.1	349	27.9	36.6	1,361	18.8	30.9	1.012*	1.008–1.015
% time irritable, past 2 wk	1,012	13.1	24.3	349	15.7	25.9	1,361	13.7	24.7	1.004*	1.003–1.005
% time elevated, past 2 wk	1,013	4.5	13.6	349	5.3	13.4	1,362	4.7	13.6	1.003*	1.001–1.005
Depressive symptoms (count)	1,016	2.4	2.1	349	2.8	2.0	1,365	2.5	2.1	1.092*	1.031–1.158
Manic symptoms (count)	1,016	0.9	1.3	349	1.0	1.3	1,365	1.0	1.3	1.062	0.970–1.164
CGI-S score (first recovered visit)	1,013	2.0	0.9	348	2.1	0.8	1,361	2.0	0.9	1.120†	0.980–1.289
CGI-overall severity score (study entry)	1,010	3.3	1.1	346	3.4	1.1	1,356	3.3	1.1	1.112†	0.997–1.240

*$P < .05$ for association with benzodiazepine use (variables also indicated in boldface).
†$.05 < P < .1$ for association with benzodiazepine use.
Abbreviation: CGI-S = Clinical Global Impressions-Severity of Illness.

of putative predictors included, we used imputation (mean/mode) to maximize the number of subjects included in regression models; sensitivity analyses using only complete cases, or regression-based imputation, yielded essentially the same results. We utilized Cox proportional-hazards regression models to examine recurrence hazard for those individuals with versus without benzodiazepine treatment, after confirming that the proportional hazards assumption was satisfied. Recurrence was defined as a manic, hypomanic, mixed, or depressive episode, with data right-censored after 2 years of follow-up.

All Cox models were first run without adjustment, ie, examining the association between benzodiazepine treatment status and recurrence. The models were then repeated with inclusion as covariates of all variables that differed between the 2 groups at $P < .10$, indicated in Tables 1 and 2

with a * (for $P < .05$) or † (for $.05 < P < .1$). Kaplan-Meier survival curves were generated to illustrate time course of recurrence between the 2 groups. To further address the possibility of confounding, we equated patients who were taking versus not taking benzodiazepines on all possible confounding variables[21] using Cox models with propensity-score adjustment. This approach models an individual's "risk" of being prescribed a given treatment, yielding a score corresponding to this likelihood based upon a set of clinical and sociodemographic predictors. This approach is commonly applied in large-scale pharmacovigilance studies[30–33]; for a review, see Glynn et al.[34] Propensity scores were generated using the *psmatch2* function in Stata 10.0 (StataCorp, College Station, Texas), based upon logistic regression models for the use versus nonuse of benzodiazepine treatment, incorporating all variables from Table 1. The nonparsimonious (ie, full) model yielded a *c*-statistic of 0.69, indicating adequate performance in predicting treatment type. Cox models were then stratified by propensity score quartiles.

In follow-up analyses, we used Cox regression to compare recurrence after 90 days for those individuals receiving 60 days or more of benzodiazepine treatment with those receiving no benzodiazepine treatment; subjects with fewer than 60 days of follow-up were classified as missing. We also examined the effect of including only benzodiazepines on a regular schedule (versus as-needed usage) by repeating Cox regression with this group compared to non–benzodiazepine-treated patients.

Finally, for comparative purposes, we conducted 2 additional analyses. First, for non–benzodiazepine-treated patients, we examined outcomes associated with receiving versus not receiving the anticonvulsant gabapentin, commonly prescribed as a sedative/hypnotic, again adjusted for the same covariates. Second, we examined the impact of benzodiazepine treatment in a second nonoverlapping patient cohort derived from STEP-BD, those who were euthymic at study entry (rather than syndromal).

RESULTS

The sociodemographic and clinical features of bipolar I and II patients (n = 1,365) who achieved 8 weeks of recovery in STEP-BD are listed in Tables 1 and 2. In total, 349 patients received benzodiazepine treatment at this point (25.6%). The tables also indicate odds ratios for receiving benzodiazepine treatment associated with each variable. Individuals who were female and married were significantly more likely to receive benzodiazepine treatment than male and unmarried patients, as were older patients. As expected, individuals with a current or past *DSM-IV* Axis I anxiety disorder and with greater proportion of time with any mood or anxiety symptoms in the past 2 weeks and in the year prior to study entry were more likely to be receiving benzodiazepine treatment. Lithium-treated patients were less likely to be receiving benzodiazepine treatment than non–lithium-treated patients, whereas antidepressant-, atypical antipsychotic–, trazodone-, lamotrigine-, and other anticonvulsant–treated individuals were more likely to receive such treatment. Finally, while the differences did not reach statistical significance, benzodiazepine use was associated with greater clinician impression of overall bipolar disorder severity at study entry, and with greater clinician impression of current severity at first recovered visit.

Table 3. Crude and Adjusted Models of Recurrence Risk for Benzodiazepine-Treated or -Untreated Groups

Model	n	HR	95% CI
Crude model	1,365	1.298	1.096–1.538
Adjusted model	1,365	1.208	1.009–1.446
Adjusted, stratified by propensity score quartile	1,365	1.216	1.101–1.460
Adjusted, excluding events within 90 d and subjects with < 60 d of benzodiazepine use	860	1.342	1.053–1.711
Adjusted, excluding prn benzodiazepine use	1,301	1.244	1.033–1.499
Comparison: "well-at-entry" cohort			
Crude model	721	1.516	1.134–2.026
Adjusted model	721	1.248	0.908–1.716
Comparison: gabapentin treatment			
Crude model	1,016	1.115	0.778–1.599
Adjusted model	1,016	1.043	0.596–1.822

Abbreviations: CI = confidence interval, HR = hazard ratio, prn = as needed.

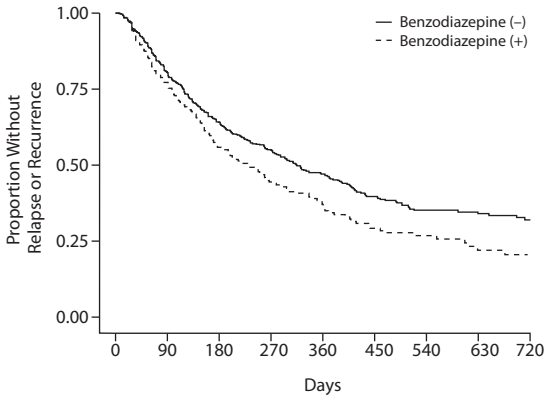
Hazard ratios for recurrence of a mood episode among individuals with or without benzodiazepine treatment are displayed in Table 3. In the unadjusted analysis, as well as the analysis adjusted for all potential confounders from Tables 1 and 2, risk for recurrence to either depression or hypomanic/manic/mixed states was significantly greater among benzodiazepine-treated patients (Table 3 and Figure 1). The adjusted model yielded a hazard ratio of 1.21 (95% CI, 1.01–1.45), indicating an approximately 21% greater risk of recurrence among benzodiazepine-treated patients. Examining polarity of recurrence separately suggested similar magnitude of effect, but with a qualitatively different time course, for depression or mood elevation (eFigure 1), with manic recurrence occurring earlier and depressive recurrence relatively later. Further analyses incorporating propensity score adjustment yielded similar results to the Cox regression models. Repeating analysis within each stratum yielded HRs ranging from 1.16 to 1.43, with no apparent trend across strata.

When the 460 subjects who relapsed or left the study within 90 days of observation following initial recovery were excluded, along with the 45 who received less than 60 days of benzodiazepine treatment in this interval, risk was again elevated in the adjusted model (HR = 1.34; 95% CI, 1.05–1.71; Table 3). Likewise, including only subjects who received standing (versus as needed) benzodiazepine yielded an HR of 1.24 (95% CI, 1.03–1.50).

When risk associated with gabapentin use was examined among 1,016 subjects not treated with benzodiazepines,

Figure 1. Time to Relapse or Recurrence of Depression or Hypomanic/Manic/Mixed States Among Bipolar I and II Patients Who Did (+) or Did Not (–) Receive Benzodiazepine Treatment

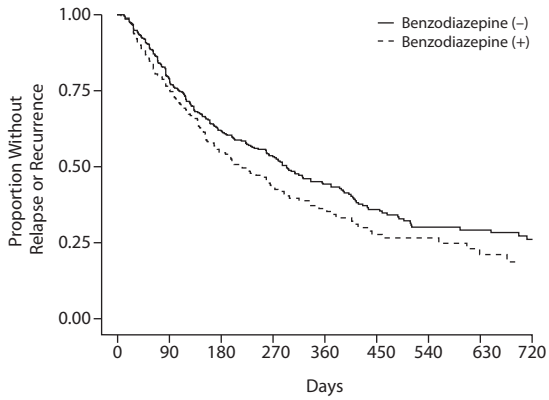
A. Any Episode, All Subjects



No. at risk

Benzodiazepine (–)	1,016	399	179	75	40
Benzodiazepine (+)	349	142	58	27	0

B. Any Episode, High Risk Stratum Only[a]



No. at risk

Benzodiazepine (–)	547	217	99	41	22
Benzodiazepine (+)	255	104	39	18	0

[a]Based on propensity score.

after adjustment for potential confounding variables, no association with recurrence risk was identified (crude HR = 1.04; 95% CI, 0.60–1.82). Finally, we examined a second cohort of 721 subjects in remission at study entry, including 132 (18.3%) benzodiazepine-treated patients, who were excluded from our primary analysis focusing on patients in-episode at entry into STEP-BD. In this cohort, recurrence hazards of similar magnitude were observed, with benzodiazepine-treated patients at 38% higher risk of recurrence (adjusted HR = 1.25; 95% CI, 0.91–1.72).

DISCUSSION

Benzodiazepine use was associated with greater hazard of recurrence in this cohort of bipolar I and II patients drawn from the STEP-BD study. This hazard persisted after adjustment for potential confounding variables, including anxiety comorbidity and residual mood and anxiety symptoms. A confirmatory analysis using adjustment with propensity scores yielded similar evidence of risk, as did analysis of an independent cohort of euthymic patients also drawn from STEP-BD. Conversely, in a parallel analysis examining a nonbenzodiazepine commonly used as an anxiolytic, far smaller magnitude of risk was observed.

The risk for confounding-by-indication in an analysis of this type is extremely high. That is, if more severely ill patients are more likely to be prescribed benzodiazepines, and these patients are also more likely to experience recurrent illness, a spurious association between benzodiazepines and outcome could be detected. Indeed, a previous report examining the first 500 patients to enter STEP-BD[35] found poorer outcomes associated with comorbid anxiety disorder. For this reason, we adjusted for numerous potential confounding variables that might be proxies for greater illness severity, a more recurrent course of prior illness, and greater psychiatric comorbidity. Most notably, adjustment for both current anxiety symptoms and comorbid anxiety disorders failed to eliminate the association between benzodiazepine use and poor outcome. We also conducted a parallel analysis examining another widely-prescribed anticonvulsant anxiolytic, gabapentin, which should be similarly confounded. Our intention was not to directly compare these 2 treatments. Rather, we anticipated that if our adjusted models do not adequately account for confounding by indication, we should see a similarly elevated recurrence risk with gabapentin. As noted above, we instead found no association between use of gabapentin and poorer outcomes, suggesting some specificity for benzodiazepines rather than anxiolytics in general.

Taken together, our results strongly suggest association, but cannot establish causation. Only a double-blind study with randomized treatment assignment can directly clarify the risks associated with benzodiazepine use in bipolar disorder. Despite the clinical importance of these questions, randomized studies of adjunctive benzodiazepines are unlikely to be conducted for ethical reasons. Naturalistic studies provide an alternative, albeit less well-controlled, means of addressing the same questions. Furthermore, the large size and detailed assessments in STEP-BD facilitate control of confounding variables. At minimum, our results suggest that the requirement for a benzodiazepine is an indicator of greater recurrence risk, and one that cannot be accounted for by considering anxiety or any of the wealth of clinical and sociodemographic features measured here.

The mechanism by which benzodiazepines might contribute to recurrence risk remains to be elucidated. Adverse effects of benzodiazepines, including sedation and memory impairment, could exacerbate underlying depressive symptoms or interfere with patients' ability to comply with other treatment plans. One study[36] suggested an association

between better performance on cognitive tests and faster recovery in bipolar disorder. γ-Aminobutyric acid (GABA) agonists have been shown to interfere with cognitive functioning among schizophrenia patients.[37] It is also possible that benzodiazepines yield interdose "rebound" activation or agitation[38] for some patients, which might increase recurrence risk. Notably, results among the small number of subjects (n = 38) receiving the short half-life benzodiazepine alprazolam were very similar to those observed in the cohort as a whole (results not shown), with greatest risk for depressive rather than manic recurrence.

In sum, our results suggest that regardless of mechanism, caution is warranted in using benzodiazepines in recovered bipolar patients. They highlight the need to better understand the role of GABAergic mechanisms in the pathophysiology of bipolar disorder.

Drug names: alprazolam (Xanax, Niravam, and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others).
Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, alprazolam, gabapentin and trazodone are not approved by the US Food and Drug Administration for the treatment of bipolar disorder, and trazodone is not approved for the treatment of insomnia.
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Supplementary material: eFigure 1 is available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Benzodiazepine Use and Risk of Recurrence in Bipolar Disorder: A STEP-BD Report

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List of Supplementary Material for the article

1. eFigure 1 Time to Relapse or Recurrence Among Benzodiazepine-Treated or -Untreated Bipolar I and II Patients, by Polarity of New Episode

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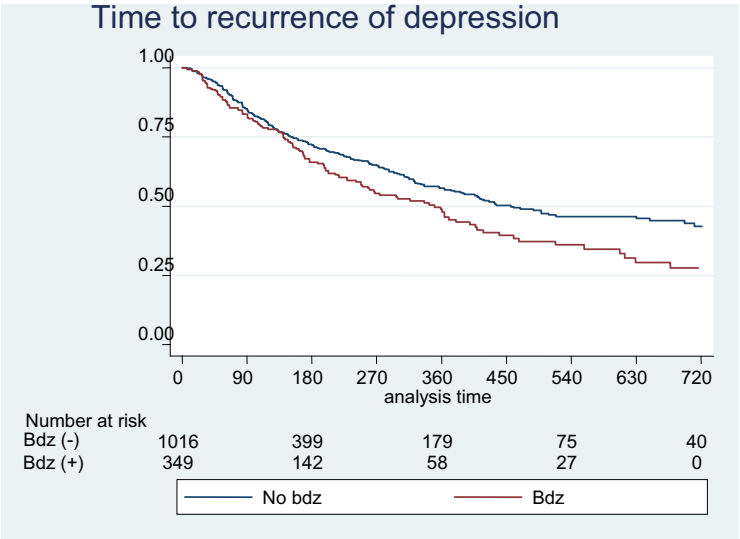
Supplemental Figure 1. Time to relapse or recurrence, by polarity of new episode



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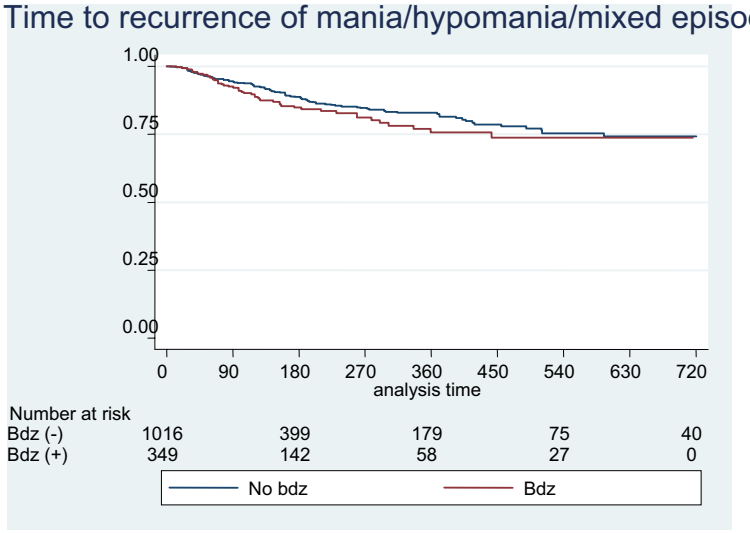

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