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Effect of adjunctive benzodiazepines on clinical outcomes in lithium- or quetiapine-treated outpatients with bipolar I or II disorder: Results from the Bipolar CHOICE trial

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Contributors

Author WVB wrote the paper. Author DJR, conducted the statistical analysis and assisted with the integrity of study data. Authors DAS and SVF helped develop the statistical analysis plan, and DAS oversaw the statistical analyses. Authors TAK, BDB, GK, DEK, RCS, SLM, ESF, VS, MT, CLB, TD, JRC, MET, and MK all served as study physicians and/or site Principal Investigators and thus, contributed to the collection and data and scientific oversight of the study and this paper. Author LGS assisted in writing/editing of this paper. Authors NAR and AAN served on the National Coordinating Center of the CHOICE study and thus, oversaw all data collection and ensured data integrity of this study as well as contributed to writing /editing this paper.

Abstract

Background—Little is known about the longer-term effects of adjunctive benzodiazepines on symptom response during treatment in patients with bipolar disorders.

Methods—The study sample consisted of 482 patients with bipolar I or II disorder enrolled in a 6-month, randomized, multi-site comparison of lithium- and quetiapine-based treatment. Changes in clinical measures (BISS total and subscales, CGI-BP, and CGI-Efficacy Index) were compared between participants who did and did not receive benzodiazepine treatment at baseline or during follow-up. Selected outcomes were also compared between patients who did and did not initiate benzodiazepines during follow-up using stabilized inverse probability weighted analyses.

Results—Significant improvement in all outcome measures occurred within each benzodiazepine exposure group. Benzodiazepine users (at baseline or during follow-up) experienced significantly less improvement in BISS total, BISS irritability, and CGI-BP scores than did benzodiazepine non-users. There were no significant differences in these measures between patients who did and did not initiate benzodiazepines during follow-up in the weighted analyses. There was no significant effect of benzodiazepine use on any outcome measure in patients with comorbid anxiety or substance use disorders.

Limitations—This is a secondary analysis of data from a randomized effectiveness trial that was not designed to address differential treatment response according to benzodiazepine use.

Conclusions—Adjunctive benzodiazepines may not significantly affect clinical outcome in lithium- or quetiapine-treated patients with bipolar I or II disorder over 6 months, after controlling for potential confounding factors.

Keywords

benzodiazepines; bipolar disorder; lithium; quetiapine; clinical outcome

Introduction

Benzodiazepines are among the most commonly prescribed classes of medications for patients with bipolar disorders (Baldessarini et al., 2007; Clark et al., 2004). Outside of acute settings, this approach is controversial due to the abuse liability and lack of controlled evidence about the long-term safety and effectiveness of benzodiazepines as adjuncts to foundational mood stabilizing medications such as lithium, selected anticonvulsants, and atypical antipsychotics (Brunette et al., 2003). Adjunctive benzodiazepine use at the time of symptom remission has been linked with higher risk of mood episode recurrence, as compared with no benzodiazepine use, in patients with bipolar I or II disorder (Perlis et al., 2010). On the other hand, effects of adjunctive benzodiazepines on core bipolar mood symptoms and associated symptoms such as anxiety and irritability have not been extensively investigated, and little is known about benzodiazepine treatment outcomes in bipolar disorder patients with comorbid anxiety and alcohol use disorders. In this report, the effects of benzodiazepines as adjuncts to lithium- and quetiapine-based pharmacotherapy on core bipolar mood symptoms, anxiety, irritability and global clinical state were examined using data from a recently completed randomized comparative effectiveness study.

Methods

The Comparative Effectiveness of a Second Generation Antipsychotic Mood Stabilizer and a Classic Mood Stabilizer for Bipolar Disorder (Bipolar CHOICE) study was a 6-month, randomized comparative effectiveness trial. Bipolar CHOICE rationale, design, and methods were published elsewhere (Nierenberg et al., 2013), but will be briefly reviewed here. Subjects (aged 18–68 years) who met DSM-IV-TR diagnostic criteria for bipolar I or II disorder, were at least mildly symptomatic at study entry (Clinical Global Impressions-Bipolar scale [CGI-BP] ≥ 3) (Spearing et al., 1997), and were in need of a change in pharmacotherapy were recruited between 2011 and 2012. Inclusion criteria were broad and exclusion criteria were limited in order to increase the generalizability of the Bipolar CHOICE sample. The study protocol was approved by the Institutional Review Boards of the 11 study sites.

Eligible subjects who provided written informed consent were randomized to treatment with either lithium or quetiapine. Regardless of allocation group, study subjects also received adjunctive personalized treatment (APT) that consisted of additional medications as deemed necessary by study clinicians. Data on the use of benzodiazepines and other prescribed medications were collected by trained clinical research coordinators at each study visit using standardized forms. Patients who were taking short- or long-acting benzodiazepines on either a scheduled or as-needed basis at baseline or at any follow-up time point were considered benzodiazepine users. Remaining subjects were considered benzodiazepine non-users.

Prior to treatment allocation, trained clinical research coordinators collected clinical and demographic data, and assessed current general medical conditions and psychiatric diagnoses, using standardized forms. Bipolar disorder, comorbid psychiatric and substance use diagnoses were confirmed using the Extended Mini-International Neuropsychiatric Interview (Sheehan et al., 1998). Psychopathology measures included the Bipolar Inventory of Signs and Symptoms (BISS) total and subscale scores for manic, depressive, anxious, and irritability symptoms at baseline and at 2-, 4-, 6-, 8-, 12-, 16-, 20- and 24 weeks (Bowden et al., 2007; Thompson et al., 2010). Global clinical state (as measured by the CGI-BP) and an integrated measure of treatment effectiveness and tolerability (the Clinical Global Impressions Efficacy Index [CGI-EI]) (Guy, 1976), were assessed at the same follow-up time points. The CGI-EI was rescaled to show differences between benefit and harm. Values greater than zero indicated greater therapeutic relative to adverse effects.

Summary statistics were used to describe the characteristics of the Bipolar CHOICE sample. The effect of any benzodiazepine use during follow-up (including at baseline) on treatment response was examined using mixed effects models that included a random intercept and slope over time and fixed effects for benzodiazepine use, log-time, study site, and the interaction between benzodiazepine use and log-time. To examine the effect of any benzodiazepine use on clinical outcome in patients with comorbid alcohol use disorders, a third interaction term indicating presence of current alcohol abuse or dependence was added to the mixed effects models. A similar approach was used to determine the effect of any benzodiazepine use on clinical outcome in patients with comorbid anxiety disorders.

Because of high potential for residual confounding, statistically significant results from the mixed effects models were subjected to additional analyses that compared treatment outcomes in patients who initiated benzodiazepines post-baseline (benzodiazepine initiators) and those who did not (non-initiators) using stabilized inverse probability weighting (sIPW) (Hernan et al., 2000). For IPW, each observation is weighted by the inverse of the propensity score (the probability of being a benzodiazepine initiator conditional on potential confounding factors). Stabilized weights were then calculated by using the probability of being a benzodiazepine initiator for those who received benzodiazepines (and of not being a benzodiazepine initiator for those who did not receive benzodiazepines) as the numerator, and the propensity score as the denominator (variables for IPW shown in Supplemental Table 1).

Analyses were conducted using SAS 9.2 statistical software (SAS Institute, Inc., 1994). Additional statistical procedures included unpaired t-tests for comparisons of continuous variables, and chi-square or Fisher's exact tests as indicated for comparisons of categorical variables. A two-tailed significance threshold of $p<0.05$ was used with no correction for multiple comparisons.

Results

A total of 482 subjects were enrolled in Bipolar CHOICE, 138 (28.6%) of whom were benzodiazepine users at baseline or during follow up. 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. Any current substance use disorders (n=296, 61.4%), alcohol abuse or dependence (n=235, 48.8%), anxiety disorders (n=277, 57.5%), and panic disorder diagnoses (n=112, 23.2%) were common. A significantly higher proportion of benzodiazepine users were female (68.8% vs. 54.7%, p=.004), had a comorbid anxiety disorder diagnosis (66.7 vs. 53.8%, p=.01), history of psychiatric hospitalization (56.2% vs. 43.0%, p=.009), bipolar I disorder subtype (77.5% vs. 64.5%, p=.006), current antidepressant use (29.0 vs. 14.8%, p<.001), current antipsychotic use (18.1% vs. 11.3%, p<.05), and current complex polydrug regimens (≥4 concomitant psychotropic drugs, 34.1% vs. 21.8%, p=.005). No significant differences in benzodiazepine use occurred between patients randomized to lithium (n=71 [29.6%]) or quetiapine (n=67 [27.7%]).

Significant improvement from baseline to 6 months occurred for all outcome measures in the entire study sample, and for both benzodiazepine users and non-users (Table 1). However, significantly less improvement in BISS total, BISS irritability, and CGI-BP scores was observed for benzodiazepine users than non-users (Table 1). In general, significant between-group differences in these measures were observed at all follow-up time points, beginning at week 2 (Supplemental Figure 1). There were no significant between-group differences in baseline to 6 month change for any other outcome measure, although a trend-level difference for improvement in CGI-EI favoring benzodiazepine non-users was observed (Table 1).

Similar levels of improvement in BISS total, BISS irritability, and CGI-BP were observed between baseline and 6 months for benzodiazepine initiators (n = 65) and non-initiators (n = 336) in the sIPW analysis as for benzodiazepine users and non-users in the primary analysis (Table 2). However, differences between benzodiazepine initiations and non-initiators in the degree of improvement in these measures were not statistically significant in the weighted analyses (Table 2).

There was no evidence of a moderating effect of benzodiazepine use on treatment response in lithium- or quetiapine-treated patients analyzed separately, or in patients with a comorbid anxiety disorder, panic disorder (separately), current alcohol use disorder, or current anxiety and alcohol use disorders (data not shown).

Discussion

In this study of Bipolar CHOICE participants, significant improvement from baseline in all outcome measures was observed in the overall sample and within each benzodiazepine exposure group. Benzodiazepine users (at baseline or during follow-up) experienced significantly less improvement in BISS total, BISS irritability, and CGI-BP scores than did benzodiazepine non-users. However, there were no significant differences in these measures between patients who initiated benzodiazepines during post-baseline follow-up only (benzodiazepine initiators) and benzodiazepine non-initiators after using stabilized inverse probability weighting to balance these exposure groups on several potential confounding variables. There was no evidence of a moderating effect of benzodiazepine use on any other outcome measure.

Benzodiazepines have been used as adjuncts to mood stabilizers or antipsychotic drugs during acute treatment in patients with bipolar disorder (Chouinard, 2004; Malhi et al., 2012). Adjunctive benzodiazepines are also commonly used during longer-term treatment (Clark, Xie, and Brunette, 2004), but few studies have evaluated the effectiveness of adjunctive benzodiazepines outside of the acute setting. One retrospective chart-review of 70 hospitalized patients with bipolar I disorder showed that administration of benzodiazepines during admission and after discharge was associated with a significantly higher number of outpatient follow-up days, as compared with no benzodiazepine administration (Hwang et al., 2006). A smaller retrospective chart-review of 15 outpatients patients with bipolar I disorder showed no significant difference in clinical outcome between patients who received concomitant clonazepam treatment and those who did not (Winkler et al., 2003). Interpretation of these results is limited by their small sample sizes and retrospective designs.

Only two studies, including ours, have prospectively evaluated longer-term clinical outcomes associated with benzodiazepine use. Both involved secondary analysis of effectiveness trial data. Perlis and colleagues reported significantly higher risk of mood episode recurrence among Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) participants who were prescribed a benzodiazepine at the time of remission, as compared with those who did not receive benzodiazepines (Perlis et al, 2010). However, the risk for confounding may be substantial for these secondary analyses since

randomization was not conducted according to benzodiazepine use. In the Perlis study (2010), adjustment of Cox models on propensity scores was used to manage residual confounding. We utilized an alternative propensity score-based method (sIPW) to balance benzodiazepine initiator and non-initiator groups on several confounding factors (Hernan, Brumback, and Robins, 2000). We chose stabilized (as opposed to nonstabilized) weights since they yield more efficient estimates (i.e., narrower confidence intervals) by reducing the occurrence of extreme values in the weighted data sets. Findings of significant attenuation of improvement in total psychopathology, irritability, and global clinical state from our initial unweighted analysis were not confirmed in the sIPW weighted comparison of benzodiazepine initiators and non-initiators. The initial analyses controlled for effects of study site and baseline values of dependent variables. However, residual confounding may have partially explained the observed differences in the initial unweighted analyses.

Our study has notable strengths including detailed characterization of a large cohort of bipolar I and II disorder patients and incorporation of a wide variety of confounding variables in the weighted analyses. Lack of overall additional benefit and potential attenuation of improvement for some symptoms with adjunctive benzodiazepines is an important finding considering how commonly these agents are used during longer-term treatment of patients with bipolar disorder, the possibility of adverse effects on recurrence risk and cognition, their abuse potential, and high prevalence of alcohol/substance use disorders among individuals with bipolar disorder (Barker et al., 2004; Brunette, Noordsy, Xie, and Drake, 2003; Perlis et al., 2010; Stewart, 2005). There are also noteworthy limitations. The Bipolar CHOICE sample consisted of patients who sought treatment at academic medical centers, which may limit study generalizability in spite of broad inclusion and minimal exclusion criteria. Our sample size, though substantial, may have had limited power to detect statistically significant differences in outcome conditional on benzodiazepine use, particularly when considering subgroups such as benzodiazepine initiators (n=65). However, absolute between-group differences in outcome measures were modest in both the weighted and unweighted comparisons, and may be of only modest clinical significance. We were unable to examine benzodiazepine effects on mood episode recurrence following remission or cognitive functioning, or their effects on clinical outcome beyond 6 months of follow-up. Finally, patients were not randomized according to benzodiazepine use, thus limiting our ability to draw definitive conclusions about the effect of adjunctive benzodiazepines based on this study alone.

In summary, we found no evidence of a moderating effect of benzodiazepines on psychopathology or global clinical state when used as adjuncts to lithium- or quetiapine-based treatment over 6 months in a large and well-characterized sample of patients with bipolar I or II disorder, after controlling for several potential confounding factors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

Dr. Ketter, between May 14, 2010 and May 14, 2013, had the following financial interests/arrangements or affiliations that could be perceived as real or apparent conflicts of interest: Grant/Research Support from the AstraZeneca Pharmaceuticals LP, Cephalon Inc., Eli Lilly and Company, Pfizer Inc., and Sunovion Pharmaceuticals; Consultant Fees from Allergan, Inc., Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Cephalon Inc., Forest Pharmaceuticals, Janssen Pharmaceutica Products, LP, Merck & Co., Inc., Sunovion Pharmaceuticals, Teva Pharmaceuticals; Lecture Honoraria from Abbott Laboratories, Inc., AstraZeneca Pharmaceuticals LP, GlaxoSmithKline, and Otsuka Pharmaceuticals; and Publication Royalties from American Psychiatric Publishing, Inc. In addition, Dr. Ketter's spouse is an employee of and holds stock in Janssen Pharmaceuticals.

Dr. Brody has received salary support over the past 3 years from grants funded by Forrest, Agency for Healthcare Quality and Research, and Pritzker neuropsychiatric disorders research consortium.

Dr. Kinrys has received research support from Astra-Zeneca, Bristol-Myers Squibb Company, Cephalon, Elan Pharmaceuticals, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, Sanofi/Synthelabo, Sepracor Inc., Pfizer Inc, UCB Pharma, and Wyeth-Ayerst Laboratories. He has been an advisor or consultant for Astra-Zeneca, Cephalon, Eli Lilly & Company, Forest Pharmaceuticals Inc., GlaxoSmithkline, Janssen Pharmaceutica, Pfizer Inc, Sepracor Inc., UCB Pharma, and Wyeth-Ayerst Laboratories. Dr. Kinrys has been a speaker for Astra-Zeneca, Forest Pharmaceuticals Inc., GlaxoSmithkline, Sepracor Inc., and Wyeth-Ayerst Laboratories.

Dr. Sylvia was a shareholder in Concordant Rater Systems and serves as a consultant for Bracket Global, Inc and Clintara. She also receives royalties from New Harbinger Publishers.

Dr. Friedman receives grant support from Repligen, Astra-Zeneca, Roche, Takeda, Neosync. He has been a consultant for Pamlab. He receives royalties from Springer. He has

served as an expert forensic consultant for Thomson Rhodes & Cowie P.C. and Berger and Zavesky Co. L.P.A.

Dr. Kocsis has received research grants and contracts from AHRQ, NIMH, NIDA, Burroughs Wellcome Trust, Pritzker Consortium, Takeda, Forest, Astra Zeneca, Roche. He is on the speaker's bureau at Pfizer and Merck and on the advisory board at Corcept.

Dr. Kemp serves on the speakers bureau for Pfizer and AstraZeneca, is a consultant for Bristol-Myers Squibb, Teva, Corcept, Janssen. His spouse is a minor stockholder for Sanofi and Abbott.

Dr. Shelton has served as a consultant to Bristol-Myers Squibb, Cyberonics, Inc., Elan, Corp., Eli Lilly and Company, Euthymics Bioscience, Forest Pharmaceuticals, Janssen Pharmaceutica, Medtronic, Inc., Otsuka Pharmaceuticals, Pamlab, Inc., Pfizer, Inc., Ridge Diagnostics, Takeda Pharmaceuticals. Dr. Shelton has received research grant support from Appian Labs, Bristol-Myers Squibb, Elan, Corp., Eli Lilly and Company, Euthymics Bioscience, Forest Pharmaceuticals, Janssen Pharmaceutica, Naurex, Inc., Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Pamlab, Inc., Repligen, Corp., Ridge Diagnostics, St. Jude Medical, Inc., Takeda Pharmaceuticals.

Dr. McElroy is a consultant to or member of the scientific advisory boards of Alkermes, Bracket, Corcept, MedAvante, Shire, Sunovian, and Teva. She is a principal or co-investigator on studies sponsored by the Agency for Healthcare Research & Quality (AHRQ), Alkermes, AstraZeneca, Cephalon, Eli Lilly and Company, Forest, Marriott Foundation, National Institute of Mental Health, Orexigen Therapeutics, Inc., Pfizer, Shire, Takeda Pharmaceutical Company Ltd., and Transcept Pharmaceutical, Inc. She is also an inventor on United States Patent no. 6,323,236 B2, Use of Sulfamate Derivatives for Treating Impulse Control Disorders, and along with the patent's assignee, University of Cincinnati, Cincinnati, Ohio, has received payments from Johnson & Johnson, which has exclusive rights under the patent.

Dr. Sylvia was a shareholder in Concordant Rater Systems and serves as a consultant for Bracket Global, Inc and Clintara. She also receives royalties from New Harbinger Publishers.

Dr. Kocsis has received research grants and contracts from AHRQ, NIMH, NIDA, Burroughs Wellcome Trust, Pritzker Consortium, Takeda, Forest, Astra Zeneca, Roche. He is on the speaker's bureau at Pfizer and Merck and on the advisory board at Corcept.

Dr. McInnis has received grants for research support from NIMH, the Heinz C Prechter Research Fund, and the Michigan Institute for Clinical Health Research (MICHR). MM has received consulting income from the Qatar National Research Foundation and Merck Pharmaceuticals.

Dr. Freedman received grant support from NIMH, AHRQ, Novartis, St. Jude Medical, Medtronics, Repligen, Astra-Zeneca, Roche, and Takeda. He receives royalties from Springer. He has been a consultant for PamLab.

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Dr. Deckersbach has received research support from NIMH, NARSAD, TSA, OCF, Tufts University, NIH, NIA, Janssen Pharmaceuticals, the Forest Research Institute, Shire Development Inc., Medtronic, Cyberonics, Northstar. He has received honoraria, consultation fees and/or royalties from the following: Medacorp, MGH Psychiatry Academy, BrainCells Inc., Systems Research and Applications Corporation, Boston University, Tufts University, the Catalan Agency for Health Technology Assessment and Research, the National Association of Social Workers Massachusetts, the Massachusetts Medical Society, and Oxford University Press.

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Dr. Thase has been an advisor/consultant: to Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Janssen Pharmaceuticals, Lundbeck, MedAvante, Merck, Mylan, Neuronetics, Otsuka, Pamlab, PharmaNeuroboost, Pfizer, Rexahn, Roche, Shire, Sunovion, Supernus, Takeda, and Teva, as well as the US Food and Drug Administration and the National Institute of Mental Health. During the same time frame, Dr. Thase has received honoraria for talks from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Merck, and Pfizer and he has received research grants from Alkermes, AstraZeneca, Eli Lilly, Forest, GlaxoSmithKline, Otsuka, PharmaNeuroboost, and Roche, as well as the National Institute of Mental Health and the Agency for Healthcare Research and Quality.

Dr. Nierenberg is a consultant for Abbott Laboratories, Astra Zeneca, Basilea, BrainCells Inc., Brandeis University, Bristol-Myers Squibb, Cephalon, Corcept, Eli Lilly & Co., Forest, Genaissance, GlaxoSmithKline, Innapharma, Janssen Pharmaceutica, Jazz Pharmaceuticals,

Lundbeck, Merck, Novartis, PamLabs, PGx Health, Pfizer, Ridge Diagnostics, Roche, Sepracor, Schering-Plough, Shire, Somerset, Sunovion, Takeda, Targacept, and Teva. He is a stakeholder in Appliance Computing, Inc. (MindSite); Brain Cells, Inc., InfoMed (potential share of income). He receives research support from AHRQ, Bristol-Myers Squibb, Cederroth, Cyberonics, Elan, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Lichtwer Pharma, Eli Lilly, Mylin (formerly Dey Pharmaceuticals), NARSAD, NIMH, Pamlabs, Pfizer, Shire, Stanley Foundation, and Wyeth-Ayerst. Honoraria include MGH Psychiatry Academy in the past 3 years (Prior to 3 years ago, honoraria from Bristol-Myers Squibb, Cyberonics, Forest Pharmaceuticals, GlaxoSmithKline, Eli Lilly, Shire, Wyeth-Ayerst). Dr. Nierenberg receives other income from legal case reviews for CRICO, MBL Publishing for past services as Editor-in-chief of CNS Spectrums, Slack Inc. for services as Associate Editor of Psychiatric Annals, and Editorial Board, Mind Mood Memory, Belvior Publications. He has copyright joint ownership with MGH for Structured Clinical Interview for MADRS and Clinical Positive Affect Scale and additional honoraria from ADURS, American Society for Clinical Psychopharmacology and Zucker Hillside Hospital and Forest and Janssen, Biomedical Development, Boston Center for the Arts, University of Pisa, University of Wisconsin at Madison, University Texas Southwest at Dallas, Health New England and Harold Grinspoon Charitable Foundation and Eli Lilly and AstraZeneca, Brandeis University, International Society for Bipolar Disorder, 2nd East Asian Bipolar Forum, Mid-Atlantic Permanente Research Institute, Up-to-Date.

Mr. Rabideau reports no competing interests in the past three years.

Dr. Schoenfeld has an ongoing consulting relationship with the following pharmaceutical companies, Biogen, Neuronova, Cytokinetics, Edison Pharmaceuticals, Galaxo Smith Kine, Merck, Agennix, Alexion and Pfizer. He also has a consulting relationship with Aptiv a contract research organization.

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

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Table 1

Effect of benzodiazepine (BZD) use at any time during follow-up[a,b]

	Baseline			Estimated change from baseline			Estimated difference in 6 month change
		BZD use during study			BZD use during study		BZD use during study
	Overall	No use	Any use	Overall	No use	Any use	Difference[c] (Any use – No use)
	Mean ± SD	*Mean ± SD*	*Mean ± SD*	*Mean (95% CI), p-value*	*Mean (95% CI), p-value*	*Mean (95% CI), p-value*	*Mean (95% CI), p-value*
BISS total	56.1 ± 18.8	54.8 ± 19.0	59.2 ± 18.1	−28.39 [−30.18,− 26.59] p<.0001	−29.30 [−31.41,− 27.19] p<.0001	−25.04 [−28.35,− 21.73] p<.0001	**4.26 [0.38,8.14] p = 0.03**
BISS mania	9.2 ± 6.4	9.2 ± 6.4	9.1 ± 6.2	−4.98 [−5.53,− 4.44] p<.0001	−4.94 [−5.59,− 4.29] p<.0001	−4.33 [−5.35,− 3.31] p<.0001	0.62 [−0.58,1.82] p = 0.31
BISS depression	17.5 ± 7.3	17.0 ± 7.3	18.8 ± 7.3	−8.89 [−9.62,− 8.16] p<.0001	−9.25 [−10.3,− 8.38] p<.0001	−8.04 [−9.41,− 6.67] p<.0001	1.21 [−0.40,2.82] p = 0.14
BISS anxiety	15.9 ± 8.5	15.0 ± 8.5	18.2 ± 8.2	−7.10 [−7.86,− 6.34] p<.0001	−7.35 [−8.26,− 6.44] p<.0001	−6.44 [−7.88,− 5.01] p<.0001	0.91 [−0.77,2.59] p = 0.29
BISS irritability	16.8 ± 8.5	16.4 ± 8.4	17.7 ± 8.7	−7.98 [−8.80,− 7.16] p<.0001	−8.47 [−9.44,− 7.50] p<.0001	−6.60 [−8.12,− 5.08] p<.0001	**1.87 [0.09,3.65] p = 0.04**
CGI-EI difference	…	…	…	1.61 [1.38,1.84] p<.0001	1.68 [1.41,1.95] p<.0001	1.20 [0.77,1.63] p<.0001	−0.48 [−0.98,0.02] p = 0.06
CGI-BP overall	4.5 ± 0.9	4.4 ± 0.8	4.7 ± 0.9	−1.61 [−1.73,− 1.50] p<.0001	−1.64 [−1.78,− 1.51] p<.0001	−1.36 [−1.57,− 1.15] p<.0001	**0.28 [0.03,0.53] p = 0.03**

[a] Exposure groups included patients who were prescribed benzodiazepines (BZDs) at baseline or at any time during post-randomization follow-up (any use) and those who were not prescribed BZDs at baseline or at any time during post-randomization follow-up (no use).

[b] Within- and between-group comparisons were made using mixed effects models that included a random intercept and slope over time and fixed effects for benzodiazepine use, log-time, study site, and the interaction between benzodiazepine use and log-time.

[c] Statistically significant results for between-group differences in estimated 6 month change for a given outcome measure appear in **bold** type. These results were subjected to further analysis to test robustness of findings (shown in Table 2).

Table 2

Effect of benzodiazepine initiation following randomization, using stabilized inverse probability weights[a,b]

	Estimated change from baseline		Estimated difference in 6 month change
	Benzodiazepine initiator status		
	Non-initiators	Initiators	Difference (Initiators – Non-initiators)
	Mean (95% CI), p-value	Mean (95% CI), p-value	Mean (95% CI), p-value
BISS total	−28.92 [−31.11, −26.72] p<.0001	−26.08 [−32.29, −19.87] p<.0001	2.83 [−3.75, 9.41] p = 0.40
BISS irritability	−8.68 [−9.70, −7.66] p<.0001	−7.36 [−10.12, −4.60] p<.0001	1.32 [−1.62, 4.27] p = 0.38
CGI-BP overall	−1.67 [−1.81, −1.53] p<.0001	−1.34 [−1.72, −0.95] p<.001	0.34 [−0.08, 0.75] p = 0.11

[a] Analysis included 401 patients who were not taking benzodiazepines at baseline. Exposure groups included patients who were prescribed benzodiazepines (BZDs) at any time during post-randomization follow-up (BZD initiators, n=65) and those who did not initiate BZDs during post-randomization follow-up (BZD non-initiators, n=336).

[b] Within- and between-group comparisons were made using stabilized inverse probability weighted effect estimates. Weighting was based on age, sex, race, current comorbid anxiety disorder diagnosis, bipolar (I vs. II) subtype, history of psychiatric hospitalization, antidepressant treatment, antipsychotic treatment, and complex polypharmacy (use of ≥ 4 psychotropic medications concurrently, not counting benzodiazepines) at baseline.