Research paper

Comorbid anxiety in bipolar CHOICE: Insights from the bipolar inventory of symptoms scale

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ABSTRACT

Background: Approximately 86–89% of patients with BD have a comorbid anxiety disorder associated with poor quality of life and reduced likelihood of recovery from an acute mood episode. The purpose of this study is to assess the prevalence and impact of comorbid anxiety using the Bipolar Inventory of Symptoms Scale (BISS) in patients with BD who participated in a 6-month pragmatic trial.

Methods: Participants (N = 482) in the Bipolar Clinical Health Outcomes Initiative in Comparative Effectiveness (CHOICE) study were adults with BD I or II. Anxiety diagnoses were assessed with the MINI. Global illness severity was assessed using the Clinical Global Impression-Bipolar Version. Mood symptoms and anxiety severity were assessed using the BISS.

Results: 61% of the study sample met criteria for a current anxiety disorder. Patients with a higher BISS anxiety score at baseline had a higher overall BD illness severity, depressive severity, and manic episode severity ($p < 0.001$). A single cutoff value of BISS anxiety had great sensitivity, yet poor specificity for determining a comorbid anxiety diagnosis. There were no significant differences in outcomes for individuals treated for anxiety disorders with anxiolytics compared with those who were not treated with anxiolytics.

Limitations: Sample size limitations prevented an analysis of whether the BISS cutoff score of 10 performed differently across varied anxiety disorders.

Conclusions: Given its ability to identify patients with co-occurring anxiety, the BISS anxiety subscale shows clinical utility as a screening measure though its application as a clinical assessment measure may not be advisable.

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1. Introduction

Bipolar disorder (BD), characterized by episodes of mania, hypomania, depression, and mixed features, is marked by high rates of comorbidity with other mental illnesses: up to 97.7% of patients with BD receive an additional lifetime psychiatric disorder diagnosis. Anxiety disorder prevalence rates are similar across the BD subtypes: approximately 86% of patients with BD I have a lifetime comorbid anxiety disorder compared with 89% of patients with BD II (Merikangas et al., 2007). Ultimately, comorbid anxiety in BD is linked to reduced quality of life, increased rates of suicidality, and poor likelihood of BD recovery. Comorbid anxiety also poses a unique difficulty for the pharmacological treatment of BD. Serotonergic antidepressants, which are commonly used to treat anxiety, have been linked to manic episodes and may increase the number of manic and depressive episodes in patients with BD (Henry and Demotes-Mainard, 2003). Further, patients with BD who have comorbid anxiety tend to exhibit lower response rates to anticonvulsants used as mood stabilizers (Henry and Demotes-Mainard, 2003).

The increased illness burden and worsened treatment response associated with comorbid anxiety in BD suggests the need for improved assessment of anxiety that can be applied across illness stages to ensure that a given patient with BD is receiving treatment maximally targeted to their anxiety symptoms. To that end, the Bipolar Inventory of Symptoms Scale (BISS) is a structured interview scale developed to address the full range of symptoms experienced by patients with BD (Gonzalez et al., 2008). The BISS is a unique BD assessment tool due to its broad assessment of BD symptomatology such that, unlike other rating scales, the BISS includes characteristics associated with impulsive behavior, sharpened thinking, elevated energy, risky behavior, and affective lability (Gonzalez et al., 2008). Five domains are assessed through the BISS: mania, depression, irritability, anxiety, and psychosis (Thompson et al., 2010). Within anxiety, the BISS measures psychic worry, subjective feelings of anxiety, reported somatic anxiety, and fearfulness.

The aims of the present study were to: 1) examine the specific relationships between anxiety symptoms and mood symptoms in a large, naturalistic sample of individuals with BD; 2) assess the utility of the BISS in research and clinical care by investigating the relationship between anxiety on the BISS and current anxiety diagnoses on the MINI International Neuropsychiatric Interview (MINI; 17); and 3) determine the effects of comorbid anxiety diagnoses on treatment outcomes in a representative sample of patients with BD.

2. Methods

2.1. Procedure

Bipolar CHOICE was a six-month, randomized comparative effectiveness trial conducted across 11 sites that compared lithium, a mood stabilizer, with quetiapine, an antipsychotic commonly used to treat BD (Nierenberg et al., 2016, 2014). Study inclusion criteria were intentionally broad with the aim of enhancing the generalizability of study findings. Details regarding study rationale, design, methods, and results are reported elsewhere (Nierenberg et al., 2016, 2014).

2.2. Participants

The Bipolar CHOICE study enrolled 482 patients aged 18–68 years across 11 sites. Participants had received a MINI DSM-IV diagnosis of BD I or II and were at least mildly symptomatic at study entry (CGI-BP ≥ 3) (Nierenberg et al., 2016). Participants were randomized to lithium plus adjunctive personalized therapy (Li + APT) or quetiapine plus adjunctive personalized therapy (QTP + APT). APT enabled clinicians to prescribe additional medications as needed provided they were consistent with the guideline-based treatment of BD and

personalized to the patient's current symptoms, prior medication exposure, treatment response, and medication tolerability.

2.3. Assessments

Global illness severity was assessed using the CGI-BP (Spearing et al., 1997) and mood symptoms and anxiety severity were assessed using the BISS (Bowden et al., 2007; Gonzalez et al., 2008).

2.4. Statistical analysis

The BISS anxiety domain score (BISS anxiety) was re-scaled to range from 0 to 40 while individual BISS items are reported on the original scale ranging from 0 to 4. Summary statistics are reported as means and standard deviations or frequencies, as appropriate. Pearson correlation coefficients were produced to determine any associations between BISS anxiety and other clinical variables, such as symptom severity and age of onset. One-way analysis of variance (ANOVA) models were used to assess whether mean BISS anxiety differed among patients with different mood episodes (e.g., depressive, manic/hypomanic, mixed) at study entry. BISS anxiety cutoffs (e.g., 8, 10, 12, 15) were compared with comorbid anxiety diagnoses at baseline to determine whether this scale could potentially be used as a clinical tool.

A mixed effects regression model was fit to determine whether patients improved in anxiety severity over the study; this model included a fixed effect for time and random effects for patient intercepts and slopes. A term for the randomized treatment group and a group-by-time interaction were introduced into the model to determine whether treatment predicted differential improvement over the six-month study period. Similar models were fit to determine whether mood episode at baseline or use of anti-anxiety medications (e.g., gabapentin, topiramate, any benzodiazepines) within the lithium group predicted differential improvement.

Two-tailed p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using SAS 9.4 (Cary, NC, USA) and R version 3.1.2 (www.r-project.org). Due to the exploratory nature of this analysis, no adjustments for multiple comparisons were made.

3. Results

Of the 482 patients in the study sample, 283 (59%) were female and 68% of the sample was diagnosed with BD I. The proportion of patients with any comorbid anxiety disorder at baseline were as follows: agoraphobia (176/482; 37%), social phobia (119/482; 25%), panic disorder (112/482; 23%), generalized anxiety disorder (107/480; 22%), obsessive-compulsive disorder (51/481; 11%), post-traumatic stress disorder (58/482; 12%) (Nierenberg et al., 2016).

Patients had a mean BISS anxiety score of 15.9 (SD = 8.2). A majority of patients were diagnosed with any current DSM-IV anxiety disorder (n = 295; 61%) including agoraphobia, generalized anxiety disorder, obsessive–compulsive disorder, post-traumatic stress disorder, panic disorder, and social anxiety disorder. Patients with higher anxiety severity at baseline also had a higher overall BD illness severity, depressive episode severity, manic episode severity, and an earlier age of BD onset (Table 1). We also found a significant association between current BD episode at baseline and anxiety severity such that those in a DSM-IV mixed episode had the highest mean BISS anxiety (20.4), those with MDE only had lower anxiety (16.1), and those with a manic/hypomanic episode only or neither episode had the lowest mean BISS anxiety (12.1 and 13.0, respectively) (Table 2).

We found that a single cutoff value of BISS anxiety had great sensitivity, yet poor specificity to determine a diagnosis of a comorbid anxiety disorder. For example, among the 295 patients with any current anxiety disorder, 262 (89% sensitivity) had a BISS anxiety of at least 10 (e.g., 10, 12, 15); however, among the 187 without an anxiety disorder,

Table 1

Baseline associations with BISS anxiety

Variable	Parameter Estimate (95% CI)	*p*-value
BISS depression	0.61 (0.51, 0.70)	< 0.0001
BISS mania	0.24 (0.12, 0.37)	< 0.0001
CGI overall	4.80 (4.01, 5.59)	< 0.0001
CGI depression	4.12 (3.55, 4.69)	< 0.0001
CGI mania	1.24 (0.64, 1.84)	< 0.0001
Age of onset of first mood episode	−0.13 (−0.23, −0.03)	0.01
Age of onset of first depressive episode	−0.13 (−0.23, −0.03)	0.007
Age of onset of first manic episode	−0.07 (−0.16, 0.01)	0.07

CI: confidence interval. Results are based on linear regression.

Table 2

Baseline BISS anxiety means for baseline mood episodes

Characteristic	*N* (%)	BISS (anxiety, mean + SD)	Overall *p*-value
Current episode at baseline[a]			< 0.0001
Major depressive episode	269 (56)	16.1 + 8.5	
Manic/hypomanic episode	56 (12)	12.1 + 8.0	
Mixed episode	82 (17)	20.4 + 7.2	
Not in mood episode	75 (16)	13.0 + 8.0	

[a] All pairwise comparisons significantly different except manic/hypomanic vs. not in mood episode.

only 73 (40% specificity) had a BISS anxiety below 10 (e.g., 8).

During the study, both groups (Li + APT and QTP + APT) experienced general improvement in anxiety such that patients experienced, on average, approximately a seven-point decrease in BISS anxiety over six months (both *p* < 0.0001). There was no differential effect of randomized treatment on BISS anxiety improvement over the six-month study period (*p* = 0.32). Similarly, mood episode at baseline or use of anti-anxiety medications within the lithium group did not predict differential improvements (*p* > 0.05 for all comparisons), with the latter finding being consistent with other analyses in this study sample that did not find a significant effect of benzodiazepine use on treatment outcomes (Bobo et al., 2014).

4. Discussion

In our representative sample of patients with BD, we found that higher scores on the anxiety subscale of the BISS were linked to a more severe BD illness. Moreover, our analyses suggest that heightened anxiety was more strongly associated with increased depression scores (as opposed to increased mania scores) on the BISS. This finding supports previous literature suggesting that anxiety and depression are more closely linked than anxiety and mania. Similar underlying processes (e.g., worry, rumination) may characterize both anxiety and depression.

We assessed the utility of specific cutoff scores that could be used to provide screening information about anxiety disorders; to that end, we applied cutoff scores of 8, 10, 12, and 15. We found that the BISS anxiety subscale showed high sensitivity but a low specificity rate at cutoff scores of 8, 10, and 12. The sensitivity of the measure was slightly decreased at a cutoff score of 15, whereas the specificity rate was slightly increased. In this manner, the BISS anxiety subscale shows clinical utility as a screening measure. One limitation of this study is that we were not able to assess whether the BISS cutoff score of 10 performed better for some anxiety disorders relative to others; sample size limitations precluded us from conducting this analysis.

Of note, we found no differences in anxiety improvement between the quetiapine and lithium groups. This finding, which contrasts with previous literature finding quetiapine to be particularly effective in

reducing comorbid anxiety in patients with BD (Calabrese et al., 2005; Hirschfeld et al., 2006; Thase, 2008), warrants further investigation.

Finally, our analyses found no between-group differences in outcome for individuals who were being treated for anxiety with anxiolytics compared with those who were not. This finding may be explained by the fact that individuals with higher levels of anxiety at baseline would be more likely to be taking medications for their anxiety symptoms at baseline and less likely to improve over the course of the study. It should be noted, however, that there was no differential improvement between groups and that both groups experienced reductions in anxiety symptoms over the course of the study. The primary analysis of a randomized, double-blind, placebo-controlled study of patients with bipolar I or II depression, generalized anxiety disorder, and other comorbid disorders including a current substance use disorder did not find that quetiapine-XR was superior to placebo in reducing depressive and anxiety symptoms (Gao et al., 2014). However, a secondary analysis of patients with and without a current substance use disorder found that quetiapine-XR was more efficacious than placebo in reducing depressive symptoms in patients with a current substance disorder, but not in those without a current substance use disorder (Gao et al., 2017). These findings suggest that the impact of anxiety symptoms in patients with BD may be mediated/moderated by other psychiatric comorbidities. It is also worth considering the possibility that anxiety symptoms are an integral part of BD (Vazquez et al., 2014), which would explain why an intervention targeted towards the treatment of BD could also help reduce anxiety symptoms across both study groups. Indeed, the high prevalence of co-occurring anxiety disorders in this sample may lend some support to theories that the elevated rates of comorbidity between mood and anxiety disorders reflect a weakness of our current categorical diagnostic system. Specifically, under our current classification system for mental disorders, patients with mood and anxiety symptoms may receive separate mood and anxiety disorder diagnoses. However, their illness presentation may be better represented as a single, unified disorder(Goes et al., 2012; Goldberg, 1996; Maj, 2005; Vazquez et al., 2014).

5. Conclusion

Findings from this study provide further support for the negative clinical implications of comorbid anxiety disorders for patients with BD (Gao et al., 2013; Simon et al., 2004). Patients with BD who are diagnosed with anxiety have exhibited a more severe BD illness, increased suicidal behavior, and elevated depressive symptoms (Gao et al., 2013). In this study, the BISS anxiety subscale demonstrated utility in identifying patients with BD experiencing anxiety and in linking current illness severity to comorbid anxiety status. Moreover, a large proportion of the sample who did not meet criteria for a specific anxiety disorder exhibited a notable level of anxiety symptomatology on the BISS. Such information holds important clinical relevance for the potential of the BISS as a brief screening measure; based on our findings, clinicians administering the BISS to their patients may be able to detect anxiety symptoms in their patients that are notable, even if such symptoms do not map onto an anxiety disorder at the diagnostic level. Future research incorporating the BISS as an assessment of anxiety symptoms will further elucidate the scale's potential to serve as an easily-administered anxiety screening tool to identify individuals who might benefit from more detailed questioning on their anxiety symptoms. However, for a thorough screening of anxiety, the BISS is not likely to be the measure of choice.

Conflicts of interest

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-

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Dr. Bowden is conducting a biological study in mood disorders sponsored by Myriad Inc. He has no competing interests.

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Dr. Tohen is a former full-time employee at Lilly (1997 to 2008). He has been a consultant for AstraZeneca, Abbott, BMS, Lilly, GSK, J&J, Otsuka, Roche, Lundbeck, Elan, Alkermes, Merck, Pamlab, Alexza, Forest, Teva, Sunovion, Gedeon Richter, and Wyeth. His spouse is a former employee at Lilly (1998–2013).

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Author contributions

Author GK wrote the paper and served on the Bipolar CHOICE study, contributing to data collection and scientific oversight for this study and this manuscript. Authors CLB, KG, MK, WVB, MT, TD, SLM, TAK, RCS, ESF, JRC, MGM, JK, MET, and VS served as study clinicians and/or site Principal Investigators, thereby contributing to data collection, scientific oversight for this study and this manuscript, and editing of this manuscript. Author LGS served as the Director of Clinical Operations for the National Coordinating Center of the CHOICE study and was involved in overseeing data collection and ensuring data integrity for the study and this manuscript. Author DJR conducted the statistical analyses and assisted with integrity of the study data. Authors AKG and CMH assisted with editing and writing of the paper. Author AAN served as the overall Principal Investigator and directed the National Coordinating Center of the CHOICE study, overseeing data collection and data integrity, and assisted in the writing/editing of this paper. Author NRH assisted with writing of the paper and served as the Director of Training and Assessments for the National Coordinating Center of the CHOICE study, thus overseeing rater training, data collection, and ensuring data integrity. All authors approved the final article.

Study limitations

Sample size considerations prevented an analysis of whether the BISS cutoff score of 10 performed differently across varied anxiety disorders.

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References

Bobo, W.V., Reilly-Harrington, N.A., Ketter, T.A., Brody, B.D., Kinrys, G., Kemp, D.E., Shelton, R.C., McElroy, S.L., Sylvia, L.G., Kocsis, J.H., McInnis, M.G., Friedman, E.S., Singh, V., Tohen, M., Bowden, C.L., Deckersbach, T., Calabrese, J.R., Thase, M.E., Nierenberg, A.A., Rabideau, D.J., Schoenfeld, D.A., Faraone, S.V., Kamali, M., 2014. 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. J. Affect. Disord. 161, 30–35.

Bowden, C.L., Singh, V., Thompson, P., Gonzalez, J.M., Katz, M.M., Dahl, M., Prihoda, T.J., Chang, X., 2007. Development of the bipolar inventory of symptoms scale. Acta Psychiatr. Scand. 116, 189–194.

Calabrese, J.R., Keck Jr., P.E., Macfadden, W., Minkwitz, M., Ketter, T.A., Weisler, R.H., Cutler, A.J., McCoy, R., Wilson, E., Mullen, J., 2005. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am. J. Psychiatry 162, 1351–1360.

Gao, K., Ganocy, S.J., Conroy, C., Brownrigg, B., Serrano, M.B., Calabrese, J.R., 2017. A placebo controlled study of quetiapine-XR in bipolar depression accompanied by generalized anxiety with and without a recent history of alcohol and cannabis use. Psychopharmacology 234, 2233–2244.

Gao, K., Wang, Z., Chen, J., Kemp, D.E., Chan, P.K., Conroy, C.M., Serrano, M.B., Ganocy, S.J., Calabrese, J.R., 2013. Should an assessment of Axis I comorbidity be included in the initial diagnostic assessment of mood disorders? Role of QIDS-16-SR total score in predicting number of axis I comorbidity. J. Affect. Disord. 148, 256–264.

Gao, K., Wu, R., Kemp, D.E., Chen, J., Karberg, E., Conroy, C., Chan, P., Ren, M., Serrano, M.B., Ganocy, S.J., Calabrese, J.R., 2014. Efficacy and safety of quetiapine-XR as monotherapy or adjunctive therapy to a mood stabilizer in acute bipolar depression with generalized anxiety disorder and other comorbidities: a randomized, placebo-controlled trial. J. Clin. Psychiatry 75, 1062–1068.

Goes, F.S., McCusker, M.G., Bienvenu, O.J., Mackinnon, D.F., Mondimore, F.M., Schweizer, B., Depaulo, J.R., Potash, J.B., 2012. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of comorbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. Psychol. Med. 42, 1449–1459.

Goldberg, D., 1996. A dimensional model for common mental disorders. Br. J. Psychiatry 44–49 Supplement.

Gonzalez, J.M., Bowden, C.L., Katz, M.M., Thompson, P., Singh, V., Prihoda, T.J., Dahl, M., 2008. Development of the Bipolar Inventory of Symptoms Scale: concurrent validity, discriminant validity and retest reliability. Int. J. Methods Psychiatric Res. 17, 198–209.

Henry, C., Demotes-Mainard, J., 2003. Avoiding drug-induced switching in patients with bipolar depression. Drug Saf. 26, 337–351.

Hirschfeld, R.M., Weisler, R.H., Raines, S.R., Macfadden, W., 2006. Quetiapine in the treatment of anxiety in patients with bipolar I or II depression: a secondary analysis from a randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 67, 355–362.

Maj, M., 2005. "Psychiatric comorbidity": an artefact of current diagnostic systems? Br. J. Psychiatry 186, 182–184.

Merikangas, K.R., Akiskal, H.S., Angst, J., Greenberg, P.E., Hirschfeld, R.M.A., Petukhova, M., Kessler, R.C., 2007. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry 64, 543–552.

Nierenberg, A.A., McElroy, S.L., Friedman, E.S., Ketter, T.A., Shelton, R.C., Deckersbach, T., McInnis, M.G., Bowden, C.L., Tohen, M., Kocsis, J.H., 2016. Bipolar CHOICE (clinical health outcomes initiative in comparative effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. J. Clin. Psychiatry 77, 90–99.

Nierenberg, A.A., Sylvia, L.G., Leon, A.C., Reilly-Harrington, N.A., Shesler, L.W., McElroy, S.L., Friedman, E.S., Thase, M.E., Shelton, R.C., Bowden, C.L., Tohen, M., Singh, V.,

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Deckersbach, T., Ketter, T.A., Kocsis, J.H., McInnis, M.G., Schoenfeld, D., Bobo, W.V., Calabrese, J.R., Group, t.B.C.S., 2014. Clinical and health outcomes initative in comparative effectiveness for bipolar disorder (Bipolar CHOICE): a pragmatic trial of complex treatment for a complex disorder. Clin. Trials 11, 114–127.

Simon, N.M., Otto, M.W., Wisniewski, S.R., Fossey, M., Sagduyu, K., Frank, E., Sachs, G.S., Nierenberg, A.A., Thase, M.E., Pollack, M.H., 2004. 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 161, 2222–2229.

Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the clinical global impressions (CGI) scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 73, 159–171.

Thase, M.E., 2008. Quetiapine monotherapy for bipolar depression. Neuropsychiatr. Dis. Treat. 4, 11–21.

Thompson, P.M., Gonzalez, J.M., Singh, V., Schoolfield, J.D., Katz, M.M., Bowden, C.L., 2010. Principal domains of behavioral psychopathology identified by the bipolar inventory of signs and symptoms scale (BISS). Psychiatry Res. 175, 221–226.

Vazquez, G.H., Baldessarini, R.J., Tondo, L., 2014. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. Depress. Anxiety 31, 196–206.