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Associations of Comorbid Anxiety with Medication Adherence and Psychiatric Symptomatology in a Population of Non-Adherent Bipolar Disorder Subjects

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Abstract

This analysis was conducted on baseline data from 178 non-adherent Bipolar Disorder (BD) subjects in a randomized controlled trial. Medication adherence was measured with Tablets Routine Questionnaire (TRQ) as percentage of days with missed doses. Inclusion criteria required at least 20% non-adherence. Medication adherence, symptomatology and functioning in individuals with and without a comorbid anxiety disorder were compared. 78.9% of subjects had at least one or more current anxiety disorder, with the most common being PTSD, panic disorder and generalized anxiety disorder. The percentage of days with missed doses over the past month was significantly lower in those with anxiety disorders compared to those without (40.1% vs 50.5%, $p=0.03$). Those with comorbid anxiety disorders and those with greater number of anxiety disorder diagnoses had significantly worse mean scores on Montgomery–Åsberg Depression

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Conflicts of Interest

Other authors report no disclosures.

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Rating Scale, Brief Psychiatric Rating Scale, Clinical Global Impression–Bipolar Version, and Global Assessment of Functioning.

Keywords

Medication Adherence; Bipolar Disorder; Anxiety Disorders; Randomized Controlled Trial; Secondary Analysis

1. INTRODUCTION

Anxiety disorders are commonly comorbid with Bipolar Disorder (BD), with current anxiety disorders reported in 32% of bipolar subjects from STEP-BD (Otto et al, 2006) and lifetime anxiety disorder comorbidity may be as high as 93% reported in National Comorbidity Survey (Freeman et al, 2002); comorbid anxiety disorders are linked to a number of negative clinical outcomes in bipolar disorder. Such outcomes include reduced time spent in euthymic mood, lower likelihood of timely recovery from depression, longer time to remission during depressive episodes, increased side-effects from treatment, a need for more medications, increased risk of earlier relapse, greater functional impairment, lower quality of life, and an increased suicide risk (Feske et al, 2000; Otto et al, 2006; Simon et al, 2004; Simon et al, 2007; Yuen et al, 2016). These negative outcomes are reported to be greater with multiple anxiety disorders (Otto et al, 2006).

Literature on the association between comorbid anxiety and treatment adherence in BD is inconsistent and sparse. In two different studies, Sajatovic et al. (Sajatovic et al, 2006a; Sajatovic et al, 2008) found no significant difference in the presence of current or lifetime anxiety disorders in those adherent (never missed medication) and non-adherent (took less than half of prescribed, or stopped entirely) at baseline or over a period of 3 years. Based on analyses of STEP BD data, Perlis et al. reported that current anxiety at study entry was associated with poor adherence, and anxiety symptoms at each visit were associated with a greater likelihood of nonadherence (Perlis et al, 2010), defined as missing at least 25% of doses of at least one medication. Baldessarini et al. found that obsessive-compulsive disorder was significantly associated with non-adherence with a Relative Risk (RR) of 4.90 (Baldessarini et al, 2008). In that study, adherence was defined strictly as taking all doses of psychotropic medicines for BD, as prescribed, for the previous 10 days, and missing even one dose on any day was considered non-adherence. In an 18-month prospective study, Arvilommi et al. found that non-adherence to mood stabilizers at the 18-month follow-up was independently associated with having some current anxiety disorder at the 6-month interview (Arvilommi et al, 2014). Medication adherence was defined as 'being on medication regularly'; all other patients were considered non-adherent. Feske et al. reported a history of panic attacks, but neither current nor past anxiety symptoms were a predictor for poor adherence (Feske et al, 2000). One of the difficulties in drawing conclusions from the current literature is the huge variation in how medication adherence or non-adherence was defined in these studies.

Literature suggests that approximately one in two individuals with BD is non-adherent with medication treatment (Lingam et al, 2002; Sajatovic et al, 2007; Sajatovic et al, 2006b), and

at least one-third of individuals fail to take more than 70% of their prescribed medication (Jamison et al, 1979; Scott et al, 2002b). BD medication non-adherence can have severe consequences (Mander, 1988; Mander et al, 1988; Muller-Oerlinghausen et al, 1992; Strakowski et al, 1998; Svarstad et al, 2001) that impose personal and financial burden (Begley et al, 2001; Colom et al, 2005; Durrenberger et al, 1999) from illness relapse, such as an increased rate of suicide in BD patients (Gonzalez-Pinto et al, 2006), greater healthcare costs (Simon, 2003), more lost work-days (Gardner et al, 2006), and intangible costs such as family burden and impaired health-related quality of life (Kleinman et al, 2003).

The present analysis was derived from cross-sectional baseline data collected from an ongoing National Institute of Mental Health (NIMH)-funded randomized controlled trial (RCT) testing a novel behavioral intervention to promote medication adherence. This secondary analysis examines BD symptom severity and adherence in those with and without comorbid anxiety disorders. This well-characterized, poorly-adherent BD sample was assessed on a self-reported medication adherence measure as well as standardized ratings of depression, mania and global psychopathology, and aimed to further examine the relationships between anxiety, medication adherence and psychiatric symptomatology in BD.

2. METHODS

Overall study description

This NIMH-funded RCT tested a novel customized adherence enhancement intervention intended to promote BD medication adherence against an educational control in poorly-adherent individuals with BD (1R01MH093321-01A1; Principal Investigator MS). Study inclusion criteria included having bipolar I disorder (BD-I) or bipolar II disorder (BD-II) – confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV) – for at least two years duration, treatment with at least one evidence-based medication to stabilize mood for at least six months, and 20% non-adherence with prescribed BD medication treatment (i.e., lithium, anticonvulsant, or antipsychotic mood stabilizer). Study inclusion criteria were purposely broad in order to generalize to real-world patients with BD and only individuals who were unable to participate in study procedures, unable/unwilling to provide informed consent, and those at immediate risk of harm to self or others were excluded. The study was approved by the local Institutional Review Board (IRB) and all study participants provided written informed consent.

Medication adherence

Adherence was measured with the Tablets Routine Questionnaire (TRQ). The TRQ is a self-report measure which identifies the proportion of days with missed medication in the past seven and past 30 days (Peet et al, 1991; Scott et al, 2002a). Lower scores represent better adherence, while higher scores represent worse adherence. The TRQ has demonstrated a statistically significant association with adherence in the past month and in the past week, and has been shown to correlate highly with lithium levels (Scott et al, 2002b). In this RCT, past week and past month TRQ were assessed for each evidence-based BD maintenance

medication (lithium, anticonvulsant, antipsychotic) prescribed for 3 months. For individuals who were on more than one medication, an average TRQ was calculated.

Symptoms and Functioning

Symptoms were measured with the Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery et al, 1979), the Young Mania Rating Scale (YMRS) (Young et al, 1978), and the Brief Psychiatric Rating Scale (BPRS) (Overall et al, 1962). DSM-IV Anxiety disorders were diagnosed using SCID-IV. Subjects were also rated with Clinical Global Impression, Bipolar Version (CGI-BP) (Spearing et al, 1997) and Global Assessment of Functioning (GAF) (Jones et al, 1995).

The MADRS is a 10-item depression severity scale widely utilized in studies with patients with serious mental illness (Montgomery et al, 1979). Possible scores range from 0 to 60 with higher scores indicating worse depression. The BPRS (Overall et al, 1962) measures psychotic and non-psychotic symptoms in serious mental illness. Possible scores range from 7 to 126, with higher scores indicating greater symptom severity. YMRS rates the severity of manic symptoms (Young et al, 1978). It has 11 items with possible scores ranging from 0 to 44, with higher scores indicating greater severity of mania. The CGI-BP is a modification of the CGI scale for use in bipolar disorder (Spearing et al, 1997). It is a broad measure of global psychopathology that evaluates illness severity on a 1 to 7 point continuum. Possible scores range from 0 to 7, with higher scores indicating greater psychopathology. The GAF is a 100-point single-item scale that measures global functioning (Jones et al, 1995). Possible scores range from 1 to 100, with higher scores indicating better functioning.

Data analysis

This analysis used baseline (demographic, TRQ, and clinical information) data from 178 RCT enrollments. The percentages of participants with specific current anxiety disorders were calculated. Clinical characteristics of individuals with and without a comorbid anxiety disorder were compared using t-tests. Medication adherence and symptomatology across anxiety burden, as measured by the number of anxiety disorder diagnoses, were compared using ANOVAs. Study data were collected and managed using REDCap electronic data capture tools hosted at University Hospitals Cleveland Medical Center (Harris et al, 2009).

3. RESULTS

Out of 178 subjects, 131 subjects (78.9%) were found to have at least one or more current anxiety disorder. The most common anxiety disorders were PTSD, panic disorder and generalized anxiety disorder. Percentages of subjects with specific anxiety disorders are illustrated in Figure 1.

Comparison findings of baseline clinical characteristics of individuals with and without a comorbid anxiety disorder diagnosis are summarized in Table 1. There was no difference in the demographic characteristics between the two groups with the exception of age; those with anxiety disorders were on average 4 years younger than those without anxiety disorder.

The percentage of days with missed doses over the past month as reported on TRQ was significantly lower in those with anxiety disorders compared to those without (40.1% vs 50.5%, $p=0.03$). No significant difference was found for past week adherence on TRQ (42.7% vs 47.4%, $p=0.88$).

Those with comorbid anxiety disorders were found to have significantly higher mean scores on YMRS, MADRS, BPRS, and CGI-BP, and significantly lower mean scores on GAF, indicating greater severity of manic symptoms, worse depression, worse psychiatric symptomatology, worse illness severity and worse functioning.

No significant difference in TRQ for BD medications was found when adherence was compared across number of anxiety disorder diagnoses ($p=0.81$ and $p=0.16$ for past week and past month adherence comparisons, respectively). The TRQ scores are detailed in Table 2.

Those with a greater number of anxiety disorder diagnoses had significantly higher YMRS scores ($p=0.02$), MADRS scores ($p<0.01$), BPRS scores ($p=0.01$), CGI-BP scores ($p<0.01$) and lower GAF scores ($p<0.01$).

Results are summarized in Table 2.

4. DISCUSSION

This is the first analysis to report on the associations of comorbid anxiety disorders with the degree of medication adherence and psychiatric symptomatology in a sample of well-characterized, poorly-adherent BD patients.

78.9% of our sample had at least one or more anxiety disorder, which is considerably higher than the prevalence of 32% comorbid anxiety reported in the data from STEP-BD bipolar disorder subjects. This may indicate a higher frequency of anxiety disorders in patients with self-identified BD medication non-adherence. PTSD was the most common current DSM-IV anxiety disorder in our sample with 40.5% prevalence. This high prevalence of PTSD may be particular to our sample as only 4.8% of subjects in the STEP-BD study had current comorbid PTSD (Otto et al, 2006), and lifetime prevalence of PTSD in bipolar subjects was 38.8% in the National Comorbidity Survey (Freeman et al, 2002).

The high rates of comorbidity anxiety disorders may be related to another conceptual consideration. It is possible that some of the symptoms related to manic/hypomanic and depressive states may also be present in anxiety disorders (inner tension, somatic symptoms, insomnia, etc.). In this sense, strictly categorical diagnoses such as DSM-IV diagnoses could leave out sub-threshold conditions and anxiety symptoms could be, at least partially, an artifact of the diagnostic category.

The significant difference in age between those with and without anxiety comorbidity may be a reflection of the fact that anxiety disorders in general are less prevalent in older adults than younger adults (Flint, 2005). Previous studies in the BD patient population have either found no association between anxiety and medication adherence or have reported a negative

association of anxiety with adherence. As such, further exploration is needed to discover why those in our sample with comorbid anxiety disorders had better medication adherence compared to those without a comorbid anxiety disorder. Compared with previous studies which looked at adherence versus non-adherence in relation to anxiety, our entire sample was comprised of poorly-adherent patients. As such, we examined the degree of medication adherence in relationship to comorbid anxiety diagnoses. Secondly, while we analyzed active comorbid anxiety diagnoses, we do not have information on the clinical severity of anxiety symptoms in these patients. An inverted U-shaped relationship between anxiety severity and functioning has been described in the literature (Salehi et al, 2010), and it is possible that the severity of anxiety symptoms in our sample was enough to make them worry about missing their medications, thereby resulting in relative improved adherence. The discrepancy between past week and past month adherence is unexpected. The discrepancy may suggest the possibility that the significant result with regards to past month – but not past week – may have been a chance finding. This discrepancy may also be a result of recall bias, such that participants were more likely to misremember their adherence over past month rather than past week.

Similar to other bipolar disorder literature, our study found those with anxiety comorbidity had on average greater severity of manic symptoms, worse depression scores, worse psychiatric symptomatology, worse illness severity, and worse functioning (Feske et al, 2000; Otto et al, 2006; Simon et al, 2004; Simon et al, 2007; Yuen et al, 2016). Likewise, this study replicated previously reported negative clinical associations of comorbid anxiety disorders in a sample of non-adherent patients. This relationship was also demonstrated across anxiety burden, as those with higher number of anxiety disorders had worse scores on measures of psychiatric symptomatology and functioning.

We did not find any significant difference in self-reported BD medication adherence across anxiety burden. This may have been a result of the relatively small sample size for each group, or could also reflect the absence of an association between medication adherence and anxiety burden in our subjects.

There are several potential limitations to our analysis including the cross-sectional design (therefore casual inferences cannot be made), moderate sample size, small number of individuals with no anxiety diagnoses, lack of clinical data on anxiety severity, low levels of manic symptoms among enrolled BD participants, and the reliance on a self-report measure for medication adherence.

This analysis, however, has many strengths which emphasize the valuable contribution to literature on the topic: a well-characterized population of patients with BD with quantified poor adherence (a poorly studied group that is of substantial clinical importance due to their high risk of relapse and poor prognosis), use of standardized instruments as a measure of adherence, objective diagnoses of anxiety disorders using standardized SCID-IV, and use of standardized measures of psychiatric symptomatology and functioning. Our novel findings offer insight and information that might not be obtained in a typical therapeutic clinical trial where such individuals are typically excluded.

6. CONCLUSION

This cross-sectional analysis of poorly-adherent BD patients suggests that anxiety comorbidity is common, is associated with worse BD symptoms, illness severity and functioning, but is not associated with worse adherence compared to poorly-adherent patients with BD and no comorbid anxiety.

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Figure 1.
Prevalence of Anxiety Disorders in a Non-Adherent Bipolar Disorder Subjects

Table 1

Baseline clinical characteristics of individuals with and without a comorbid anxiety disorder diagnosis

Variable	Anxiety Diagnosis (N=131) Mean (SD) or N (%)	No Anxiety Diagnosis (N=47) Mean (SD) or N (%)	P value
Age (mean, SD)	46.36 (10.51)	50.77 (10.08)	0.014
Gender Female (N, %)	89 (67.9)	32 (68.1)	0.985
Race (N, %)			
-Caucasian	39 (29.8)	11 (23.4)	0.705
-African-American	84 (64.1)	33 (70.2)	
-Other	8 (6.1)	3 (6.4)	
Lifetime BD diagnostic type N (%)			
BD-I	98 (77.2)	35 (79.5)	0.743
BD-II	29 (22.8)	9 (20.5)	
No. of psychiatric medications Mean (SD)	1.58 (.85)	1.47 (.58)	0.405
No. of psychiatric hospitalizations Mean (SD)	5.12 (7.24)	5.65 (8.77)	0.688
TRQ for BD medications (mean, SD)			
Past Week	42.68 (31.06)	47.42 (33.42)	0.381
Past Month	40.14 (27.52)	50.53 (30.97)	0.033
YMRS (mean, SD)	8.53 (5.11)	6.64 (4.87)	0.029
MADRS (mean, SD)	19.26 (8.64)	14.26 (8.21)	0.001
BPRS (mean, SD)	35.69 (7.87)	31.89 (7.39)	0.004
CGI-BP (mean, SD)	3.53 (0.96)	2.96 (1.00)	0.001
GAF (mean, SD)	58.37 (8.63)	62.89 (7.87)	0.002

Adherence rates and symptomatology across anxiety disorder diagnoses)

Table 2

Adherence Measures	0 (N=47)	1 (N=35)	2 (N=36)	3 (N=60)	p-value
TRQ for BD medications (mean, SD)					
Past Week	47.42 (33.42)	44.41 (33.26)	43.09 (30.36)	41.43 (30.62)	0.809
Past Month	50.53 (30.97)	43.38 (29.16)	40.15 (25.71)	38.25 (27.88)	0.156
PSYCHIATRIC SYMPTOMATOLOGY					
YMRS (mean, SD)	6.64 (4.87)	8.71 (5.06)	6.89 (4.71)	9.40 (5.20)	0.015
MADRS (mean, SD)	14.26 (8.21)	18.34 (8.39)	17.12 (9.54)	20.90 (8.03)	0.001
BPRS (mean, SD), N	31.89 (7.39)	35.53 (6.77)	34.03 (8.70)	36.78 (7.87)	0.012
CGI-BP (mean, SD)	2.96 (1.00)	3.43 (0.92)	3.31 (1.09)	3.72 (0.89)	0.001
GAF (mean, SD)	62.89 (7.87)	57.94 (9.19)	60.47 (7.81)	57.37 (8.67)	0.005