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Differential Interactions between Comorbid Anxiety Disorders and Substance Use Disorder in Rapid Cycling Bipolar I or II Disorder

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Abstract

Objective—Anxiety disorders (AD) and substance use disorders (SUD) commonly co-occur with bipolar disorder. This study was undertaken to assess AD-SUD-bipolar subtype interactions.

Methods—Extensive clinical interview and MINI were used to ascertain DSM-IV diagnoses of rapid cycling bipolar I (RCBPDI) or II (RCBPDII) disorder, SUDs, and ADs including generalized anxiety disorder (GAD), panic disorder (PD), and obsessive-compulsive disorder (OCD). Data at the initial assessment of four studies was used to compare the prevalence differences in ADs between RCBPDI and RCBPDII by using protocol-defined SUD categories, “Never,” “Lifetime, but not recent,” or “Recent.”

Results—Five-hundred sixty-six of 568 patients (RCBPDI n=320, RCBPDII n=246) were eligible for analyses. In the “Never” group (n=191), patients with RCBPDI and RCBPDII had similar risk for ADs. In the “Lifetime, but not recent” group (n=195), RCBPDI patients had significantly higher risks for GAD (OR=3.29), PD (OR=2.95), but not OCD, compared with their RCBPDII counterparts. Similarly, in the “Recent” group (n=180), RCBPDI patients also had significantly higher risks for GAD (OR=3.6), PD (OR=3.8), but not OCD, compared with their RCBPDII counterparts.

Limitations—Data were cross-sectional and not all ADs were included.

Conclusion—In this large cohort of patients with rapid cycling bipolar disorder, risk for having GAD, PD, but not OCD increased significantly in patients with bipolar I disorder compared to their bipolar II counterparts when a history of SUD was present. However, there were no significant differences in the risk for GAD, PD, or OCD between the subtypes among patients without a history of SUD.

Keywords

Rapid cycling bipolar disorder; anxiety disorder; substance use disorder; comorbidity; interaction

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Introduction

Epidemiologic studies have shown that anxiety disorders (AD) and substance use disorders (SUD) are the most commonly comorbid conditions in bipolar disorder (BPD) (Grant et al., 2005; Kessler et al., 1997; Regier et al., 1990). For example, in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), Grant and colleagues (Grant et al., 2005) found that in patients with BPD (n=1411), 56 % had at least one lifetime AD; 58% had a lifetime history of alcohol use disorders; and 38% had lifetime drug use disorders. There is growing recognition that both AD and SUD frequently co-occur together in individuals with BPD (Bauer et al. 2005; Kolodziej et al. 2005; Levander et al. 2007; Simon et al. 2004). How these comorbid conditions are related in terms of prevalence, etiology, and effects on the course of each illness, however, remains unclear.

Of particular importance to our understanding of these complex comorbidities is the fact that within each of these disorders are diagnostic subtypes that differ in prevalence, clinical characteristics, and treatment responsiveness. It is not well understood whether different subtypes of BPD, AD, or SUD are more likely to co-occur with each other. In a study from the Stanley Foundation Bipolar Network (SFBN), Levander et al. (2007) reported that patients with BPD and a lifetime alcohol use disorder had significantly lower rates of specific phobia and obsessive-compulsive disorder (OCD) than those without a history of alcohol use disorder. However, comparison of bipolar subtypes was not performed. Other studies have compared the rate differences of ADs or SUDs according to bipolar subtypes (Bauer et al., 2005; Boylan et al., 2004; Chengappa et al., 2000; Judd et al., 2003; Kolodziej et al., 2005; McElroy et al., 2001; Rihmer et al., 2001; Simon et al., 2004), but none assessed the interactions. Therefore, we proposed to analyze data from a cross-sectional dataset of a cohort of patients with rapid cycling bipolar I (RCBPD I) or II (RCBPD II) disorder to investigate the AD-SUD-bipolar subtype interactions.

Methods

Patient Population

Data at the initial assessment of a cohort of patients with RCBPD who were recruited for three NIMH (Study I, II, and III)- and one Stanley Medical Research Institute (Study IV) – funded, randomized, double-blind, placebo- controlled clinical trials were used for this study. The study designs, study index, inclusion and exclusion criteria, and stages of the four studies at the time of this analysis are summarized in Table 1. A “recent” SUD was defined as having a diagnosis of substance dependence and continuing to meet abuse or dependence criteria for a substance (s) in the last 6 months at the initial assessment or having a diagnosis of substance abuse and continuing to abuse a substance(s) in last the last 3 months (-Study IV) or 6 months (Study III). Subjects were referred from specialty clinics, private and public mental health centers, and advertisements. The respective institutional review board approval was obtained and patients provided written, informed consent for each study. Data of patients enrolled up to June 2005 were analyzed.

Initial Assessments

Diagnoses of RCBPD, ADs including GAD, PD, and OCD, and SUDs were ascertained by extensive clinical interview (ECI) alone for the first 391 patients by an experienced research psychiatrist (JRC) (Calabrese et al., 2005) and with the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) for the remaining subjects by research psychiatrists and research assistants. The detailed procedures have been described somewhere else (Gao et al, in press). Briefly, the ECI not only consists of questions and criteria for the diagnosis of DSM-IV Axis I disorders, but also contains items to assess mental status, severity of suicidality,

demographics, and other variables of interest. The ECI and the MINI combination typically included a 60–90-minute initial interview followed by a 30–45 minute second evaluation by a research psychiatrist and administration of the MINI by a certified research assistant. If any inconsistency occurred with the first and second evaluations during the MINI administration, a psychiatrist would re-evaluate the patient. Collateral information from the mandatory presence of significant other(s) of patients was required in all cases during the initial assessment. A lifetime history of AD was defined as meeting anxiety disorder criteria prior to or at the time of initial assessment. A lifetime history of SUD was defined as meeting substance abuse or dependence criteria prior to or at the initial assessment.

Procedures

Over-representation of male patients in the “recent” SUD studies was observed, but the mean age and race in the four studies were similar. In order to further minimize the heterogeneity, we divided patients into three groups according to the history of SUD, “Never,” “Lifetime, but not recent,” and “Recent.” The “Never” group was defined as those who never had a diagnosis of SUD at the initial assessment. The “lifetime, but not recent” group was defined as those who had a diagnosis of SUD prior to the initial assessment, but did not meet the protocol-defined “recent” SUD at the initial assessment. Patients in these two groups were derived from those who were enrolled in Study I or Study II. Patients in the “Recent” group were enrolled in Study III or Study IV. Any SUD, “Lifetime, but not recent” or “Recent,” referred to the presence of alcohol or drug (legal or illegal) abuse or dependence with the exception of nicotine and caffeine. Any AD referred to the presence of GAD, PD, and/or OCD.

Statistical Analysis

Analysis of variance (ANOVA) was used to analyze the continuous variables and standard deviation was used to reflect the magnitude of variance. For categorical data, Chi-Square tests were used for significance testing. Interactions among AD, SUD, and bipolar subtypes were first explored with maximum likelihood analysis of variance. Odds ratios (OR) were used for risk estimate and are presented with confidence interval (CI). When multiple comparisons occurred, Bonferroni’s adjustment was applied. Given the exploratory nature of the study, statistical significance was set at $\alpha = 0.05$, two-tailed, in order to detect potentially clinically meaningful associations.

Results

Demographics

Of 568 patients with RCBPDI, 566 of them were eligible for analysis (RCBPDI, $n=320$; RCBPDII, $n=246$). The mean age of the whole sample was 36.5 ± 10.4 years, with no difference between patients with RCBPDI and RCBPDII, 36.5 ± 10.2 vs. 36.3 ± 10.6 ($p = 0.80$). Overall, 47% were male and 53% female. More male patients presented with RCBPDI than with RCBPDII, 53.3% vs. 38.9% ($p < 0.001$), but more female patients presented with RCBPDII than with RCBPDI, 61.1% vs. 46.7% ($p < 0.001$).

Differential Interactions between AD and SUD in RCBPDI and RCBPDII

The maximum of likelihood analysis of variance for three-way interactions (anxiety*bipolar subtype* history of SUD) showed an existence of significance ($DF = 2$, $X^2 = 7.36$, $p = 0.0252$). The magnitude of the risk for any AD, GAD, PD, or OCD in patients with RCBPDI compared to those with RCBPDII was estimated by OR calculations.

In the “Never” group, both patients with RCBPDI ($n=84$) and RCBPDII ($n=107$) had similar rates of any AD, GAD, PD, and OCD (Table 2). There was no gender difference between the

two subtypes although more males presented with RCBPDI and more females presented with RCBPDII (Table 2).

In the “Lifetime, but not recent” group (n=195), those with RCBPDI (n=102) had significantly higher rates of any AD, GAD, and PD than those with RCBPDII (n=93) (Table 2). However, there was no difference between bipolar subtypes in the rates of OCD. There were also no differences in age and gender. The differences in any AD, GAD, and PD between the two subtypes were still significant after Bonferroni’s adjustment.

In the “Recent” group (n=180), those with RCBPDI (n=134) had significantly higher rates of any AD, GAD, and PD than those with RCBPDII (n=46) (Table 2). Again, patients with different subtypes of RCBPD did not differ in their rates of comorbid OCD. Age and gender were also not significantly different between the subtypes (Table 2). Similar to the “Lifetime, but not recent group,” the differences in any AD, GAD, and PD between the two subtypes were still significant after Bonferroni’s adjustment.

Discussion

In this large sample of patients with RCBPD (n=566), we found that differential interactions between comorbid GAD, PD or OCD and SUD occurred in patients with RCBPDI or RCBPDII. The presence of a history of SUD, whether past or recent, was associated with significantly increased risk for having any AD, GAD, and PD, but not OCD in those with RCBPDI compared to those with RCBPDII (Table 2). For those without a history of SUD, there was a similar risk for these anxiety disorders in both subtypes.

The high rates of comorbid PD and GAD in this study are consistent with previous findings in non-rapid cycling population (Chen and Dilsaver, 1995a; Perugi et al., 2001; Simon et al., 2004). However, the rates of OCD in this study, regardless of the subtypes, were lower than those reported in non-rapid cycling populations, especially in the subgroup of patients with bipolar II disorder (Chen and Dilsaver, 1995b; Masi et al., 2004; Perugi et al., 1999). Our data do not allow us to draw a conclusion about whether there was a causal relationship between AD and SUD. However, a reciprocal causal relationship over time between alcohol dependence and ADs has been reported (Kushner et al., 1999; Zimmermann et al., 2003).

This is the first report of significantly higher rates of GAD and PD in patients with BPDII than in those with BPDII. The results are unlikely due to a selection bias because the significant differences only occurred in those with a history of SUD. In a smaller study (n=138), Boylan et al. (2004) also found that patients with BPDII had more ADs than those with BPDII. However, other previous studies have shown that patients with BPDII had similar rates of any AD, GAD, and PD as those with BPDII (McElroy et al., 2001; Simon et al., 2004) or lower rates of ADs than patients with BPDII (Henry et al., 2003; Judd et al., 2003; Perugi et al., 1999; Rhimer et al., 2001).

The discrepancy of the results between this study and other studies is more likely due to selection bias, sample sizes, or variables used for comparisons. According to some national surveys (Grant et al., 2005; Kessler et al., 1997; Regier et al., 1990), patients with BPDII had high rates of AD (any AD 56%–93%) and SUD (any SUD 61–71%). Although the rates of double comorbidities of ADs and SUDs are unknown from these studies, it is reasonable to assume that a significant proportion of overlap between ADs and SUDs exists. A sample with fewer patients with SUDs is likely to underestimate the rates of ADs. This is the first study to our knowledge to include patients with lifetime SUD close to the rates of these national studies. In previous studies the lifetime rate of any SUD in BPDII was from 42% to 50% (Judd et al., 2003; McElroy et al., 2001). In contrast, the Epidemiologic Catchment Area study (Regier et al., 1990) and the National Comorbidity Survey (Kessler et al., 1997) found that 61% and 71%

of patients with BPDI had a lifetime history of any SUD. In our study, 74% patients with RCBPDI had a lifetime any SUD (Gao et al, 2006). In term of alcohol use disorder, in our study, 23% of patients with BPDI had alcohol abuse and 44% had alcohol dependence, which is close to results of the NESARC, in which 17% had lifetime alcohol abuse and 41% had lifetime alcohol dependence (Grant et al 2005). The proportion of patients with SUD in the other clinical studies mentioned above was unknown.

Variables used for comparison may cause different conclusions too. With the exception of one study (McElroy et al., 2001), there has never been a study including all possible DSM-IV ADs. Therefore, using any AD as a variable for comparison in some of these studies may be misleading. For example, in the CDS (Judd et al., 2003), patients with BPDII had significantly more any AD than those with BPDI, but there were no significant differences between the two groups in GAD or PD. Conversely, in the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorder) study, there was no difference in lifetime prevalence of any AD between BPDI and BPDII, but significantly more patients with BPDI had agoraphobia than those with BPDII (Simon et al., 2004). Similarly, in our study, there were significant differences between patients with RCBPDI and RCBPDII in any AD, GAD, and PD, but not OCD.

Limitations

These findings must be considered in view of several methodological limitations. First, data obtained in this study was cross-sectional and involved four studies over a period of 10 years. Second, not all ADs were assessed. Some of those without an AD might be misclassified. However, this potential misclassification would only affect the any AD categories, but not the individual AD. Third, the diagnoses based on the recall by patients might not be accurate although the required presence of a significant other(s) during the initial evaluation was used to minimize such potential inaccuracy. Fourth, compared with other studies, our sample included the largest proportion of patients with BPDII (43.5%) (Judd et al., 2003; McElroy et al., 2001; Rhimer et al., 2001; Simon et al., 2004), but patients with BPDII were still under-represented. Fifth, this study only included patients with RCBBD. Therefore, the results may not be generalizable to those without RCBBD.

Conclusions

A past or recent history of SUD was associated with increased rates of GAD and PD in those with RCBPDI compared to those with RCBPDII. The prevalence of OCD was similar between two subtypes regardless of the SUD status.

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Table 1
Study Designs of the Four Studies in Patients with Rapid Cycling Bipolar Disorder with or without Substance Use Disorder

	Without recent substance use disorder		With recent substance use disorder	
	Study I (n=254) [*]	Study II (n=110) ^{**}	Study III (n=137) ^{**}	Study IV (n=66) ^{**}
Study design	Open stabilization (Li + Val for 24 W) Placebo-controlled Discontinuation (Li + PBO or Val + PBO for 52 W)	Open treatment (Li + Val for up to 24 W) Placebo-controlled acute depression study (Li + Val + PBO or Li + Val + LTG for 6 W)	Open stabilization (Li + Val for 24 W) Placebo-controlled Discontinuation (Li + Val or Li + PBO for 24 W)	Open treatment (Li + Val for up to 24 W) Placebo-controlled acute depression study (Li + Val + PBO or Li + Val + LTG for 6 W)
Mood State	Manic/hypomanic/mixed in 3 M Any mood at screening/baseline BPI or BPPI, RC, ≥ 18 years old No contraindication to Li or Val	Major depression At the screening/baseline BPI or BPPI, RC, ≥ 16 years old No contraindication to Li, Val, or LTG	Manic/hypomanic/mixed in 3 M Any mood at screening/baseline BPI or BPPI, RC, ≥ 16 years old No contraindication to Li or Val SUD in 6 M	Major depression At the screening/baseline BPI or BPPI, RC, ≥ 16 years old No contraindication to Li, Val, or LTG Substance abuse in 3 M, dependence in 6 M
Exclusion criteria	Contraindication to Li or Val SUD in 6 M	Contraindication to Li, Val, or LTG Substance abuse in 3 M, dependence in 6 M	Contraindication to Li or Val	Contraindication to Li, Val, or LTG
Data Collection	September 1995 to January 2003 Study was completed	July 2001 to June 2005 Study was ongoing	October 1997 to June 2005 Study was ongoing	July 2002 to June 2005 Study was ongoing

* Calabrese et al. 2005 (Study I)

** www.clinicaltrials.gov, NCT00063362 (Study II), NCT 00194129 (Study III), & NCT00221975 (Study IV).

Abbreviations: BPI, bipolar type I; BPPI, bipolar type II; Li, lithium; LTG, lamotrigine; M, month; PBO, placebo; RC, rapid cycling; SUD, substance use disorder; Val, valproate; W, week.