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Co-morbid anxiety disorders in bipolar disorder and major depression : familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder

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Abstract

Background—Co-morbidity of mood and anxiety disorders is common and often associated with greater illness severity. This study investigates clinical correlates and familiarity of four anxiety disorders in a large sample of bipolar disorder (BP) and major depressive disorder (MDD) pedigrees.

Method—The sample comprised 566 BP families with 1416 affected subjects and 675 MDD families with 1726 affected subjects. Clinical characteristics and familiarity of panic disorder, social phobia, specific phobia and obsessive-compulsive disorder (OCD) were examined in BP and MDD pedigrees with multivariate modeling using generalized estimating equations.

Results—Co-morbidity between mood and anxiety disorders was associated with several markers of clinical severity, including earlier age of onset, greater number of depressive episodes and higher prevalence of attempted suicide, when compared with mood disorder without co-morbid anxiety. Familial aggregation was found with co-morbid panic and OCD in both BP and MDD pedigrees. Specific phobia showed familial aggregation in both MDD and BP families, although the findings in BP were just short of statistical significance after adjusting for other anxiety co-morbidities. We found no evidence for familiarity of social phobia.

Conclusions—Our findings suggest that co-morbidity of MDD and BP with specific anxiety disorders [OCD, panic disorder and specific phobia] is at least partly due to familial factors, which may be of relevance to both phenotypic and genetic studies of co-morbidity.

Keywords

Anxiety disorders; familial; mood disorders; obsessive-compulsive disorder; panic; phobia

Introduction

Mood and anxiety disorders are the most common mental disorders across the lifespan, with epidemiological surveys estimating that over 20 % of the US population will suffer from one

or more such disorder during their lifetime (Kessler et al. 2005). Although mood and anxiety disorders are classified separately, co-morbidity is common in both clinical (McElroy et al. 2001 ; Zimmerman et al. 2002) and epidemiological samples (Kessler et al. 2003; Merikangas et al. 2007), and is often associated with longer illness duration and greater clinical severity than either disorder alone (Lamers et al. 2011). Prospective studies have found that depressive episodes are more prolonged in patients with anxiety co-morbidity, both at the level of anxiety symptoms or syndromes (Coryell et al. 1992, 2009). Co-occurrence of an anxiety disorder also increases the risk of suicide attempts in people with major depressive disorder (MDD) or bipolar disorder (BP) (Sareen et al. 2005). Moreover, BP with co-morbid anxiety can pose a significant therapeutic quandary since antidepressants, the treatment of choice for most anxiety disorders, may be problematic in patients with BP, particularly those with rapid cycling (Wehr & Goodwin, 1979).

The term 'co-morbidity' was first used by Feinstein to refer to the presence of two independent disorders, with the second disorder potentially affecting 'the time of detection, prognostic anticipations, therapeutic selections, and post-therapeutic outcome of the index disease' (Feinstein, 1970). The appearance of comorbidity may be due to chance or to ascertainment bias (Berkson's bias). However, the consistent documentation of co-morbid mood and anxiety disorders in community as well as clinical samples suggests that chance or ascertainment bias is unlikely to be primary reasons for the co-occurrence of these syndromes (Kessler et al. 2007). Feinstein's initial conception of 'co-morbidity' assumed the presence of distinct disorders ; in psychopathology, however, the term often refers to overlapping symptoms rather than disorderspecific syndromes. Symptom-based overlap between mood and anxiety disorders is extremely common and may represent what has been termed 'artefactual co-morbidity' (Maj, 2005). The overlap of anxiety syndromes is likely to be closer to Feinstein's conception of co-morbidity and has the potential to be of greater clinical relevance.

All the major mood and anxiety syndromes have been shown to segregate within families (Sullivan et al. 2000; Hettema et al. 2001). Among the most studied has been the relationship between panic disorder and MDD. Most (Goldstein et al. 1994; Maier et al. 1995), though not all (Crowe et al. 1983; Weissman et al. 1993), family studies have provided evidence consistent with shared familiarity, which is consistent with findings from twin studies (Kendler et al. 1995; Mosing et al. 2009). The familial association between major depression and social phobia has been less studied, with only two family studies providing modest evidence for co-aggregation in findings that fall just short of statistical significance (Fyer et al. 1993; Stein et al. 1998). Similarly, twin studies have found only modest evidence for common genetic susceptibility between MDD and social phobia (Kendler et al. 1993, 2011). To our knowledge, no family study has investigated the co-occurrence of simple or specific phobias and MDD, although there is evidence for a modest degree of co-aggregation from twin studies (Kendler et al. 1993). Finally, perhaps because it is one of the least prevalent anxiety disorders, the relationship between obsessivecompulsive disorder (OCD) and MDD has been explored in only a few family studies of OCD, where the evidence for co-segregation has been inconsistent (Nestadt et al. 2001; Carter et al. 2004; Hanna et al. 2011).

Co-morbidity of anxiety syndromes and BP is also common (Merikangas et al. 2007), but far fewer studies have examined the familial relationships between BP and anxiety disorders. In high-risk offspring of BP parents, anxiety syndromes typically precede the onset of mood syndromes (Duffy et al. 2007; Sala et al. 2010), and often persist throughout adulthood (Mantere et al. 2010). In previous studies of the National Institute of Mental Health (NIMH) Genetics Initiative Bipolar Disorder Consortium, familial aggregation was described for panic disorder (MacKinnon et al. 2002), specific phobia and OCD (Potash et

al. 2007), but these analyses did not control for different rates of diagnoses among sites, or for additional co-morbidity amongst the anxiety disorders. To our knowledge, there has been no twin study that has specifically studied the co-morbidity of BP and anxiety disorders.

While previous studies have provided evidence for the co-familiality of certain anxiety and mood disorders, many have been limited by relatively small numbers of co-morbid cases. Moreover, comparison across these studies has been hampered by the use of varying diagnostic criteria and differing analytical methods, which have not always controlled for potential confounds such as additional co-morbid diagnoses. In the present study we extend prior findings by examining two of the largest available family samples of MDD and BP in order to have sufficient power to study the familiality of each individual anxiety disorder. The aim of this study is to determine whether : (1) cases with co-morbid anxiety have clinical correlates of greater severity than cases without co-morbid anxiety ; and whether (2) specific anxiety syndromes show evidence of familial aggregation in mood disorder pedigrees.

Method

Subject ascertainment

In both the BP and MDD family studies, subjects provided written informed consent after hearing a complete description of the study. Subjects were recruited either from in-patient or out-patient clinics, or from a response to advertisement.

The MDD sample was drawn from the Genetics of Recurrent Early-onset Major Depression (GenRED) study, which recruited families with recurrent earlyonset MDD (age of onset 30 years in the proband and 40 years in the relative) at six sites (Levinson et al. 2003). Exclusion criteria were having a relative with bipolar I disorder (BPI), schizophrenia or schizo-affective disorder. For the present analysis, we selected only subjects with a high-confidence MDD diagnosis in pedigrees with at least two first-degree affected relatives. This led to a total of 1726 affected subjects from 675 families, comprising 867 siblings, 134 children and 50 parents.

The BP sample was drawn from waves 1–4 of the NIMH Genetics Initiative Bipolar Disorder Collaborative project conducted at 10 sites. Ascertainment criteria required a proband with BPI and at least one sibling with either BPI or schizo-affective disorder, bipolar type (SABP). To compare with the MDD sample, the primary analysis included only cases with BPI or bipolar II disorder (BPII). This dataset comprised 566 probands with BPI and at least one additional first-degree relative with BPI and BPII. The analysis included 850 such relatives (651 siblings, 132 parents and 67 offspring). To determine whether familial aggregation was also seen in available family members without BP, a secondary analysis was also performed using all available BPI probands (n=652) and all available first-degree relatives (n=1908) regardless of diagnosis. This latter group, consisting of 1335 subjects with BPI and 167 with BPII, was used for the analysis of clinical correlates.

Diagnostic assessment

Both the MDD and BP studies used the Diagnostic Instrument for Genetic Studies (DIGS) (Nurnberger et al. 1994). Two research clinicians subsequently provided a best-estimate diagnosis incorporating the interview data, as well as information from family informants and medical records. Each best-estimate diagnosis was given a confidence level from one to four; for these analyses we used only the diagnoses with confidence levels of three ('probable') or four ('definite'). The DIGS has been shown to have excellent inter-rater reliability for the major mood diagnoses, with k values greater than 0.7 (Nurnberger et al.

1994). The GenRED study has also evaluated the inter-rater reliability of panic disorder ($k=0.96$), social phobia ($k=1.0$) and OCD ($k=0.67$) (Levinson et al. 2003).

Diagnoses were based on Diagnostic and Statistical Manual of Mental Disorders (DSM) third edition revised (DSM-III-R) and fourth edition (DSM-IV) criteria, where the presence of a mood disorder is not a hierarchical exclusion to the diagnosis of any of the considered anxiety disorders. The DIGS includes structured questions for the diagnoses of panic disorder (with or without agoraphobia), social phobia, specific phobia and OCD. It does not include structured questions for the diagnoses of generalized anxiety disorder or post-traumatic stress disorder.

Statistical analyses

Initial comparisons of subjects (probands and first-degree relatives) with mood disorders and co-morbid anxiety disorders versus subjects with 'pure' mood disorders were performed using Pearson's two-tailed χ^2 test for categorical variables and the Mann-Whitney-Wilcoxon test for continuous variables. Significance levels are presented as nominal two-sided p values.

Familial aggregation was tested using logistic regression and generalized estimating equations to account for within-family correlation between probands and their first-degree relatives (Zeger et al. 1988). The logistic regression analyses were conducted in hierarchical models adjusting for: age at interview and sex [adjusted odds ratio (aOR¹); additional anxiety disorder co-morbidity in relatives (aOR²); and additional anxiety disorder co-morbidity in probands (aOR³).

Familial aggregation for each co-morbid anxiety disorder was also tested across the MDD and BP samples. To test whether the effect size of the familial aggregation of each co-morbid anxiety disorder differed in the MDD versus the BP sample, we combined both samples and performed the same aggregation analyses with an interaction term derived from a study covariate (the potential effect modifier) and a covariate indicating whether the relative has a proband with the same anxiety co-morbidity or not (the dependent or predictor variable). A full regression model was run including this interaction term and the statistical significance of the interaction regression coefficient was used to test for between-study differences.

Results

Several prominent similarities were present across the MDD and BP datasets. The MDD and BP samples were comparable in their average age at interview (42.6 years *V.* 42.0 years, $p=0.11$) and there were no statistically significant differences in the prevalence of panic disorder ($p=0.21$), specific phobia ($p=0.89$) or OCD ($p=0.09$). Social phobia, however, was found to be more common in the MDD sample (13.5% *V.* 7.8%, $p<0.0001$). Further demographic and clinical characteristics are shown in Tables 1 and 2 for the MDD and BP samples, where subjects with one of four comorbid anxiety disorders were compared individually with subjects without any of the four disorders.

In the MDD sample there were relatively few demographic differences across the four groups. Subjects with any of the anxiety disorder diagnoses generally completed fewer years of education, though this difference was only statistically significant in cases with co-morbid panic disorder ($p<0.0001$). Clinical correlates were generally more severe in cases with a co-morbid anxiety disorder, with the exception of comorbid specific phobia. Panic disorder, social phobia and OCD were associated with an earlier age at onset of depression, a greater prevalence of hospitalization, a greater likelihood of treatment with electroconvulsive

therapy and an increased risk of suicide attempt (Table 1). Compared with the other anxiety disorders, co-morbidity with OCD was notable for an earlier age of first treatment ($p<0.0001$) and for an overall pattern of increased severity.

As shown in Table 2, anxiety disorder co-morbidity in BP had many similar phenotypic patterns. There were reductions in the years of education completed, which was most significant for those with panic co-morbidity ($p<0.0001$). Clinical correlates showed a similar pattern of earlier age of first depression, a substantially higher number of depressive episodes, and an increased risk of suicide attempt across all the anxiety disorders. As in the earlier MDD analysis, comorbidity with OCD was generally associated with greater severity than co-morbidity with the other anxiety disorders. In the BP sample, co-morbid OCD was associated with the earliest age of onset for depressive episodes ($p<0.0001$), the earliest age of treatment ($p=0.0031$) and the highest number of depressive episodes ($p<0.0001$).

Familial aggregation

There were important similarities seen across the MDD and BP samples in the prevalence rates of each anxiety disorder and in the overall excess of each disorder seen in the relatives of probands with the same disorder (see raw numbers in Tables 3 and 4). When all four anxiety disorders were grouped and analysed together in a logistic regression with correction for age, sex and site of ascertainment, the presence of any anxiety disorder in a proband was associated with comparably higher odds of having any anxiety disorder in relatives in both the MDD [OR 1.77, 95 % confidence interval (CI) 1.36–2.30, $p<0.001$] and BP samples (OR 1.71, 95% CI 1.22–2.37, $p=0.002$).

Analyses of specific anxiety disorders showed that panic disorder, specific phobia and OCD, but not social phobia, were familial in the MDD sample (Table 3). Familial aggregation of the three anxiety disorders remained statistically significant after controlling for additional anxiety disorders in relatives (aOR^2) and for additional anxiety disorder comorbidity in both relatives and probands (aOR^3). Similar effect sizes were seen in OCD (aOR^3 2.60, 95 % CI 1.29–5.24, $p=0.008$), specific phobia (aOR^3 2.43, 95 % CI 1.35–4.38, $p=0.003$) and panic disorder (aOR^3 1.98, 95% CI 1.40–2.78, $p<0.001$).

The primary analysis of the BP sample included cases and first-degree relatives with BPI or BPDI. Familial aggregation was seen for OCD, panic disorder and specific phobia when controlled for age, sex and site covariates (aOR^1). After controlling for the additional anxiety diagnoses in the proband and relatives, familial aggregation remained significant, albeit with an attenuated effect, in OCD (aOR^3 3.10, 95 % CI 1.31–7.09, $p=0.009$) and panic disorder (aOR^3 1.52, 95 % CI 1.00–2.30, $p=0.047$), but not in specific phobia (aOR^3 1.94, 95 % CI 0.95–3.96, $p=0.069$). As in the MDD sample, we found no evidence for statistically significant familial aggregation of social phobia.

The BP sample also included an additional 1058 first-degree relatives without a BPI or BPDI diagnosis. When familial aggregation of the co-morbid anxiety disorders was tested in these relatives similar levels of aggregation were found for OCD (aOR^3 2.51, 95 % CI 1.15–5.49, $p=0.021$) and panic disorder (aOR^3 1.51, 95 % CI 1.08–2.11, $p=0.017$) compared with the BP-only analysis. We again found no evidence of statistically significant familial aggregation of social phobia (aOR^3 1.69, 95% CI 0.84–3.39, $p=0.14$). However, this analysis did find evidence for aggregation of specific phobia (aOR^3 2.12, 95% CI 1.17–3.84, $p=0.013$), which differs from the primary analysis of BP cases although the effect sizes are similar and the confidence levels show significant overlap.

In further analyses testing differences in ORs between the two samples for each specific anxiety disorder, we found no evidence for statistically significant differences in familial aggregation across the MDD and BP samples.

Discussion

The primary aim of this study was to examine and compare the clinical correlates and familial aggregation of four co-morbid anxiety disorders in MDD and BP pedigrees. Consistent with prior studies, our findings show a strong association of co-morbid anxiety disorders with clinical markers of severity, including earlier age of onset, a greater number of depressive episodes and elevated rates of suicide attempt. In general, indices of clinical morbidity were most associated with co-morbid OCD and panic disorder, and least associated with co-morbid specific phobia. Our results also provide evidence for familial clustering of co-morbid anxiety syndromes when analysed as a group in both MDD and BP samples. In disorder-specific analyses, we found that OCD and panic disorder showed familial aggregation in both MDD and BP pedigrees, while social phobia was not found to be familial in either sample. Specific phobia was familial in MDD pedigrees and showed some evidence of familiarity in BP, although findings were just short of statistical significance.

Familial aggregation does not distinguish between genetic or environmental causes; however, the prominent heritability of most psychiatric syndromes suggests that at least part of the familial aggregation seen in this study is likely to be genetic. Several types of segregation can lead to familial aggregation (Klein & Riso, 1994), including co-segregation of the index and co-morbid phenotypes, segregation of a unitary phenotype with co-morbid features, and independent segregation of the two phenotypes. Since the samples used in this study were originally collected for genetic studies, which did not systematically ascertain all affected and unaffected relatives, our study is unable to distinguish among these segregation patterns. The BP sample did include additional first-degree relatives who were unaffected or affected with a non-BP diagnosis. An analysis of this larger sample showed very similar results, suggesting that the majority of the aggregation was driven by the co-morbidity between the anxiety disorders and the BP phenotype specifically.

In both the MDD and BP samples, OCD was found to be the most strongly familial co-morbid anxiety disorder and the most associated with clinical markers of severity. The familial relationship between mood disorders and OCD has been previously studied primarily from the side of OCD family studies. The largest of these studies has supported a familial relationship between OCD and MDD (Bienvenu et al. 2011), though this was not found in prior studies with smaller sample sizes (Carter et al. 2004; Fyer et al. 2005). BP has generally been too rare to be studied in OCD family studies and even the largest of these has not been able to find evidence for a statistically significant familial association, despite BP being found to be twice as prevalent in OCD relatives compared with control relatives (OR 2.40, $p=0.08$) (Bienvenu et al. 2011). Our current study, with much larger samples, found evidence for familial aggregation of a similar effect size, suggesting that the OCD studies have been underpowered to detect significant familiarity for BP. The familial aggregation of panic disorder with MDD or BP has been previously described in several studies (Leckman et al. 1983; Maier et al. 1995; MacKinnon et al. 1997). Our study confirms these findings and provides additional evidence that the segregation of panic disorder in both MDD and BP pedigrees remain statistically significant when controlled for other co-morbid anxiety syndromes. The association effect size was slightly greater in MDD (OR 1.98) than in BP (OR 1.52), but these differences were not statistically significant.

The familial aggregation of specific phobia appeared to differ between MDD and BP. However, both the prevalence (9.9 % in BP and 9.7 % in MDD) and the evidence for aggregation in the first adjusted regression model (aOR^1), which controls for age, sex and site differences, showed little differences across both samples (aOR^1 2.93 in MDD V. 2.38 in BP). While the evidence for aggregation in MDD remained significant after being controlled for additional anxiety diagnoses in the relatives and probands, the findings in BP fell just short of statistical significance. Findings from twin studies suggest that the risk for specific phobias is due to both genetic and individual environmental risk factors, with the latter being the more prominent of the two (Hettema et al. 2006). If the distinct findings across the two samples represent a true difference, it may indicate that phobias are genetically more associated with MDD, and/or that subjects with MDD may potentially have a greater likelihood of experiencing environmental exposures associated with phobias. On the other hand, since the MDD sample is larger than the BP sample, the difference may be due to decreased statistical power in the BP sample, particularly given the overlapping CIs and the lack of statistical significance in the formal comparison between the two ORs.

Although relatives of probands with social phobia had modestly more elevated rates of social phobia compared with relatives of probands without social phobia, we found no evidence for statistically significant familial aggregation in either BP or MDD. In a large epidemiological twin study social phobia was found to be the least heritable of the anxiety disorders, with most of the susceptibility risk coming from individual environmental risk factors (Hettema et al. 2005). Our failure to detect familial aggregation suggests that these and other risk factors do not appear to be shared between first-degree relatives with mood disorders, although our samples are unlikely to be sufficiently powered to exclude a very modest degree of familial aggregation.

In examining the co-morbidity between mood and anxiety disorders, our study has used categorical diagnoses, which can be seen as complementary to dimensional models of co-morbidity that have been proposed by factor analytical and twin modeling studies (Krueger, 1999; Hettema et al. 2006). The familial patterns of mood and anxiety co-morbidity seen in this study provide some support for Krueger's model of 'internalizing disorders', where 'anxious misery' (in this study represented by mood disorder) and 'fear' subfactors (anxiety disorders) are partly correlated and partly distinct. Furthermore, the similar patterns of familiarity across our BP and MDD samples suggest that co-morbidity with the internalizing disorders may not distinguish between the two as has been recently proposed (Goldberg et al. 2009).

Familiarity between mood and anxiety disorders may be mediated by personality traits such as neuroticism, which are heritable and strongly associated with many internalizing disorders (Bienvenu et al. 2004). Subjects with MDD or BP have been found to have higher levels of neuroticism compared with normal controls (Jylha et al. 2010; Barnett et al. 2011). This could account for some of the familiarity seen in this study since neuroticism may partially mediate the development of co-morbid anxiety disorders (Hettema et al. 2006). Unfortunately, we were not able to test this hypothesis since personality measures were not available for most participants.

This study has several strengths. It comprises one of the largest collected samples of MDD and BP pedigrees and has the benefit of a well-characterized and reliable diagnostic instrument used by trained researchers with a clinical background. The large sample size has also allowed us to isolate the effect of specific anxiety disorders rather than having to consider them as a cluster. The MDD and BP samples used identical diagnostic and best-estimate procedures, providing the methodological consistency to compare familiarity across the disorders. Diagnoses were made by at least two experienced research psychiatrists or

psychologists, which provided the clinical expertise necessary to help distinguish among the various anxiety disorders that often overlap in symptoms.

Our results must be viewed in light of several important limitations. The sample consists of familial cases of BP and MDD, which may limit the generalizability of our results to community samples, since familial cases may be more co-morbid (Verhagen et al. 2008). However, the overall co-morbidity prevalence rates in our study are broadly consistent with those from epidemiological samples (Regier et al. 1998; Merikangas et al. 2007). Our findings are also likely to be representative of cases that seek treatment since this population has been found to have high rates of familiarity. Large naturalistic treatment studies of both MDD (Nierenberg et al. 2007) and BP (Post et al. 2003), for example, have found that over half of all patients have a family history of mood disorder.

A further limitation is that ascertainment of the sample was opportunistic and focused preferentially on collecting affected relatives. For the purposes of investigating the nature of co-morbidity, a more informative family study would have included probands with 'pure' anxiety and would have ascertained all available family members (Wickramaratne & Weissman, 1993). The initial collection of the BP sample included relatives without mood disorders, but the ascertainment was not systematic and focused mostly on affected family members.

The interviews of family members were not conducted blind to the proband diagnosis, which may have biased the assessment. While the use of the DIGS as a diagnostic instrument in a strength of the study in both samples, the DIGS does not include structured questions to diagnose generalized anxiety disorder and post-traumatic stress disorder, and does not provide sufficient information to help distinguish sub-types of anxiety disorders such as generalized versus specific social phobia. Finally, as with most family studies, our diagnoses were based on a retrospective history of mood and anxiety diagnoses, whereas a prospective study would not be affected by the potential for recall bias.

In conclusion, co-morbid anxiety syndromes are common in MDD and BP families. Familial aggregation was seen with panic disorder and OCD in both MDD and BP pedigrees, while familiarity of specific phobia was statistically significant only in MDD families. OCD co-morbidity with BP and MDD was found to be most strongly associated with clinical characteristics of illness severity and was found to have the strongest degree of familiarity.

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Table 1

Clinical features of co-morbid anxiety disorders in the major depressive disorder sample

Clinical feature	Cases with co-morbid panic disorder	Cases with co-morbid social phobia	Cases with co-morbid specific phobia	Cases with co-morbid OCD	Cases with no co-morbid anxiety
Subjects, n (% of overall sample)	427 (24.7)	233 (13.5)	168 (9.7)	128 (7.4)	1039 (60.2)
Mean age, years (s.e.)	42.4 (0.6)	41.5 (0.8)	43.1 (1.0)	38.3 (1.1) ***	42.8 (13.0)
Female, n (%)	354 (82.9) *	188 (80.7)	153 (91.1) ***	96 (75)	809 (77.9)
Married, n (%)	228 (53.4)	120 (51.5)	96 (57.1)	65 (50.8)	556 (53.5)
Mean length of education, years (s.e.)	14.7 (0.1) ***	14.6 (0.2) ***	14.8 (0.2)	15.3 (0.3)	15.7 (2.9)
Employed, n (%)	348 (81.5) *	196 (84.1)	139 (82.7)	110 (85.9)	900 (86.6)
Mean MDD onset age, years (s.e.)	18.3 (0.4) ***	18.4 (0.5) **	19.1 (0.6)	16.0 (0.6) ***	19.8 (8.2)
Mean number of MDEs, n (s.e.)	7.3 (0.5) **	7.8 (0.7)	8.2 (1.0) **	8.6 (1.3)	6.4 (10.2)
Mean age at onset of anxiety, years (s.e.)	24.7 (0.6)	14.6 (0.5)	14.7 (0.9)	17.6 (1.0)	–
Alcohol abuse/dependence, n (%)	107 (25.1)	61 (26.2)	39 (23.2)	32 (25.0)	224 (21.6)
Substance abuse/dependence, n (%)	105 (24.6)	69 (29.6) *	38 (22.6)	37 (28.9)	232 (22.3)
Mean age of first treatment, years (s.e.)	24.7 (0.5)	25.3 (0.8)	26.0 (0.9)	20.5 (0.9) ***	25.3 (11.0)
Psychiatric hospitalization, n (%)	152 (35.6) ***	82 (35.2) **	40 (23.8)	49 (38.3) **	251 (24.2)
History of suicide attempt, n (%)	114 (26.7) **	66 (28.3) **	42 (25)	44 (34.4) ***	199 (19.2)
Treatment with ECT, n (%)	32 (7.5) **	12 (5.2)	5 (3.0)	15 (11.7) ***	35 (3.4)
Additional anxiety disorder, n (%)					
Panic disorder	–	97 (41.6)	76 (45.2)	61 (47.7)	–
Social phobia	97 (22.7)	–	53 (31.6)	28 (21.9)	–
Specific phobia	76 (17.8)	53 (22.8)	–	16 (12.5)	–
OCD	61 (14.3)	28 (12.0)	16 (9.5)	–	–
Mean number of anxiety disorders (s.e.)	2.1 (0.02)	1.8 (0.05)	1.9 (0.06)	1.8 (0.07)	–

MDD, Major depressive disorder; OCD, obsessive-compulsive disorder; s.e., standard error; MDE, major depressive episode; ECT, electroconvulsive therapy.

* p<0.05,

** p<0.01,

*** p<0.001 (comparisons between cases with a specific co-morbid anxiety disorder versus cases without any co-morbid anxiety disorder).

Table 2

Clinical features of co-morbid anxiety disorders in the bipolar disorder sample

Clinical feature	Cases with co-morbid panic disorder	Cases with co-morbid social phobia	Cases with co-morbid specific phobia	Cases with co-morbid OCD	Cases with no co-morbid anxiety
Subjects, n (% of overall sample)	343 (22.8)	117 (7.8)	144 (9.6)	89 (5.9)	1009 (67.2)
Mean age, years (s.e.)	40.5 (0.61) *	40.6 (1.1)	41.8 (0.9)	36.6 (1.1) ***	42.8 (0.4)
Female, n (%)	264 (77.0) ***	78 (66.7) *	116 (80.6) ***	67 (75.3) ***	561 (55.6)
Married, n (%)	168 (49.0)	52 (44.4)	82 (56.9) *	42 (47.2)	459 (45.5)
Mean length of education, years (s.e.)	13.9 (0.2) ***	13.7 (0.3) **	13.7 (0.3) **	14.3 (0.3)	14.6 (0.1)
Employed, n (%)	236 (68.8)	79 (69.3)	91 (64.5)	60 (69.0)	721 (72.5)
Mean MDD onset age, years (s.e.)	18.6 (0.5) ***	19.0 (1.0) ***	19.5 (0.9) ***	15.9 (0.8) ***	21.8 (0.3)
Mean number of MDEs, n (s.e.)	18.7 (2.0) ***	18.1 (3.8) *	16.0 (2.3) ***	19.7 (3.6) ***	10.3 (0.9)
Mean age at onset of anxiety, years (s.e.)	23.7 (0.6)	12.8 (0.7)	13.2 (0.8)	18.3 (1.2)	–
Alcohol abuse/dependence, n (%)	160 (46.6) **	55 (47.0) *	54 (37.5)	39 (43.8)	372 (36.9)
Substance abuse/dependence, n (%)	52 (15.2) **	13 (11.1)	23 (16.0) *	11 (12.4)	101 (10.1)
Mean age of first treatment, years (s.e.)	22.7 (0.5)	22.4 (0.9)	23.3 (0.8)	20.8 (0.9) **	24.0 (0.3)
Psychiatric hospitalization, n (%)	258 (75.6)	81 (71.1)	91 (65.0)	59 (68.6)	719 (72.3)
History of suicide attempt, n (%)	161 (46.9) ***	48 (41.0) *	70 (48.6) ***	43 (48.3) ***	299 (29.6)
Treatment with ECT, n (%)	40 (11.7)	12 (10.3)	15 (10.4)	11 (12.4)	110 (11.0)
Additional anxiety disorder, n (%)					
Panic disorder	–	56 (47.8)	67 (46.5)	50 (56.2)	–
Social phobia	56 (16.3)	–	36 (25.0)	18 (20.2)	–
Specific phobia	67 (19.5)	36 (30.8)	–	27 (30.3)	–
OCD	50 (14.5)	18 (15.4)	27 (18.8)	–	–
Mean number of anxiety disorders (s.e.)	1.5 (0.04)	1.9 (0.08)	1.9 (0.07)	2.1 (0.09)	–

OCD, Obsessive-compulsive disorder; s.e., standard error; MDD, major depressive disorder; MDE, major depressive episode; ECT, electroconvulsive therapy.

* p<0.05,

** p<0.01,

*** p<0.001 (comparisons between cases with a specific co-morbid anxiety disorder versus cases without any co-morbid anxiety disorder).

Table 3Familial aggregation of co-morbid anxiety disorders in the major depressive disorder sample^a

Relative diagnosis	Diagnosis in relatives		aOR ^{1b} (95% CI)	P	aOR ^{2c} (95% CI)	P	aOR ^{3d} (95% CI)	P
	Proband with anxiety disorder, n (%)	Proband without anxiety disorder, n (%)						
Panic disorder	99/250 (39.6)	179/801 (22.4)	2.32 (1.69–3.19)	<0.001	2.22 (1.60–3.07)	<0.001	1.98 (1.41–2.78)	<0.001
Social phobia	30/137 (21.9)	133/914 (14.6)	1.58 (0.99–2.53)	0.057	1.40 (0.86–2.30)	0.18	1.32 (0.80–2.19)	0.28
Specific phobia	22/104 (21.2)	85/947 (9.0)	2.93 (1.69–5.10)	<0.001	2.42 (1.36–4.33)	0.003	2.43 (1.35–4.38)	0.003
OCD	14/66 (21.2)	76/985 (7.7)	2.88 (1.49–5.56)	0.002	2.64 (1.36–5.15)	0.004	2.60 (1.29–5.24)	0.008

aOR, Adjusted odds ratio; CI, confidence interval; OCD, obsessive-compulsive disorder.

^a All relatives with recurrent MDD diagnosis.^b Adjusted for age at interview, site of ascertainment, and sex.^c Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives.^d Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives and probands.

Table 4Familial aggregation of co-morbid anxiety disorders in the bipolar disorder sample^a

Relative diagnosis	Diagnosis in relatives		aOR ^{1b} (95% CI)	P	aOR ^{2c} (95% CI)	P	aOR ^{3d} (95% CI)	P
	Proband with anxiety disorder, n (%)	Proband without anxiety disorder, n (%)						
Panic disorder	67/208 (32.2)	119/642 (18.5)	1.95 (1.33–2.86)	0.001	1.70 (1.14–2.54)	0.009	1.52 (1.00–2.30)	0.047
Social phobia	7/67 (10.5)	59/783 (7.5)	1.38 (0.61–3.11)	0.44	1.13 (0.46–2.72)	0.80	1.00 (0.39–2.55)	1.00
Specific phobia	16/76 (21.1)	75/774 (9.7)	2.38 (1.25–4.50)	0.008	1.82 (0.92–3.58)	0.084	1.94 (0.95–3.96)	0.069
OCD	14/64 (21.9)	31/786 (3.9)	6.84 (3.29–14.2)	<0.001	4.62 (2.11–10.12)	<0.001	3.10 (1.31–7.09)	0.009

aOR, Adjusted odds ratio; CI, confidence interval; OCD, obsessive-compulsive disorder; BPI, bipolar I disorder; BPII, bipolar II disorder.

^a All relatives with BPI or BPII diagnoses.^b Adjusted for age at interview, site of ascertainment, and sex.^c Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives.^d Adjusted for age at interview, site of ascertainment, sex, and additional anxiety disorder co-morbidity in relatives and probands.