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Research Article

A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population

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ABSTRACT

Background: Bipolar affective disorder has a high rate of comorbidity with a multitude of psychiatric disorders and medical conditions. Among all the potential comorbidities, co-existing anxiety disorders stand out due to their high prevalence.
Aims: To determine the lifetime prevalence of comorbid anxiety disorders in bipolar affective disorder under the care of psychiatric services through systematic review and meta-analysis.
Method: Random effects meta-analyses were used to calculate the lifetime prevalence of comorbid generalised anxiety disorder, panic disorder, social anxiety disorder, specific phobia, agoraphobia, obsessive compulsive disorder and posttraumatic stress disorder in bipolar affective disorder.
Results: 52 studies were included in the meta-analysis. The rate of lifetime comorbidity was as follows: panic disorder 16.8% (95% CI 13.7–20.1), generalised anxiety disorder 14.4% (95% CI 10.8–18.3), social anxiety disorder13.3% (95% CI 10.1–16.9), post-traumatic stress disorder 10.8% (95% CI 7.3–14.9), specific phobia 10.8% (95% CI 8.2–13.7), obsessive compulsive disorder 10.7% (95% CI 8.7–13.0) and agoraphobia 7.8% (95% CI 5.2–11.0). The lifetime prevalence of any anxiety disorders in bipolar disorder was 42.7%.
Conclusions: Our results suggest a high rate of lifetime concurrent anxiety disorders in bipolar disorder. The diagnostic issues at the interface are particularly difficult because of the substantial symptom overlap. The treatment of co-existing conditions has clinically remained challenging.

1. Introduction

Bipolar disorders with the prevalence rate of 4% are among the most common psychiatric disorders (Ketter, 2010). It is considered to be the sixth leading cause of disability worldwide due to its significant economic, social, familial and individual burdens (Woods, 2000). Lifetime prevalence of bipolar disorder type I or type II (which includes at least one hypo/manic episode during a lifetime) has been estimated at 2% (Oldani et al., 2005). The relationship between bipolar disorder and anxiety disorders can create a more difficult course of treatment if comorbid (McIntyre et al., 2006). Studies suggest that the rate of anxiety disorders in individuals with bipolar disorder is in fact greater than those of the general population (Keller, 2006).

Bipolar disorder and anxiety disorders, including panic disorder, generalised anxiety disorder (GAD), social anxiety disorder (SAD), specific phobia, agoraphobia, obsessive–compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) are psychiatric illnesses that individually cause significant mortality and morbidity, as reflected in suicide rates (Allgulander and Lavori, 1991; Schneier et al., 1992; Osby et al., 2001), substance abuse rates (Chengappa et al., 2000; Grant et al., 2004), total medical burden (Klerman et al., 1991; Tolin et al., 2008; Lauterback et al., 2005), economic costs (Souètre et al., 1994; Wyatt and Henter, 1995) and quality of life (Wittchen et al., 1992; Mendlowicz and Stein, 2000).

Clinical and epidemiological studies have reported lifetime prevalence rates for comorbid anxiety disorders in bipolar disorder of 50% (Cassano et al., 1999; Pini et al., 1997; McElroy et al., 2001). The Epidemiological Catchment Area study found the lifetime prevalence for panic disorder in bipolar illness to be 20.8%, more than twice the rate of 10% reported in patients with major depressive disorder (Pini et al., 1997; Chen and Dilsaver, 1995a,b; Perugi et al., 2001). The frequency of GAD at 30% in bipolar disorder is reported by two studies (Pini et al., 1997; Young et al., 1993). The prevalence of comorbid social

Abbreviations: GAD, generalised anxiety disorder; PTSD, posttraumatic stress disorder; OCD, obsessive–compulsive disorder; SAD, social anxiety disorder; DSM, Diagnostic and Statistical Manual; ICD, International Classification of Diseases.

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anxiety disorder ranges between 7.8% (Szadoczky et al., 1998) and 47.2% (Kessler et al., 1997) and the prevalence rate of OCD has been found to be between 3.2% and 35% (Pini et al., 1997; Perugi et al., 2001; Szadoczky et al., 1998; Krüger et al., 1995). Although the association between PTSD and bipolar disorder has been less extensively studied, the rate of comorbidity between these two conditions may exceed by 40% (Musser et al., 1998).

Previous studies have suggested that multiple anxiety disorder comorbidities occur in a significant minority of patients with bipolar disorder. For example, Young et al. (1993) found multiple anxiety disorders in 32% of bipolar disorder outpatients. Cassano et al. (1999) studied 77 inpatients presenting with severe mood disorders with psychotic features, including bipolar I, and found the presence of one anxiety disorder in 34% of cases, while 14% of patients had two or three. Similarly, Henry et al. (2003) studied 318 inpatients most of whom had bipolar I disorder and found the rate of one or more lifetime comorbid anxiety disorders to be 24% and 11%, respectively. The extent to which anxiety and the presence of single or multiple anxiety disorders impact on course and outcome in bipolar disorder has been studied only in a limited way (Ghoreishizadeh et al., 2009; Deckersbach et al., 2014).

Compared to those with uncomplicated bipolar disorder, this co-occurrence with anxiety disorders is associated with increased suicide attempts and ideation (Young et al., 1993; Simon et al., 2003; Lee and Dunner, 2008; Frank et al., 2002; Angst et al., 2005), substance abuse (Young et al., 1993; Simon et al., 2003; Lee and Dunner, 2008; Angst et al., 2005; Toniolo et al., 2009), increased severity of mood episodes (Frank et al., 2002; Angst et al., 2005; Toniolo et al., 2009; Gaudiano and Miller, 2005), and more mood episodes. Young et al. (1993) and Feske et al. (2000) also found a decrease in lithium responsiveness in the presence of anxiety disorders. Other studies showed this combination has led to a longer recovery time (Feske et al., 2000; Otto et al., 2006) and an earlier age at the onset of bipolar illness (Simon et al., 2003; Lee and Dunner, 2008; Pini et al., 2006).

The co-occurrence of an anxiety disorder leads to a particularly difficult challenge in the treatment of bipolar illness since antidepressant medication, the mainstay of pharmacologic treatments for anxiety, may adversely alter the course of bipolar disorder. Furthermore, the common co-occurrence of alcohol and substance use disorders with bipolar disorder, limits the utility of benzodiazepines. Identification of anxiety disorders in bipolar patients is important. The treatment plan needs to balance the potential benefits to harm of antidepressant administration (El-Mallakh and Hollifield, 2008) and benzodiazepines (Brunette et al., 2003) administration.

In view of the presence of a high heterogeneity about the lifetime prevalence of anxiety disorders in patients with bipolar disorder, we aimed to quantitatively summarise the lifetime prevalence of robustly defined anxiety disorders in co-occurrence bipolar disorder (mainly type I) in psychiatric inpatient and outpatient population.

2. Methods

2.1. Search Strategy and Selection Criteria

BN and AJM designed the review protocol and extraction form in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A systematic search of PsycINFO, Medline, and CINAHL abstract databases was done by BN, from 1992 to 2013.

We included studies with data for the lifetime comorbidity between bipolar affective disorder and anxiety disorders among population of patients with bipolar affective disorder under the care of psychiatric services, and we excluded the data from any community-based samples. When it was possible, we only included the data from bipolar I studies in order to minimise selection bias, as previous studies suggested different prevalence of comorbidity between bipolar I and II with anxiety disorders. Otherwise, we used the data of those studies, which had clearly reported no significant differences in their findings regarding the type of bipolar disorder. Hence, the term of 'bipolar affective disorder' in this paper mainly indicates bipolar disorder type I. The included studies were stratified into those comorbidities with all anxiety disorders and those with a specific subtype of anxiety disorder, including GAD, panic disorder, OCD, PTSD, SAD, specific phobia and agoraphobia. We excluded the data from any diagnoses of cyclothymia. In order to minimise selection bias, we also excluded the community-based studies, as well as the data from child and adolescent studies. We took extra care to exclude duplicate publications (i.e. two or more studies investigating the same sample) in order to avoid multiple or duplication bias (Fig. 1).

3. Validity Assessment

3.1. Data Abstraction and Classification

We extracted the primary data independently, which was reviewed systematically. Based on the Cochrane Bias Method Group recommendations, a four-point quality rating and a five-point bias risk were applied to each study. The quality rating score was used to assess the study sample size, design, attrition, criterion method and method of dealing with possible confounders using the following scale: 1 = low quality; 2 = low-to-medium quality; 3 = medium-to-high quality; and 4 = high quality. The bias rating score was similarly used to assess possible bias in assessments of age, clinical setting with the following score: 1 = low bias risk; 2 = low-to-medium bias risk; 3 = medium-to-high bias risk; and 4 = high bias risk. Finally the sampling method was assessed for each study, because this could affect the interpretation of the comorbidity data. Any area of disagreement was resolved by BN and AJM.

3.2. Outcome Measures

We defined the main outcomes of interests as the lifetime prevalence of comorbidity between bipolar affective disorder type I and anxiety disorders, as well as any specific type of anxiety disorders, defined by the DSM-III, DSM-III-R and DSM-IV, ICD-9 and ICD-10 criteria.

3.3. Statistical Analysis

Overall effects estimates were calculated using the DerSimonian–Laird meta-analysis. Heterogeneity was invariably moderate to high. Therefore, a random effects meta-analysis was chosen over a fixed effects model with StatsDirect (version 2.7.7). For comparative and sub-analyses, we needed a minimum of three independent studies to justify analysis according to convention. The impact of heterogeneity on the pooled estimates of the individual outcomes of the meta-analysis was assessed using Cochran's Q, a χ^2 statistic. This was used to test whether the differences between studies was due to chance. A P value close to 1 suggests a high probability that the observed heterogeneity was due to sampling error. We also used the I^2 test to assess heterogeneity (thresholds were ≥80% = moderate and ≥90% = high).

We examined the presence of publication bias with the Begg funnel plot (Dear and Begg, 1992). In addition, we used the following three tests to see if asymmetry in the funnel plot is caused by publication bias. 1) Begg–Mazumdar test (Begg and Mazumdar, 1994), which tests the inter-dependence of variance and effect size with a rank correlation method. B) The Egger test (Egger et al., 1997), which tests for asymmetry of the funnel plot. C) The Harbord test (Harbord et al., 2006), which is similar to the Egger test but uses a modified linear regression method to reduce the false-positive rates. We also used Spearman correlation with adjusted r^2 to assess the association between linear variables.

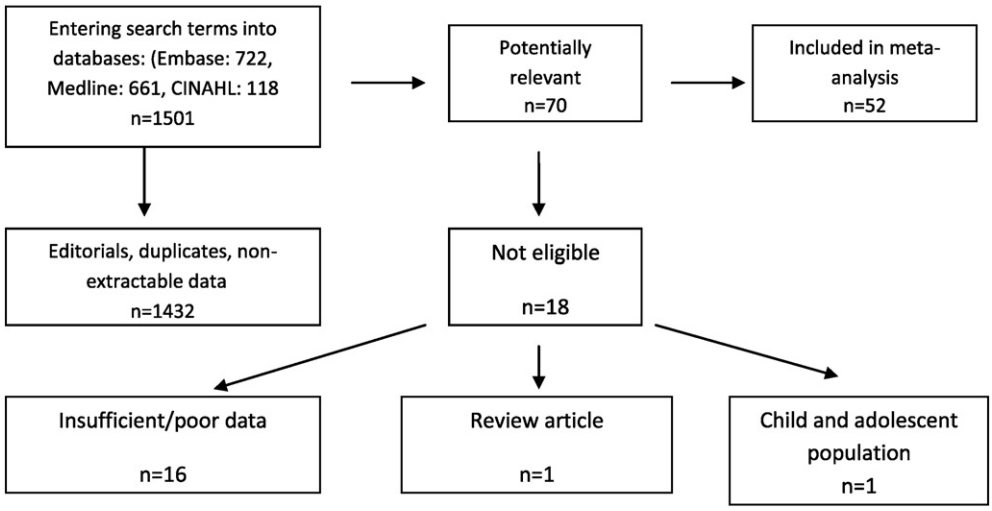

Fig. 1. Trail flow of selecting studies.

4. Results

We identified 1501 relevant articles, with 70 including lifetime prevalence of bipolar patients with anxiety disorders' comorbidity who were assessed using an interview-based diagnostic method (Fig. 1). A total of 18 out of 70 studies were excluded because they either contained insufficient data for analysis (16 studies) or were a review article. One study was excluded as it was conducted on a child and adolescent population with the mean age of 12.7 years old (Sala et al., 2010). We identified 52 relevant articles including 13,656 individuals with established diagnosis of bipolar disorder with lifetime comorbid anxiety disorders, including GAD, PTSD, SAD, specific phobia, agoraphobia, panic disorder and OCD (Table 2). The majority of the studies (32 out of 52) were carried out in outpatient clinic populations and 13 studies were conducted in inpatient settings. Seven studies included both inpatient and outpatient individuals. 36 studies used consecutive samples, whereas a further 16 studies used convenience sampling method (Table 2). Data extraction is shown in Fig. 1 in accordance with the Quality of Reporting of Meta-analyses Guidelines (Moher et al., 1999).

From the identified articles, we were unable to demonstrate the total comorbidity between bipolar disorder and all anxiety disorders confidently, as some of the individual studies examined only one or two subtypes of the anxiety disorders, e.g. GAD or OCD. However, in twenty-nine out of fifty-two articles which including 3064 individuals, we were able to extract the total lifetime comorbidity with anxiety disorders (Fig. 2). Meta-analysis pooled prevalence of lifetime comorbidity of any anxiety disorders in bipolar disorder was 42.7% (95% CI 37.5–48.0) with high heterogeneity (Table 1). It should be noted that a higher prevalence rate of comorbid anxiety disorders is mainly due to the fact that some individuals have had multiple identified anxiety disorder conditions.

4.1. Lifetime GAD Comorbidity in Bipolar Disorder

We identified 30 relevant articles which including 892 individuals with lifetime comorbid GAD in bipolar affective disorder (Fig. 3). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of GAD in individual studies ranged from 1.3% (95% CI 0.03–7.0) (Strakowski et al., 1992) to 56.8% (95% CI 46.2–66.9) (Castro e Couto et al., 2012). Meta-analysis pooled prevalence of comorbid GAD was 14.4% (95% CI 10.8–18.3) with high heterogeneity (Table 1 and Fig. 3). Infrequent reports of very low or very high prevalence in small studies suggest possible publication bias, as such studies are prone to take longer to be published; or the results not conforming to the desired outcome may not even be reported (Rothman and Greenland, 1998).

4.2. Lifetime PTSD Comorbidity in Bipolar Disorder

We identified 25 relevant articles which including 1185 individuals with PTSD lifetime comorbidity in bipolar affective disorder (Fig. 4). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of PTSD in individual studies ranged from none (Koyuncu et al., 2010) to 28.3% (95% CI 23.5–33.5) (Bauer et al., 2005). Meta-analysis pooled prevalence of comorbid PTSD was 10.8% (95% CI 7.3–14.9) with high heterogeneity (Table 1 and Fig. 4).

4.3. Lifetime SAD Comorbidity in Bipolar Disorder

We identified 32 relevant articles which including 921 individuals with lifetime social anxiety disorder comorbidity in bipolar affective disorder (Fig. 5). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of social anxiety disorder in individual studies ranged from none (Pini et al., 1997) to 38.7% (95% CI 26.6–51.9) (Fracalanza et al., 2011). Meta-analysis pooled prevalence of comorbid social anxiety disorder was 13.3% (95% CI 10.1–16.9) with high heterogeneity (Table 1 and Fig. 5).

4.4. Lifetime Agoraphobia Comorbidity in Bipolar Disorder

We identified 11 relevant articles which including 251 individuals with lifetime agoraphobia comorbidity in bipolar affective disorder (Fig. 6). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of agoraphobia in individual studies ranged from 1.4% (95% CI 0–7.7) (Altindag et al., 2006) to 24.0% (95% CI 9.3–45.1) (Sharma et al., 1995). Meta-analysis pooled prevalence of comorbid agoraphobia was 7.8% (95% CI 5.2–11.0) with high heterogeneity (Table 1 and Fig. 6).

4.5. Lifetime Specific Phobia Comorbidity in Bipolar Disorder

We identified 26 relevant articles which including 448 individuals with lifetime specific phobia comorbidity in bipolar affective disorder (Fig. 7). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of specific phobia in individual studies ranged from 0.8% (95% CI 0–4.5) (Chang et al.,

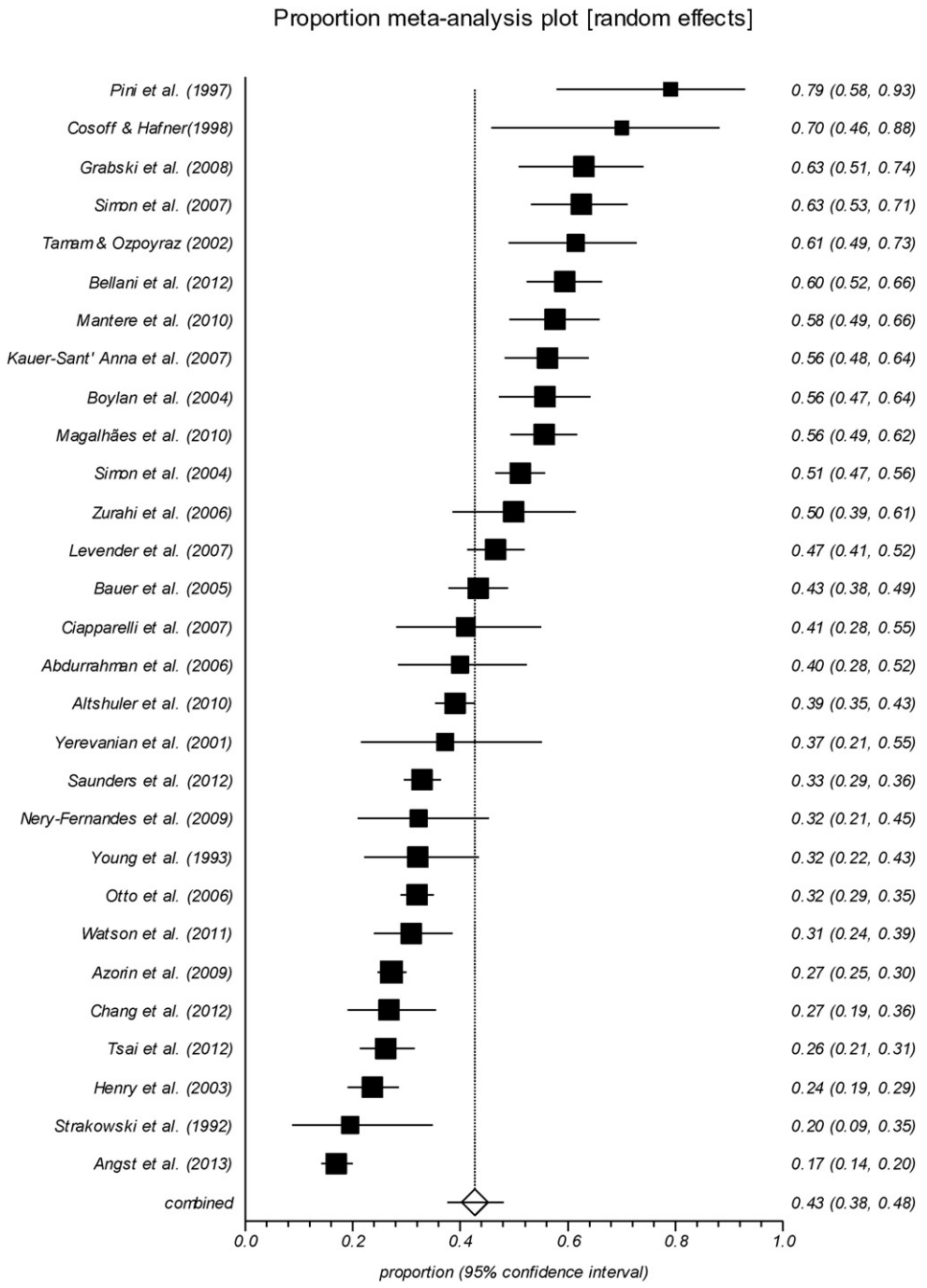

Fig. 2. Lifetime anxiety disorder comorbidity in bipolar disorder.

Table 1
Summary of lifetime prevalence of comorbid anxiety disorders in bipolar I, publication bias and heterogeneity findings.

Comorbid anxiety disorders	Number of studies	Total number of cases	Lifetime prevalence (95% CI)	Cochran Q (P value)	Heterogeneity I^2 (95% CI)	Begg-Mazumdar (P value)	Egger (95% CI)	Harbord (95% CI)
Anxiety disorders	29	3064	42.7% (37.5–48.0)	575.62 (P < 0.0001)	95.1% (94.2–95.8)	0.167 (0.210)	5.1 (2.1–8.0)	4.3 (1.4–7.2)
Panic disorder	45	1537	16.8% (13.7–20.1)	775.97 (P < 0.0001)	94.2% (93.3–94.9)	0.273 (0.007)	4.0 (2.4–5.7)	2.6 (0.2–5.0)
Generalised anxiety disorder	30	892	14.4% (10.8–18.3)	478.00 (P < 0.0001)	93.9% (92.7–94.9)	0.149 (0.256)	4.0 (1.8–6.1)	1.1 (−1.6–3.9)
Posttraumatic stress disorder	25	1185	10.8% (7.3–14.9)	678.29 (P < 0.0001)	96.5% (95.9–96.9)	0.193 (0.185)	3.9 (0.6–7.2)	−1.3 (−4.4.1.7)
Obsessive compulsive disorder	43	808	10.7% (8.7–13.0)	424.42 (P < 0.0001)	90.1% (87.9–91.7)	0.229 (0.030)	3.4 (2.4–4.3)	3.7 (1.9–5.4)
Social anxiety disorder	32	921	13.3% (10.1–16.9)	553.76 (P < 0.0001)	94.4% (93.3–95.2)	0.209 (0.095)	4.0 (2.3–5.8)	2.9 (0.1–5.7)
Specific phobia	26	448	10.8% (8.2–13.7)	185.39 (P < 0.0001)	86.5% (81.7–89.6)	0.286 (0.041)	2.7 (0.9–4.4)	1.3 (−1.1–3.7)
Agoraphobia	11	251	7.8% (5.2–11.0)	101.16 (P < 0.0001)	90.1% (84.8–93)	0.381 (0.121)	3.0 (0.7–5.3)	4.7 (0.3–9.0)

Heterogeneity interpretation: Cochrane test: a P value of <.1 is considered significant for the presence of statistical heterogeneity. I^2: greater than 80% = moderate, I^2 greater than 90% = high. Publication bias interpretation: Begg–Mazumdar test: P value < 0.05 is considered significant and indicates a presence of publication bias. Egger and Harbord tests: if the intercept differs significantly from zero, this may indicate that publication bias is present.

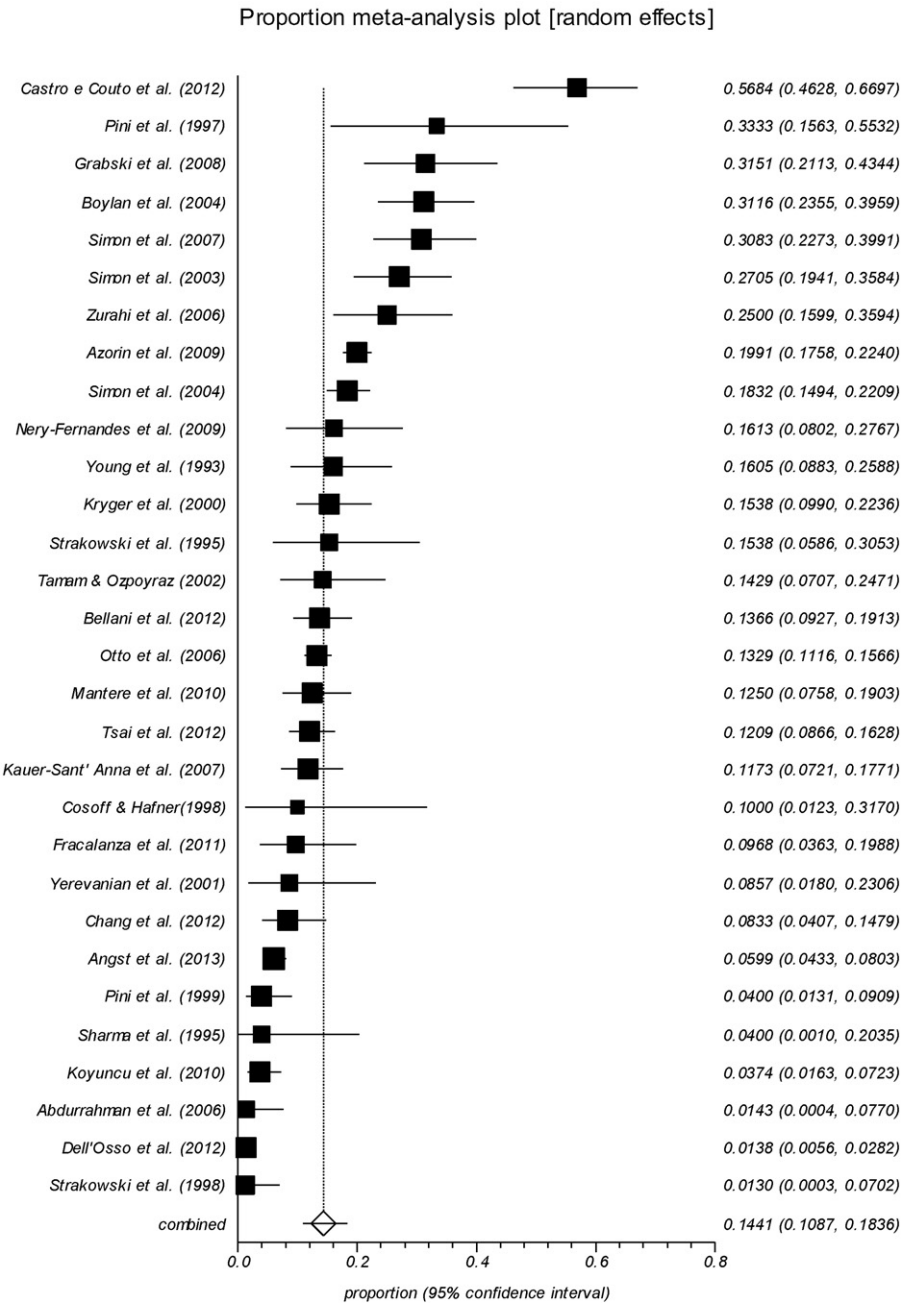

Fig. 3. Lifetime GAD comorbidity in bipolar disorder.

2012) to 32.1% (95% CI 24.9–39.8) (Kauer-Sant'Anna et al., 2007). Meta-analysis pooled prevalence of comorbid specific phobia was 10.8% (95% CI 8.2–13.7) with high heterogeneity (Table 1 and Fig. 7).

4.6. Lifetime Panic Disorder Comorbidity in Bipolar Disorder

We identified 46 relevant articles which including 1537 individuals with lifetime panic disorder comorbidity in bipolar affective disorder (Fig. 8). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of panic disorder in individual studies ranged from 2.3% (95% CI 0.5–6.6) (Vieta et al., 2001) to 54.2% (95% CI 43.7–64.4) (Okan Ibiloglu and Caykoylu, 2011). Meta-analysis pooled prevalence of comorbid panic disorder was 16.8% (95% CI 13.7–20.1) with high heterogeneity (Table 1 and Fig. 8).

4.7. Lifetime OCD Comorbidity in Bipolar Disorder

We identified 43 relevant articles which including 808 individuals with lifetime OCD comorbidity in bipolar affective disorder (Fig. 9). All studies were carried out in either psychiatric outpatient clinics or inpatient settings. The lifetime prevalence of OCD in individual studies ranged from 1.4% (95% CI 0.8–2.3) (Azorin et al., 2009) to 38.5% (95% CI 27.1–50.9) (Tamam and Ozpoyraz, 2002). Meta-analysis pooled prevalence of comorbid OCD was 10.7% (95% CI 8.7–13.0) with high heterogeneity (Table 1 and Fig. 9).

5. Discussion

To the best of our knowledge, there has been no previous meta-analysis examining the lifetime prevalence of comorbidity between

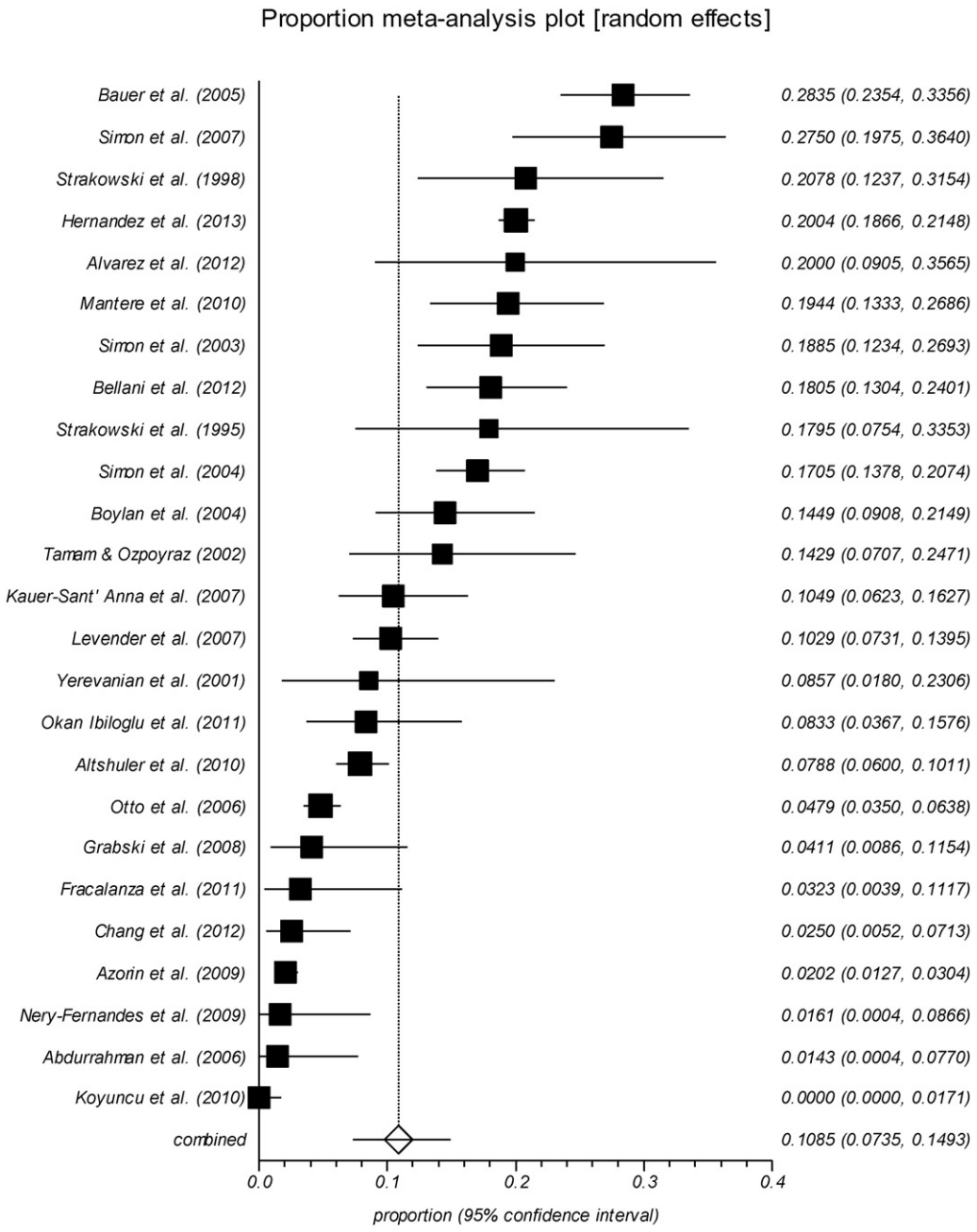

Fig. 4. Lifetime PTSD comorbidity in bipolar disorder.

bipolar disorder and anxiety disorders. As expected, a large amount of variation in prevalence across studies was found by graphical representation of estimates and by indices of heterogeneity. Despite this wide variation, pooled estimates are often useful to indicate the clinical burden of the comorbidities. All original studies were carried out according to interview-based methods of defining bipolar disorder and anxiety disorders, using comprehensive and fully structured tools, such as CIDI and SCID-IV and were conducted by trained interviewers. In total, we were able to identify 52 studies consisting of 13,656 individuals with bipolar affective disorder, for whom the lifetime comorbid anxiety disorders had been examined (Table 2). Meta-analysis pooled prevalence of the lifetime comorbidity of any anxiety disorders in 29 out of 52 studies was 42.7% (95% CI 37.5–48.0). However, it is to be noted that the total number of individuals with comorbid anxiety disorders was less than the above number, as some individuals had more than one identified anxiety disorder comorbidity. To examine the impact of single versus multiple anxiety disorder comorbidities, Boylan et al. (2004) found no significant differences between the groups of patients with 1, 2, 3 or more anxiety disorders for any of the outcome measures (all P values > 0.15).

Whenever possible, we only used the data for bipolar type I, as some studies such as the Bridge Study (Angst et al., 2013) found higher prevalence of lifetime comorbidity in type II (27.5% vs. 16.9%). Otherwise we only included the data when the authors clearly reported no significant differences in their findings between types I and II.

We found the overall rate of anxiety disorders, as well as the type of anxiety disorder in clinical samples varied widely. To explain such variety, we found no significant differences in sampling settings as to be either inpatient or outpatient. One explanation may be the cross-national variability of the primary studies. Other suggested contributory factors include having different methodological approaches, such as being

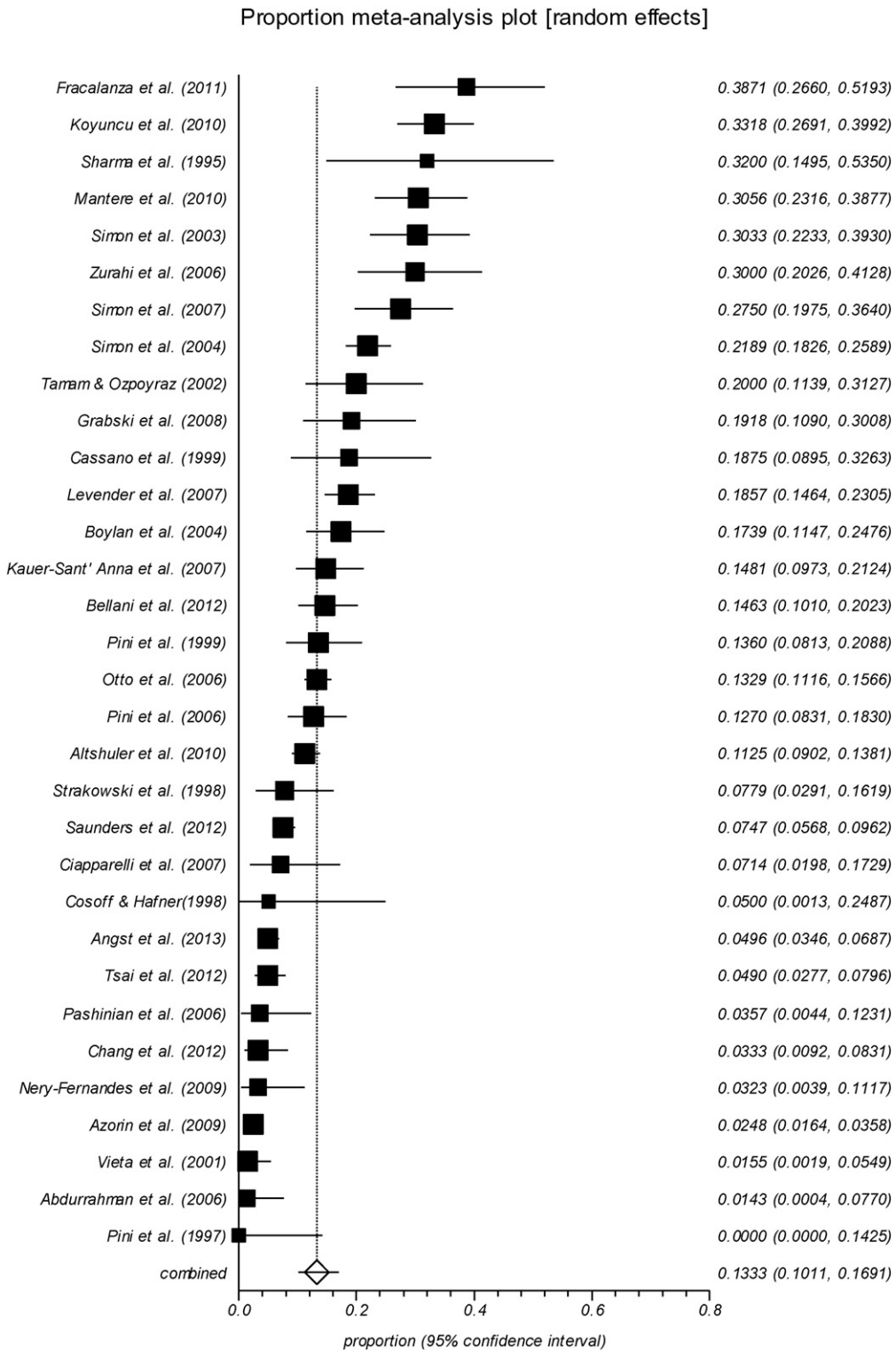

Fig. 5. Lifetime social anxiety disorder comorbidity in bipolar disorder.

in different phase of bipolarity at comorbidity assessment; and assessment method used in diagnosis and evaluation of period or lifetime prevalence.

Some of primary studies (Boylan et al., 2004; Angst et al., 2013; Grabski et al., 2008) found GAD to be the most common comorbid anxiety disorder in bipolar disorder. However the majority of studies found panic disorder as the most common comorbid anxiety disorder in bipolar disorder (Okan Ibiloglu and Caykoylu, 2011; Shoaib and Dilsaver, 1995). Wittchen et al. (1994) reported strong lifetime comorbidity between GAD and affective disorder (mania 10.5%, major depression 62.4% and dysthymia 39.5%).

With regard to the effects of single vs. multiple comorbid anxiety disorders, in a sample of 153 bipolar I inpatient cases, Ghoreishizadeh et al. (2009) identified 43% rate of anxiety disorders with no significant relationship between anxiety disorders and the severity of bipolar disorder and the duration of hospitalisation. Their findings were consistent with the results of a study by Henry et al. (2003), but contrary to the results of some other studies (El-Mallakh and Hollifield, 2008; Sharma

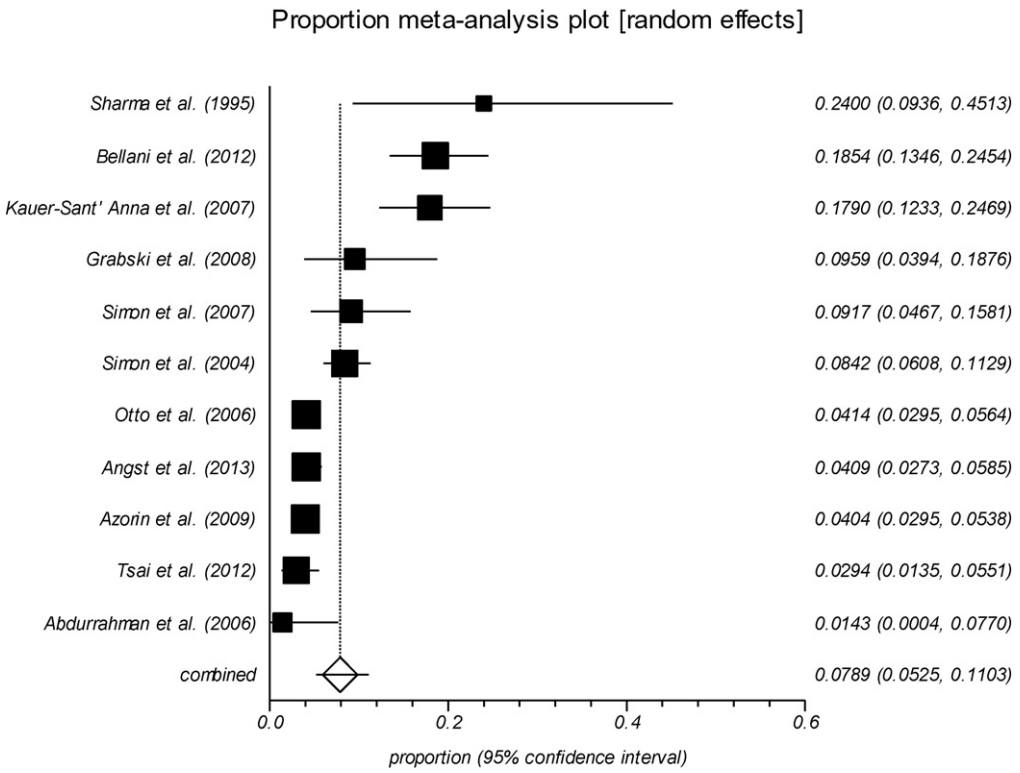

Fig. 6. Lifetime agoraphobia comorbidity in bipolar disorder.

et al., 1995; Masi et al., 2007; Dilsaver and Chen, 2003; Dineen Wagner, 2006). Using a random effect meta-analysis in our pooled data, we found panic disorder to be the most common comorbid anxiety disorder in bipolar disorder: 16.8% (95% CI 13.7–20.1), followed by GAD and social anxiety disorder with a prevalence of 14.4% (95% CI 10.8–18.3) and 13.3% (95% CI 10.1–16.9), respectively. We also estimated the rate of lifetime comorbidity between bipolar disorder and PTSD, specific phobia, OCD and agoraphobia to be 10.8% (95% CI 7.3–14.9), 10.8% (95% CI 8.2–13.7), 10.7% (95% CI 8.7–13.) and 7.8% (95% CI 5.2–11.0), respectively.

Finally, in limited studies it has been suggested that the presence or absence of any particular comorbid anxiety disorders may alter the pattern and prognosis of bipolar disorder. For instance, Pini et al. (1997) suggested three patterns in association with anxiety and affective disorder: (i) GAD was found to be stronger associated with dysthymia than bipolar or unipolar depression; (ii) panic disorder was found to have a greater tendency to co-occur with bipolar disorder than with dysthymia and possibly than with unipolar depression; (iii) social phobia was less common in bipolar cases. Duffy et al. (2010) suggested a staging model: anxiety disorders appear as an early manifestation of psychopathology in high-risk youth who go on to develop bipolar illness. Perugi et al. (2001) suggested that social phobia most often precedes mania and then resolves, while other comorbid anxiety disorders tend to persist.

5.1. Strengths and Limitations

Based on our experience with previous meta-analyses, we acknowledge that we may have missed studies and/or made data entry errors. We encourage readers to inform us of any missing studies or errors in the data. Updated lists of relevant studies and raw data will be available from the authors. We note several limitations to this analysis.

1. Due to the large degree of variation across studies, the heterogeneity and publication bias were present. It is possible that some studies were not identified in the searches if they were not published in mainstream journals. There may have been some time lag bias, with smaller studies, or studies with unremarkable results, coming through to publication slower than larger studies.
2. The included studies were of a variable quality. Although they all received a high methodological quality score, their findings cannot be easily compared or generalised. Prevalence studies have often used different diagnostic instruments, sampling procedures, case definitions and time frames for the diagnoses (e.g. lifetime, six month prevalence or current diagnoses), as well as different severity ratings for diagnostic decisions (Weissman et al., 1989).
3. We acknowledge that the definitions of prevalence could vary slightly across studies, typically relying on cross-sectional assessment at different stages of the illness, and occasionally used convenience sampling.
4. Lifetime prevalence rate in comparison to current or point prevalence usually provides a higher rate, as it comprises the proportion of the population who have ever had the disease. In contrast, current and period prevalence rate gives a figure at a single point or period in time (Jekel et al., 2001).
5. Interview methods commonly underestimate the prevalence of anxiety disorders when compared with self-report scales. However, the consensus is that interview is methodologically superior to self-report, as it is objective and comparable between individuals, which may reduce the rate of false positive.
6. We were unable to extract many correlates of different anxiety disorders because of limitations in the underlying dataset. It is unlikely that it would ever be possible to measure and record all potentially important covariates.
7. A further limitation was the scarcity of data for non-DSM defined anxiety disorders, as none of the studies used explicit ICD criteria.

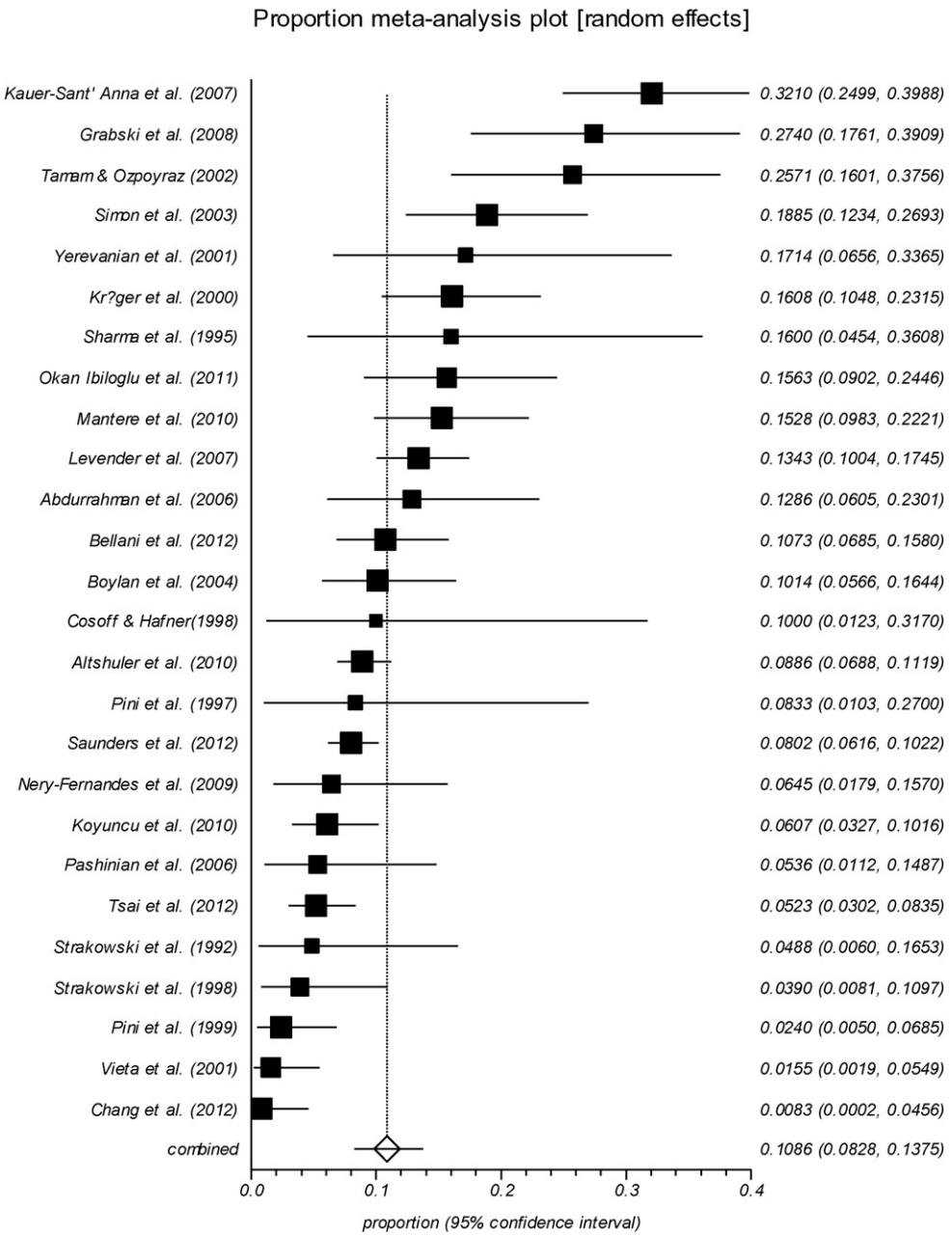

Fig. 7. Lifetime specific phobia comorbidity in bipolar disorder.

8. Some criticism directed at the studies demonstrates how the association of bipolar disorder with anxiety disorders are with regard to the diagnostic criteria employed. For instance, in GAD, as well as in PTSD, there are criteria which prevail over those of bipolar disorder (Cox et al., 1990).

5.2. Clinical Implications

Previous studies suggest that patients with high anxiety scores were more likely to have made a suicide attempt. Since anxiety itself is related to suicidal behaviour, anxiety symptoms in bipolar patients may be an important risk factor for suicide (Weissman et al., 1989). Similarly, the strong relationship between anxiety disorders and alcohol abuse (Cox et al., 1990; Kushner et al., 1990) also suggest that bipolar patients with high anxiety scores may be at risk of alcohol misuse. Kessler et al. (1997) suggested a high comorbidity with substance misuse, including alcohol in bipolar disorder could represent attempts to modulate the mood liability associated with bipolar disorder or that they could be symptoms of mood disturbance. Young et al. (1993) observed a trend toward lithium non-responsiveness in his high anxiety group of patients. There is also some contradictory evidence between anxiety and impulsivity in bipolar disorder. While some studies (Oosterlaan, 1998; Pliszka et al., 1999; Brown, 2000; Manassas et al., 2000) found anxiety as a protective factor for impulsiveness, others (Summmerfeldt et al., 2004; Taylor et al., 2008) found it an aggravating factor.

With regard to the psychopharmacologic treatment of anxiety disorders in bipolar disorder, in the absence of any robust evidenced-based data, it will remain challenging and perhaps risky, particularly because of the concern that antidepressants may destabilise mood in bipolar patients, and benzodiazepines are problematic in patients with comorbid alcohol/substance use disorders. In the presence of bipolar disorder, the first choice of anxiolytic medication may be shifted towards a

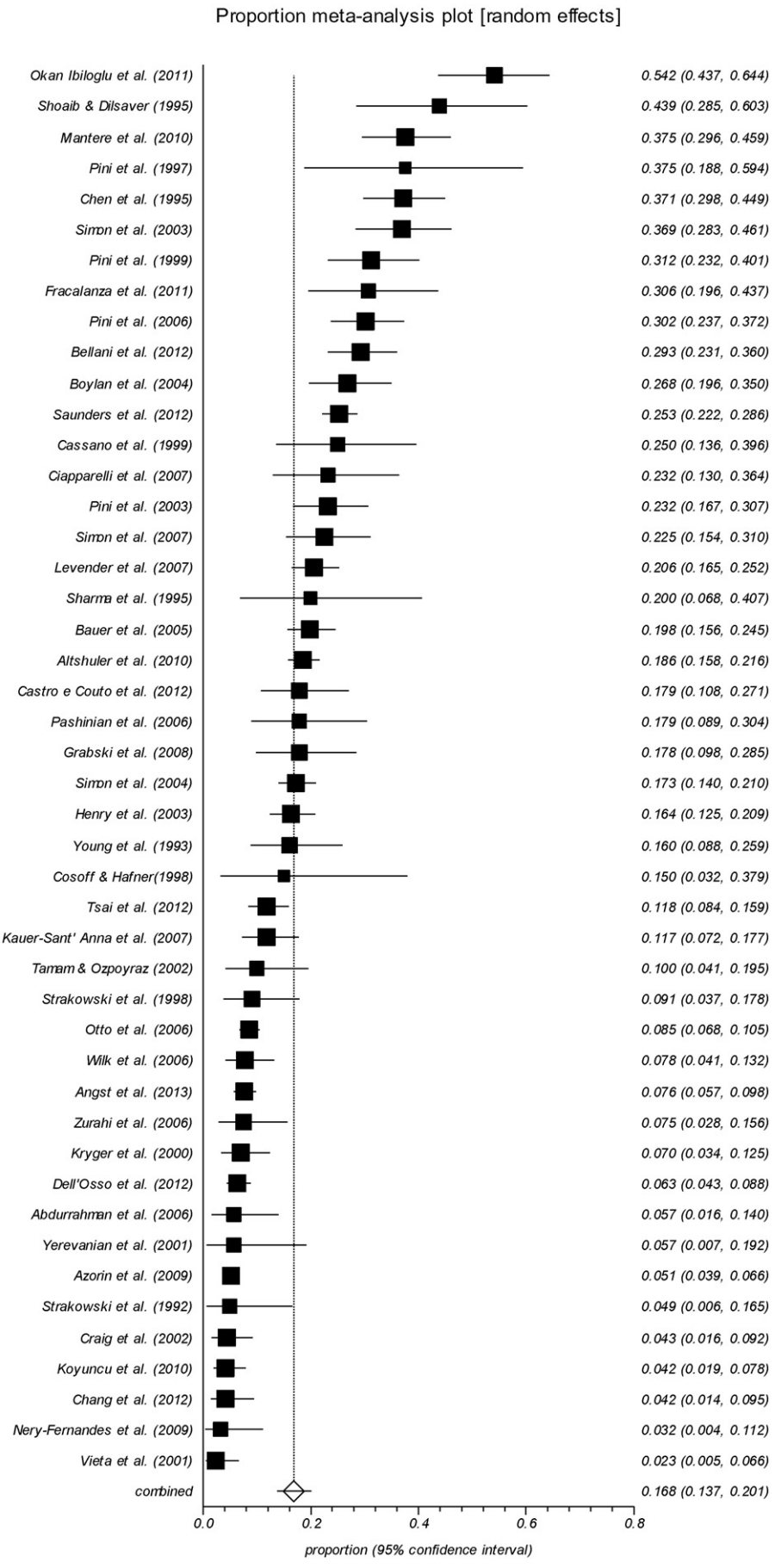

Fig. 8. Lifetime panic disorder comorbidity in bipolar disorder.

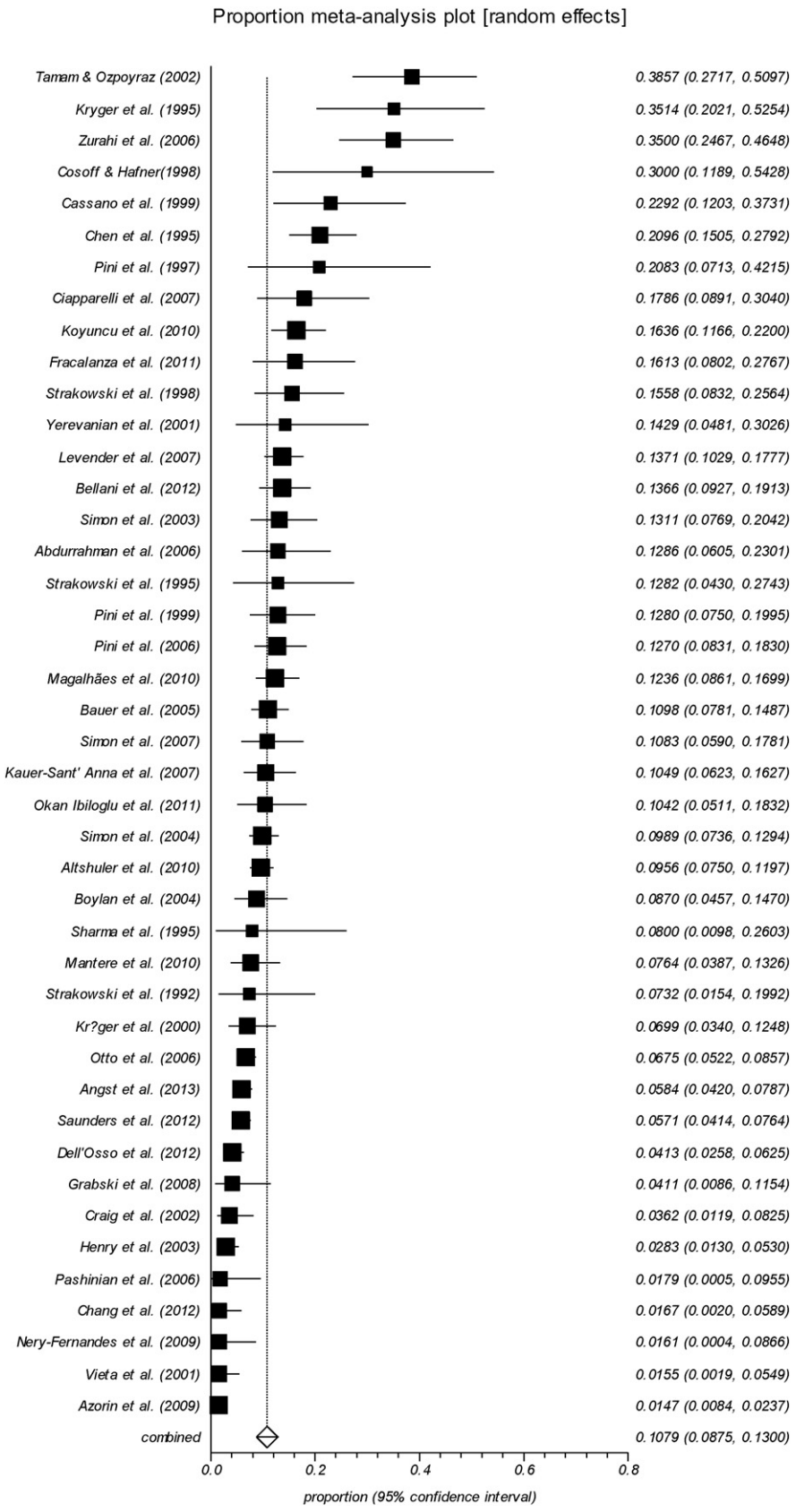

Fig. 9. Lifetime OCD comorbidity in bipolar disorder.

medication covering both conditions, such as a typical or atypical antipsychotic. However, the effect of atypical antipsychotic (e.g. olanzapine, quetiapine and lurasidone) on anxiety during bipolar depression should be viewed with caution and as preliminary (Tohen et al., 2003; Calabrese et al., 2005; Loebel et al., 2014a,b). It is also suggested that comorbid anxiety disorders can be effectively treated in bipolar patients

Table 2
Overview of prevalence studies of anxiety disorders in patients with bipolar disorder.

Authors	Sampling method[a] Setting[b]	Quality[c]	Bias risk[d]	No with bipolar disorder	Mean age (years)	Type of anxiety disorders	Country
Angst et al. (2013)	1 IN/OP	4	1	685	44.1	GAD, SAD, AGR, PD, OCD, AD	USA
Hernandez et al. (2013)	1 OP	4	1	3158	39.9	PTSD	USA
Alvarez et al. (2012)	0 OP	4	1	40	39.4	PTSD	Spain
Bellani et al. (2012)	1 OP	4	0	205	36.6	GAD, SAD, SP, PD, PTSD Agoraphobia, OCD AD	USA
Castro e Couto et al. (2012)	1 OP	4	0	95	40.9	GAD, PD	Brazil
Chang et al. (2012)	1 OP	4	1	120	31.4	GAD, PTSD, SAD, PD, SP, OCD, AD	Taiwan
Dell'Osso et al. (2011)	0 OP	4	1	508	44.4	GAD, PD, OCD	Italy
Saunders et al. (2012)	0 IN/OP	4	1	736	42.6	SAD, SP, PD, OCD, AD	USA
Tsai et al. (2012)	0 OP	4	0	306	37.0	GAD, SAD, SP, AGR, PD, AD	Taiwan
Fracalanza et al. (2011)	1 OP	4	0	62	40.0	GAD, PTSD, SAD, PD, OCD	Canada
Okan Ibiloglu and Caykoylu (2011)	0 IN/OP	4	0	96	38.7	PTSD, SP, PD, OCD	Turkey
Watson et al. (2011)	0 OP	4	0	165	39.5	AD	Australia
Altshuler et al. (2010)	1 OP	4	1	711	41.9	PTSD, SAD, SP, PD, OCD, AD	USA
Koyuncu et al. (2010)	0 OP	4	1	214	34.7	GAD, PTSD, SAD, SP, PD, OCD	Turkey
Magalhães et al. (2010)	0 OP	4	0	259	41.6	OCD, AD	Brazil
Mantere et al. (2010)	0 IN/OP	4	0	144	38.0	GAD, PTSD, SAD, SP, PD, OCD, AD	Finland
Azorin et al. (2009)	0 IN	4	1	1090	43.0	GAD, PTSD, SAD, AGR, PD, OCD, PD	France
Nery-Fernandes et al. (2009)	0 OP	4	1	62	42.0	GAD, PTSD, SAD, AGR, PD, OCD, PD	Brazil
Grabski et al. (2008)	0 OP	4	0	73	44.6	GAD, SAD, SP, PD, PTSD Agoraphobia, OCD AD	Poland
Ciapparelli et al. (2007)	0 OP	4	1	56	35.8	SAD, PD, OCD, AD	Italy
Kauer-Sant'Anna et al. (2007)	0 OP	4	1	162	43.1	GAD, SAD, SP, PD, PTSD Agoraphobia, OCD AD	Brazil
Levander et al. (2007)	1 OP	4	0	350	41.7	PTSD, SAD, SP, PD, OCD, AD	USA
Simon et al. (2007)	1 OP	4	1	120	44.2	GAD, PTSD, SAD, AGR, PD, OCD, AD	USA
Altindag Abdurrahman et al. (2006)	0 OP	4	1	70	34.7	GAD, SAD, SP, PD, PTSD Agoraphobia, OCD AD	Turkey
Otto et al. (2006)	0 OP	4	0	918	40.6	GAD, PTSD, SAD, AGR, PD, OCD, AD	USA
Pashinian et al. (2006)	0 OP	4	1	56	28.9	SAD, SP, PD, OCD	Israel
Pini et al. (2006)	0 IN	4	1	189	33.5	SAD, PD, OCD	Italy
Wilk et al. (2006)	0 OP	4	1	154	NR	PD	USA
Zutshi et al. (2006)	1 OP	4	1	80	30.0	GAD, SAD, PD, OCD, AD	India
Bauer et al. (2005)	1 IN	4	0	328	46.6	PTSD, PD, OCD, AD	USA
Boylan et al. (2004)	0 OP	4	0	138	42.0	GAD, PTSD, SAD, SP, PD, OCD, AD	Canada
Simon et al. (2004)	1 OP	4	0	475	41.7	GAD, PTSD, SAD, AGR, PD, OCD, AD	USA
Henry et al. (2003)	0 IN	4	1	318	53.3	PD, OCD, AD	France
Pini et al. (2003)	0 IN	4	0	151	36.2	PD	Italy
Simon et al. (2003)	1 OP	4	1	122	40.8	GAD, PTSD, SAD, SP, PD, OCD, AD	USA
Craig et al. (2002)	1 IN/OP	4	0	138	NR	PD, OCD	USA
Tamam and Ozpoyraz (2002)	0 OP	4	1	70	33.4	GAD, PTSD, SAD, SP, PD, OCD, AD	Turkey
Vieta et al. (2001)	0 OP	4	0	129	40.9	SAD, SP, PD, OCD	Spain
Yerevanian et al. (2001)	0 OP	4	1	35	39.8	GAD, PTSD, SP, PD, OCD, AD	USA
Krüger et al. (2000)	1 IN	4	1	143	44.0	GAD, SP, PD, OCD	Germany
Cassano et al. (1999)	0 IN	4	1	48	33.5	SAD, PD, OCD	Italy
Pini et al. (1999)	0 IN	4	0	125	24.7	GAD, SAD, SP, PD, OCD	Italy
Cosoff and Hafner (1998)	0 IN	4	1	20	34.8	GAD, SAD, SP, PD, OCD, AD	Australia
Strakowski et al. (1998)	0 IN	4	0	77	25.0	GAD, PTSD, SAD, SP, PD, OCD	USA
Pini et al. (1997)	0 OP	4	0	24	37.9	GAD, SAD, SP, PD, OCD, AD	Italy
Chen and Dilsaver (1995a,b)	0 OP	4	0	167	20.6	PD, OCD	USA
Krüger et al. (1995)	1 IN	4	1	37	49.0	OCD	Canada
Sharma et al. (1995)	0 IN/OP	4	1	25	37.8	GAD, SAD, SP, AGR, PD, OCD	Canada
Shoaib and Dilsaver (1995)	0 IN	3	1	41	33.1	PD	USA
Strakowski et al. (1995)	0 IN/OP	4	1	39	29.6	GAD, PTSD, OCD	USA
Young et al. (1993)	0 OP	4	1	81	37.6	GAD, PD, AD	Canada
Strakowski et al. (1992)	0 IN	4	1	41	31.6	SP, PD, OCD, AD	USA

AD = anxiety disorders. GAD = generalised anxiety disorder. NR = not reported. OCD = obsessive compulsive disorder. PD = panic Disorder. PTSD = posttraumatic stress disorder. RDC = research diagnostic criteria. SAD = social anxiety disorder. SP = simple phobia.
All studies used DSM (III, III-R, IV) criteria for the diagnoses of bipolar and anxiety disorders, except Young et al. (1993), using RDC (Research Diagnostic Criteria) criteria.
[a] 1 = convenience sample, 0 = consecutive sample.
[b] (IN) = Inpatient, (OP) = outpatient.
[c] 1 = low quality, 2 = low-to-medium quality, 3 = medium-to-high quality, 4 = high quality.
[d] 0 = no appreciable bias risk, 1 = low bias risk, 2 = low-to-medium bias risk, 3 = medium-to-high bias risk, and 4 = high bias risk.

using psychological interventions. There is some evidence in favour of CBT (Baer et al., 1985; Bowen and D'Arcy, 2003; Hamblen et al., 2004; Mueser et al., 2008; Mueser et al., 2007; Provencher et al., 2010; Rosenberg et al., 2004) (Cognitive Behavioural Therapy), and mindfulness-based cognitive therapy (Miklowitz et al., 2009; Williams et al., 2008), in the treatment of anxiety comorbid to bipolar disorder. On the other hand, interpersonal therapy (Frank et al., 2005) and family therapy (Gaudiano and Miller, 2005) would not seem to offer any significant benefit to this group. Finally, the co-occurrence of more than one anxiety disorder in an individual may limit the utility of psychotherapy in patients with bipolar disorder (Deckersbach et al., 2014).

6. Conclusion

Interest in the co-occurrence of bipolar disorder and anxiety disorders has grown markedly in the past two decades. Our results, in line with previous studies, suggest that anxiety disorders co-occur frequently in patients with bipolar illness. However, it is unclear if this is an expression of the pathology of two independent and distinct disorders or an additive interaction of the coexisting disorders.

More detailed information on the patterns of response to psychological and psychopharmacological interventions among those with bipolar disorder with or without anxiety disorders may be useful in further

delineating the aetiological significance (e.g. shared neurobiological mechanisms) of the co-occurrence of bipolar disorder and anxiety disorders. In addition, more in-depth examinations of the temporal relationship between the onset of bipolar disorder and anxiety disorders using longitudinal designs may be helpful in understanding aetiology and developing interventions that could delay or even prevent the onset of bipolar disorder among those at high risk. The diagnostic issues at the interface of affective and anxiety disorders are particularly difficult because of the substantial symptom overlap. Although some advances have recently been made, the treatment of co-existing conditions has clinically remained challenging. As with its companion studies on the prevalence of comorbidities, we hope that the current review will populate and generate the hypotheses. Paradoxes such as this can be a powerful catalyst for advancing knowledge.

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There was no funding source for this study. AJM had access to the raw data. BN had full access to all the data and had final responsibility for the decision to submit for publication. DN revised the final draft before being submitted.

Contributor

AJM designed the study and analysed the data. BN extracted the data and AJM supervised the data extraction. BN wrote and AJM revised subsequent drafts of the report. DN revised the final draft before being submitted.

Conflicts of Interest

The authors declared no conflicts of interest.

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