Webappendix A to

The prevalence, impact, and treatment of Generalized Anxiety Disorder in Bipolar disorder − Systematic review and meta-analysis by Preti et al

Contents:

1. Material and methods

a. Review of the literature

Two authors (KF, JV) developed the search code investigating the comorbidity of GAD with BD with searches in PubMed/MEDLINE, from inception until June 6th, 2015.
One reviewer (KNF) screened the titles and abstracts resulting from the search strategy, while a second reviewer (JV) verified. When the inclusion of a study was unclear, the full-text article was screened.
This review followed the recommendations of the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses (PRISMA) statement (1). A checklist concerning the PRISMA procedure is included at the end of this webappendix.

b. Literature search key words

The PubMed database was searched using a combination of search terms as follows:

"bipolar[All Fields] OR ("bipolar disorder"[MeSH Terms] OR ("bipolar"[All Fields] AND "disorder"[All Fields]) OR "bipolar disorder"[All Fields] OR "mania"[All Fields]) OR ("bipolar disorder"[MeSH Terms] OR ("bipolar"[All Fields] AND "disorder"[All Fields]) OR "bipolar disorder"[All Fields] OR "manic"[All Fields]) AND (generalized[All Fields] AND ("anxiety disorders"[MeSH Terms] OR ("anxiety"[All Fields] AND "disorders"[All Fields]) OR "anxiety disorders"[All Fields] OR ("anxiety"[All Fields] AND "disorder"[All Fields]) OR "anxiety disorder"[All Fields])) OR GAD[All Fields]".
Also the reference lists of books and reviews were scanned (2-4)

c. Criteria for study selection

- English language.
- Studies which include primary data concerning the existence of GAD in BD patients

d. Meta-analysis

i. Data abstraction and quality assessment

Two authors (JV, KF) used a standardized coding system previously pilot tested to extract the following data from the articles: authors names, publication year, location, sample size, criteria for diagnosis, procedure for diagnosis (whether this was conducted by standardized interview, semi-standardized interview or clinical decision), number of cases with BD, number of cases with GAD, number of cases with any other diagnostic group which had been used as comparison. Relevant data from each study were abstracted by one reviewer (KNF) and verified by a second reviewer (JV). Discrepancies in scoring were resolved through discussion.

ii. Data synthesis and implementation

Prevalence estimates were calculated using the variance-stabilizing Freeman-Tukey double arcsine transformation (5). The double arcsine transformation is known to outperform other proposed methods of prevalence estimates (6).

We applied the inverse variance method using both fixed-effect and random-effects models to estimate summary effects for all combined studies. It has been shown that the inverse-variance weight in fixed-effect meta-analysis is suboptimal when dealing with data with low prevalence (7).

In each meta-analysis, we synthesized the prevalence estimates using the double arcsine transformation, and then we back-transformed the pooled estimate to a proportion, so as to have an interpretable scale. In the random-effects model, we estimated the heterogeneity variance among studies using the empirical Bayes estimator (8), also known as Paule-Mandel estimator (9), and its 95% confidence interval (CI) using the Q-Profile method (10). Under the random-effects model, we also used the Hartung and Knapp (11) method as an alternative to infer about the summary effect. The method estimates the uncertainty for the overall treatment effect based on the t-distribution (with 'number of studies-1' degrees of freedom) and a weighted extension of the inverse variance formula accounting for the between-study heterogeneity.

Heterogeneity was assessed with Cochran's Q and I^2 statistics (12). A low P value (i.e. $p<0.10$) of the Q-statistic that variation in the study-specific effect estimates is due to heterogeneity beyond chance. For I^2, values between 0–40% might not be important; 30–60% may represent moderate heterogeneity; 50–90%: may represent substantial heterogeneity; 75–100% represent considerable heterogeneity (13).

We presented fixed- and random-effects summary estimates along with a corresponding 95% CI for each analysis in forest plots. Differences between fixed- and random-effects estimates suggest that there are differences between the point estimates from smaller and larger studies: such differences were examined in outcomes with 10 or more studies using funnel plots and Egger's (14) and Begg's regression test (15).

The Baujat plot was used to detect the contribution of each study to the overall heterogeneity (16). The Baujat plot reports on the x-axis the contribution of each study to the overall heterogeneity, while on the y-axis is reported the influence of each study on the overall treatment effect, calculated as the standardized difference of the overall treatment effect with and without each study.

To control for adequacy of the models and the identification of outliers, we used the radial plot (17, 18) and the standardized residuals plot (19) in relation to the random-effects model. For a random-effects model, the radial plot shows the sampling variance of the observed effect size or outcome against the amount of heterogeneity as estimated based on the model. As far as the standardized residuals plot is concerned, if a study fits the model, its standardized residual follows (asymptotically) a standard normal distribution. A large standardized residual (> 2 SD) for a study therefore may suggest that the study does not fit the assumed model (i.e., it may be an outlier).

When possible, differences in prevalence according to characteristics of individuals or of studies were estimated by comparing prevalence between subgroups of studies. We used meta-regression techniques to evaluate the impact of clinical variables: gender ratio, mean age of the sample, diagnostic procedure. Subgroup analysis was applied to estimate

the impact of study characteristics: subtypes of bipolar disorder, on prevalence rates of generalized anxiety.

Meta-analysis was carried out with the ‘meta’ package (20) and the ‘metafor’ package (19) running in R version 3.0.2 (21).

2. Results

a. List of studies

The initial MEDLINE search returned 1300 articles, whereas another 14 papers were identified from other sources. After eliminating unrelated papers on the basis of their titles and abstracts, 431 remained for further evaluation. Eventually 30 papers were eligible (7 studies from the MEDLINE search and 23 from other sources). Fifteen of them included data with cross sectional prevalence (22-36). However the Simon et al studies (32, 35, 36) include up to the first 500 patients from the STEP-BD study while the Otto et al (31) includes the first 1000 patients from the same study. Therefore in the current analysis only the Otto et al. (31) study was utilized. Thus 13 studies were eligible for the analysis for point prevalence (22-34). One of the Simon et al studies (32) was used only to calculate the comorbidity rates separately for BD-I and BD-II patients. Another 19 papers contained data concerning the lifetime prevalence (30, 32-34, 37-51) and were included in the analysis. However, the Rihmer et al., 2001 (46) reported data that also were reported in Szadoczky et al., 1998 (48), and data from Rihmer et al., 2001 (46) was used only to calculate the comorbidity rates separately for BD-I and BD-II patients. Overall data from 28 independent studies were used in total. The PRISMA flowchart is shown in figure 1 in the main manuscript.

i. Cross sectional comorbidity studies

1. Bellani M, Hatch JP, Nicoletti MA, Ertola AE, Zunta-Soares G, Swann AC, et al. Does anxiety increase impulsivity in patients with bipolar disorder or major depressive disorder? J Psychiatr Res. 2012; 46(5): 616-21.

2. Boylan KR, Bieling PJ, Marriott M, Begin H, Young LT, MacQueen GM. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. J Clin Psychiatry. 2004; 65(8): 1106-13.

3. Chang YH, Chen SL, Chen SH, Chu CH, Lee SY, Yang HF, et al. Low anxiety disorder comorbidity rate in bipolar disorders in Han Chinese in Taiwan. Prog Neuropsychopharmacol Biol Psychiatry. 2012; 36(1): 194-7.

4. Cosoff SJ, Hafner RJ. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. Aust N Z J Psychiatry. 1998; 32(1): 67-72.

5. Dell'Osso B, Buoli M, Bortolussi S, Camuri G, Vecchi V, Altamura AC. Patterns of Axis I comorbidity in relation to age in patients with Bipolar Disorder: a cross-sectional analysis. J Affect Disord. 2011; 130(1-2): 318-22.

6. Kauer-Sant'Anna M, Frey BN, Andreazza AC, Cereser KM, Gazalle FK, Tramontina J, et al. Anxiety comorbidity and quality of life in bipolar disorder patients. Can J Psychiatry. 2007; 52(3): 175-81.

7. Koyuncu A, Tukel R, Ozyildirim I, Meteris H, Yazici O. Impact of obsessive-compulsive disorder comorbidity on the sociodemographic and clinical features of patients with bipolar disorder. Compr Psychiatry. 2010; 51(3): 293-7.

8. Mantere O, Melartin TK, Suominen K, Rytsala HJ, Valtonen HM, Arvilommi P, et al. Differences in Axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. J Clin Psychiatry. 2006; 67(4): 584-93.

9. McElroy SL, Altshuler LL, Suppes T, Keck PE, Jr., Frye MA, Denicoff KD, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry. 2001; 158(3): 420-6.

10. Otto MW, Simon NM, Wisniewski SR, Miklowitz DJ, Kogan JN, Reilly-Harrington NA, et al. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. Br J Psychiatry. 2006; 189: 20-5.

11. Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2004; 161(12): 2222-9.

12. Tamam L, Ozpoyraz N. Comorbidity of anxiety disorder among patients with bipolar I disorder in remission. Psychopathology. 2002; 35(4): 203-9.

13. Zutshi A, Reddy YC, Thennarasu K, Chandrashekhar CR. Comorbidity of anxiety disorders in patients with remitted bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2006; 256(7): 428-36.

ii. Lifetime comorbidity studies

1. Azorin JM, Kaladjian A, Adida M, Hantouche EG, Hameg A, Lancrenon S, et al. Psychopathological correlates of lifetime anxiety comorbidity in bipolar I patients: findings from a French national cohort. Psychopathology. 2009; 42(6): 380-6.

2. Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. Am J Psychiatry. 2009; 166(11): 1238-43.

3. Goldstein BI, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. Bipolar Disord. 2008; 10(1): 67-78.

4. Grabski B, Dudek D, Datka W, Mączka G, Zięba A. Lifetime anxiety and substance use disorder comorbidity in bipolar disorder and its relationship to selected variables. Gender and bipolar subtype differences in comorbidity. Arch Psychiatry Psychother. 2008; 3: 5-15.

5. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychol Med. 1997; 27(5): 1079-89.

6. Mantere O, Isometsa E, Ketokivi M, Kiviruusu O, Suominen K, Valtonen HM, et al. A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. Bipolar Disord. 2010; 12(3): 271-84.

7. McElroy SL, Altshuler LL, Suppes T, Keck PE, Jr., Frye MA, Denicoff KD, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry. 2001; 158(3): 420-6.

8. Nakagawa A, Grunebaum MF, Sullivan GM, Currier D, Ellis SP, Burke AK, et al. Comorbid anxiety in bipolar disorder: does it have an independent effect on suicidality? Bipolar Disord. 2008; 10(4): 530-8.

9. Nery-Fernandes F, Quarantini LC, Galvao-De-Almeida A, Rocha MV, Kapczinski F, Miranda-Scippa A. Lower rates of comorbidities in euthymic bipolar patients. World J Biol Psychiatry. 2009; 10(4 Pt 2): 474-9.

10. Pini S, Cassano GB, Simonini E, Savino M, Russo A, Montgomery SA. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. J Affect Disord. 1997; 42(2-3): 145-53.

11. Rihmer Z, Szadoczky E, Furedi J, Kiss K, Papp Z. Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. J Affect Disord. 2001; 67(1-3): 175-9.

12. Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry. 2004; 161(12): 2222-9.

13. Slama F, Bellivier F, Henry C, Rousseva A, Etain B, Rouillon F, et al. Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. J Clin Psychiatry. 2004; 65(8): 1035-9.

14. Szadoczky E, Papp Z, Vitrai J, Rihmer Z, Furedi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. J Affect Disord. 1998; 50(2-3): 153-62.

15. Tsai HC, Lu MK, Yang YK, Huang MC, Yeh TL, Chen WJ, et al. Empirically derived subgroups of bipolar I patients with different comorbidity patterns of anxiety and substance use disorders in Han Chinese population. J Affect Disord. 2012; 136(1-2): 81-9.

16. Tamam L, Ozpoyraz N. Comorbidity of anxiety disorder among patients with bipolar I disorder in remission. Psychopathology. 2002; 35(4): 203-9.

17. Yerevanian BI, Koek RJ, Ramdev S. Anxiety disorders comorbidity in mood disorder subgroups: data from a mood disorders clinic. J Affect Disord. 2001; 67(1-3): 167-73.

18. Young LT, Cooke RG, Robb JC, Levitt AJ, Joffe RT. Anxious and non-anxious bipolar disorder. J Affect Disord. 1993; 29(1): 49-52.

19. Zutshi A, Reddy YC, Thennarasu K, Chandrashekhar CR. Comorbidity of anxiety disorders in patients with remitted bipolar disorder. Eur Arch Psychiatry Clin Neurosci. 2006; 256(7): 428-36.

b. Meta-analysis

Sample size and males/females ratio

Sample sizes varied widely across studies (N=20 to 918 in studies with point prevalence estimates; 24 to 1411 in studies with lifetime estimates), with a median of 191 participants and interquantile range (IQR) (80, 325) in cross sectional-studies, and 119 (71-297) in lifetime studies (Figure 2).
Females were overrepresented in samples, with a median male/female ratio of 0.70 IQR (0.55-0.89) in point prevalence studies and 0.74 (0.69-0.92) in lifetime studies.

Age interval

Mean age in the studies was 37 (median = 38; IQR (34.8, 41.0); range 30 to 43) in point prevalence studies; it was 38.9 (median = 38.9; IQR (37.2, 41.9); range 30 to 44; five studies did not report the data) in lifetime studies.
There was a negative correlation between mean age in the sample and gender ratio: -0.62 (95%CI: -0.87 to -0.11; P-value = 0.021) in point prevalence studies; -0.64 (-0.87 to -0.16; P-value = 0.013) in lifetime studies. Studies with more males had younger participants than studies with more female participants.

Diagnostic procedure

In studies with point prevalence estimates, the *Structured Clinical Interview for DSM - SCID* was applied in 12 studies to derive the diagnosis, and just one applied the *Schedule for Affective Disorders and Schizophrenia – Lifetime version* (SADS-L; main document

Table 1). In studies with lifetime estimates, the SCID was applied in 10 studies, while 9 studies applied other standardized procedures to drawn the diagnosis (see main document Table 2).

Point prevalence of comorbid GAD

There were 12 studies detailing data on point prevalence of generalized anxiety disorder in patients diagnosed with bipolar disorder (Simon et al. 2004 and Otto et al., 2006 had an overlapping sample) (31, 32).
The fixed-effects point prevalence estimate of generalized anxiety disorder in patients diagnosed with bipolar disorder was 9.6% (95%CI: 8.5% to 10.7%).
The overall random-effects point prevalence estimate of generalized anxiety disorder in patients diagnosed with BD was 11.5% (95% CI: 6.6% to 17.4%) (main manuscript Figure 3).
Point prevalence of generalized anxiety disorder varied across studies, depending on the characteristics of the samples (main manuscript Figure 3).
No relevant publication bias emerged from the funnel plot (webappendix Figure A, on the left) and the Egger's or and Mazumdar rank correlation test (webappendix Figure B, on the left).

Figure A. Funnel plot of the point and lifetime prevalence of Generalized anxiety disorder (GAD) in patients with bipolar disorder

Studies with Point prevalence estimates **Studies with Lifetime estimates**

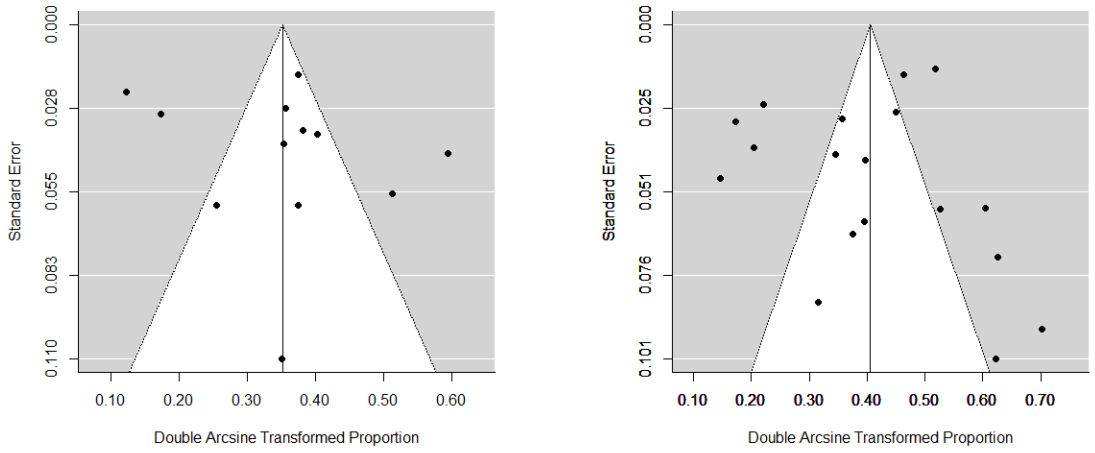
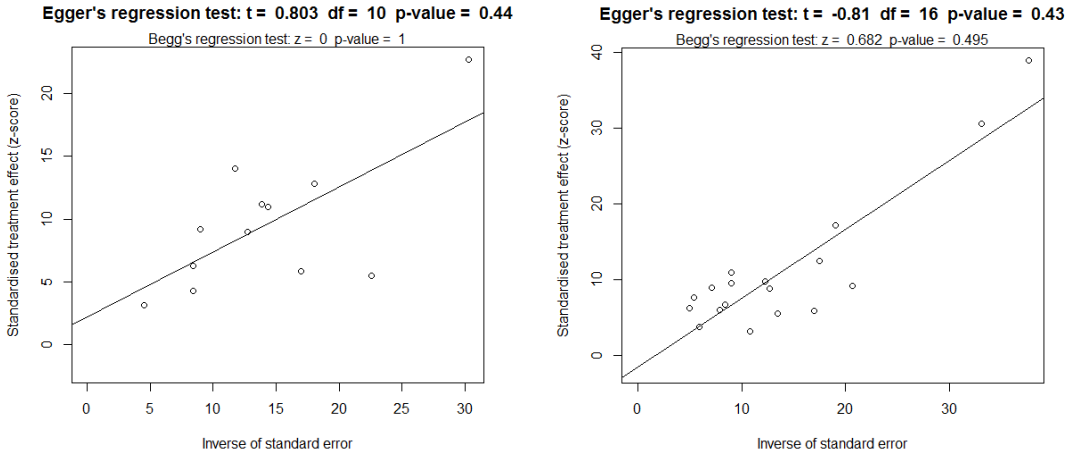


Figure B. Egger's regression test of the point and lifetime prevalence of Generalized anxiety disorder (GAD) in patients with bipolar disorder

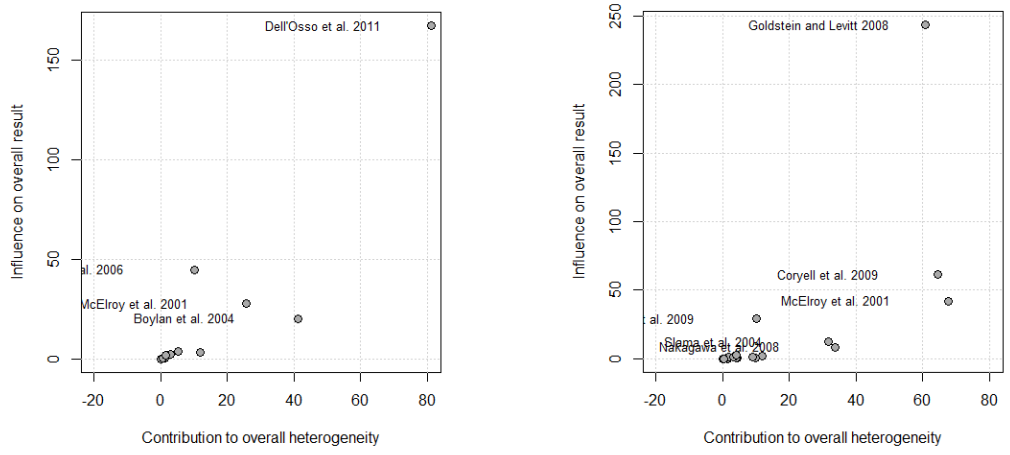
Studies with Point estimates **Studies with Lifetime estimates**



Heterogeneity was substantial: I^2 = 94% (95%CI: 91.2% – 95.9%) (main manuscript table 3). However, the Baujat plot (webappendix Figure C) suggested that the studies with the greatest contribution to the overall heterogeneity had a small influence on the result but one (26).

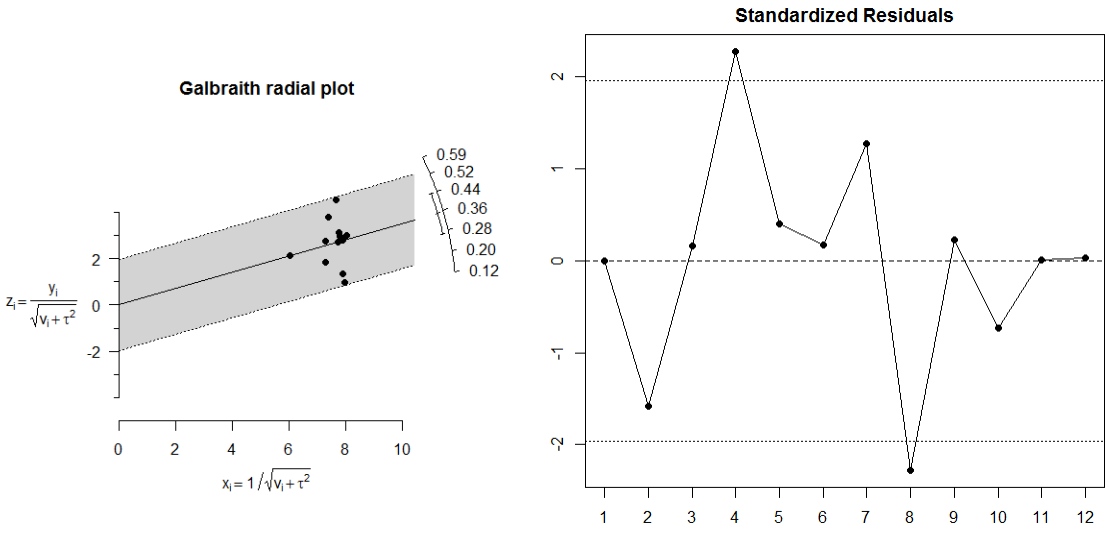
Figure C. Baujat plot of the prevalence of Generalized anxiety disorder (GAD) in patients with bipolar disorder

Studies with Point estimates **Studies with Lifetime estimates**



The standardized residuals plot, but not the radial plot, converged with the Baujat plot about one sample (26) being potential outlier (webappendix Figure D). Indeed, this sample had the lowest point prevalence estimated prevalence of GAD.

Figure D. Radial plot and standardized residuals plot of the Point prevalence of Generalized anxiety disorder (GAD) in patients with bipolar disorder – Random-effects model with empirical Bayes estimator



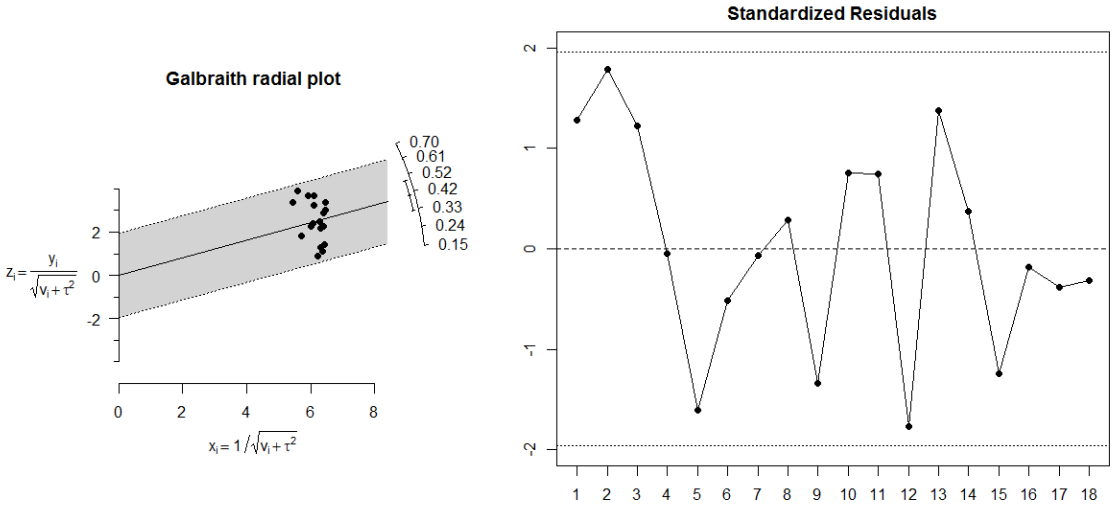
Reanalysis of data without the outlier produced a small increase in overall fixed-effects point prevalence estimate of generalized anxiety disorder in patients diagnosed with bipolar disorder, which was now 12.2% (10.9% to 13.5%), with no statistically significant change in the random-effects estimates: 12.9% (8.2% to 18.6%). This later value should be considered to be the most appropriate to consider as the cross sectional estimate. Subgroup analyses, with inclusion/exclusion of studies according to the nature of the sample, did not reveal relevant changes in the estimates of the random-effects model, nor a substantial attenuation of heterogeneity (main manuscript Table 3 for details). In meta-regression analyses, nor age (coefficient = -0.012; z = -0.75; P-value = 0.47), neither gender ratio (coefficient = 0.099; z = 0.79; P-value = 0.45) were related to the estimates in the best model (that without the outlier).

Lifetime prevalence of comorbid GAD

There were 18 studies detailing data on lifetime prevalence of generalized anxiety disorder in patients diagnosed with BD (main manuscript Figure 2), yielding 22 rates (main manuscript Table 2). The fixed-effect lifetime estimate of GAD in patients diagnosed with BD was 15.8% (95%CI: 14.8% to 16.9%). The overall random-effects lifetime estimate of generalized anxiety disorder in patients diagnosed with bipolar disorder was 15.1% (95% CI: 9.7% to 21.5%).
Again, lifetime prevalence of generalized anxiety disorder varied across studies, depending on the characteristics of the samples (main manuscript Figure 4). No relevant

publication bias emerged from the funnel plot (webappendix Figure A, on the right) and the Egger's or and Mazumdar rank correlation test (webappendix Figure B, on the right). Heterogeneity was substantial: I^2 = 94.7% (95%CI: 92.8% – 96.0%). The Baujat plot suggested that just one study among those with the greatest contribution to the overall heterogeneity also had the greatest influence on the result (webappendix Figure C, on the right). However, the radial plot and the standardized residuals plot suggested no potential outlier (webappendix Figure E).

Figure E. Radial plot and standardized residuals plot of the Lifetime prevalence of Generalized anxiety disorder (GAD) in patients with bipolar disorder – Random-effects model with empirical Bayes estimator

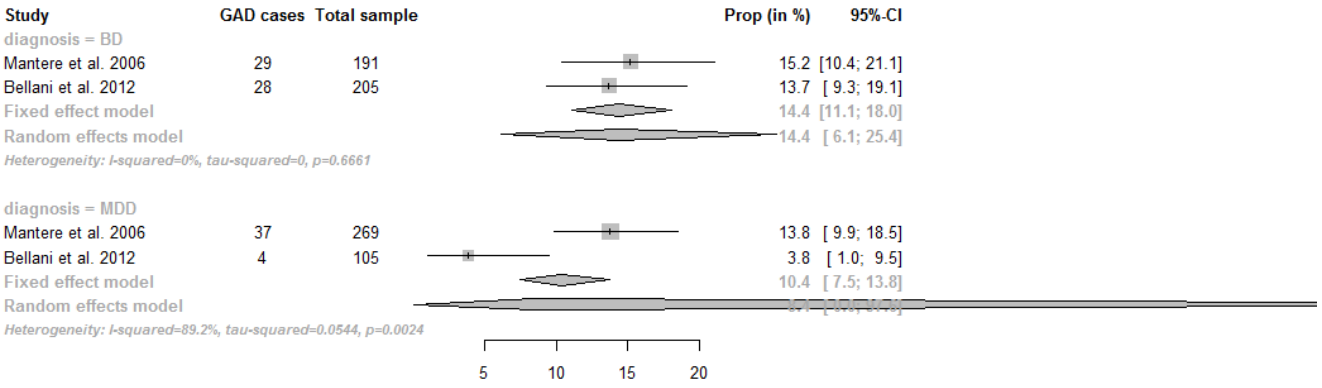


There was a trend for samples with bipolar disorder type I to have higher lifetime prevalence of GAD, while sample with bipolar disorder type II had a trend for a lower lifetime prevalence of GAD (20.1% vs. 12.5%.
Heterogeneity remained substantial in analyses by subgroup, suggesting sample diagnosis or phase of the disorder was not the main reason explaining it (main manuscript Table 3).
Meta-regression showed no relationship of estimates with age (coefficient = -0.004; z = -0.17; p = 0.86), gender ratio (coefficient = 0.195; z = 1.17; p = 0.25), or the diagnostic procedure (SCID vs any other: coefficient = -0.132; z = -0.85; p = 0.40).

Comparison of BD with other diagnosis

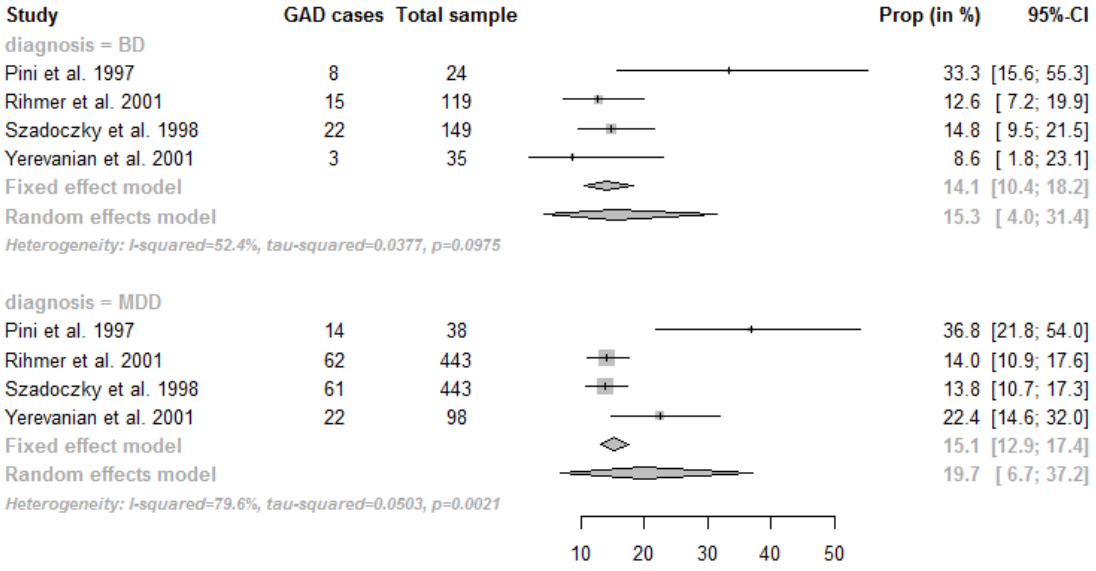
Just one study reported the prevalence of GAD in people without comorbid disorders (34). The estimated prevalence was 6%, lower than the prevalence found in patients with BD in the same study (23.8%) or the estimates found in the present meta-analysis. This might correspond to a true prevalence of 3-4% of GAD in the general population.
Two studies reported point prevalence estimates of GAD in patients with BD and with major depressive disorder (MDD). No statistically significant difference was detected in the point prevalence of GAD in patients with BD or MDD (webappendix Figure F).

Figure F. Point prevalence of generalized anxiety disorder (GAD) in patients with bipolar disorder or major depressive disorder



Test for subgroup differences (based on random-effects model): Q = 1.12, df = 1, P-value = 0.29.
Heterogeneity was substantial: I^2 = 75.2% (31.4% – 91.1%); Q = 12.1, df = 3, P-value = 0.007.
Four studies reported lifetime estimates of GAD in patients with BD and with MDD. No statistically significant difference was detected in the lifetime prevalence of GAD in patients with BD or MDD (webappendix Figure G).

Figure G. Lifetime prevalence of generalized anxiety disorder (GAD) in patients with bipolar disorder or major depressive disorder



Test for subgroup differences (based on random-effects model): Q = 0.38, df = 1, P-value = 0.53. Heterogeneity was substantial: I^2 = 66.9% (30% – 84.3%); Q = 21.1, df = 7, P-value = 0.0036.

c. Summary of results

The current meta-analysis analyzed data from 28 studies and a total of 2.975 patients from point prevalence studies and 4919 patients from lifetime studies.
The results suggest that the random-effects model was more appropriate for this dataset, and reported that the point prevalence of GAD in BD patients is 12.9% (irrespective of BD type) while the lifetime prevalence is 20.1% in BD-I and 12.5% in BD-II patients.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International Journal Of Surgery (London, England). 2010; 8(5): 336-41.
2. Fountoulakis KN. Bipolar Disorder: An Evidence-Based Guide to Manic Depression. Springer, 2015.
3. Goodwin F, Jamison K. Manic-depressive illness. 2nd ed. New York, Oxford University Press, 2007.
4. Nabavi B, Mitchell AJ, Nutt D. A Lifetime Prevalence of Comorbidity Between Bipolar Affective Disorder and Anxiety Disorders: A Meta-analysis of 52 Interview-based Studies of Psychiatric Population. EBioMedicine. 2015; 2(10): 1405-19.
5. Freeman M, Tukey J. Transformations related to the angular and the square root. Annals of Mathematical Statistics. 1950: 4.
6. Barendregt JJ, Doi SA, Lee YY, Norman RE, Vos T. Meta-analysis of prevalence. Journal Of Epidemiology And Community Health. 2013; 67(11): 974-8.
7. Miller J. The inverse of the Freeman-Tukey double arcsine transformation. The American Statistician. 1978: 32.
8. Morris CN. Parametric empirical Bayes inference: Theory and applications (with discussion). Journal of the American Statistical Association. 1983: 47-65.
9. Paule R, C., Mandel J. Consensus values and weighting factors. Journal of Research of the National Bureau of Standards. 1982: 377-85.
10. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. Statistics in medicine. 2007; 26(1): 37-52.
11. Knapp G, Hartung J. Improved tests for a random effects meta-regression with a single covariate. Statistics in medicine. 2003; 22(17): 2693-710.
12. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I2 index? Psychological methods. 2006; 11(2): 193-206.
13. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ (Clinical Research Ed). 2003; 327(7414): 557-60.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ (Clinical Research Ed). 1997; 315(7109): 629-34.
15. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics. 1994; 50(4): 1088-101.
16. Baujat B, Mahé C, Pignon J-P, Hill C. A graphical method for exploring heterogeneity in meta-analyses: application to a meta-analysis of 65 trials. Statistics in medicine. 2002; 21(18): 2641-52.
17. Galbraith RF. A note on graphical presentation of estimated odds ratios from several clinical trials. Statistics in medicine. 1988; 7(8): 889-94.
18. Galbraith R. Some Applications of Radial Plots. Journal of the American Statistical Association. 1994; (89): 1232-42.
19. Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. 2010: 1-48.
20. Schwarzer G. Meta-Analysis with R. R package version 3.7-1. 2014.
21. R Core T. R: A language and environment for statistical computing. Vienna, Austria, R Foundation for Statistical Computing. 2013.

22. Bellani M, Hatch JP, Nicoletti MA, Ertola AE, Zunta-Soares G, Swann AC, et al. Does anxiety increase impulsivity in patients with bipolar disorder or major depressive disorder? Journal Of Psychiatric Research. 2012; 46(5): 616-21.
23. Boylan KR, Bieling PJ, Marriott M, Begin H, Young LT, MacQueen GM. Impact of comorbid anxiety disorders on outcome in a cohort of patients with bipolar disorder. The Journal Of Clinical Psychiatry. 2004; 65(8): 1106-13.
24. Chang YH, Chen SL, Chen SH, Chu CH, Lee SY, Yang HF, et al. Low anxiety disorder comorbidity rate in bipolar disorders in Han Chinese in Taiwan. Prog Neuropsychopharmacol Biol Psychiatry. 2012; 36(1): 194-7.
25. Cosoff SJ, Hafner RJ. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. The Australian And New Zealand Journal Of Psychiatry. 1998; 32(1): 67-72.
26. Dell'Osso B, Buoli M, Bortolussi S, Camuri G, Vecchi V, Altamura AC. Patterns of Axis I comorbidity in relation to age in patients with Bipolar Disorder: a cross-sectional analysis. Journal Of Affective Disorders. 2011; 130(1-2): 318-22.
27. Kauer-Sant'Anna M, Frey BN, Andreazza AC, Cereser KM, Gazalle FK, Tramontina J, et al. Anxiety comorbidity and quality of life in bipolar disorder patients. Can J Psychiatry. 2007; 52(3): 175-81.
28. Koyuncu A, Tukel R, Ozyildirim I, Meteris H, Yazici O. Impact of obsessive-compulsive disorder comorbidity on the sociodemographic and clinical features of patients with bipolar disorder. Compr Psychiatry. 2010; 51(3): 293-7.
29. Mantere O, Melartin TK, Suominen K, Rytsälä HJ, Valtonen HM, Arvilommi P, et al. Differences in Axis I and II comorbidity between bipolar I and II disorders and major depressive disorder. The Journal Of Clinical Psychiatry. 2006; 67(4): 584-93.
30. McElroy SL, Altshuler LL, Suppes T, Keck PE, Jr., Frye MA, Denicoff KD, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. The American Journal Of Psychiatry. 2001; 158(3): 420-6.
31. Otto MW, Simon NM, Wisniewski SR, Miklowitz DJ, Kogan JN, Reilly-Harrington NA, et al. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. The British Journal Of Psychiatry: The Journal Of Mental Science. 2006; 189: 20-5.
32. Simon NM, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). The American Journal Of Psychiatry. 2004; 161(12): 2222-9.
33. Tamam L, Ozpoyraz N. Comorbidity of anxiety disorder among patients with bipolar I disorder in remission. Psychopathology. 2002; 35(4): 203-9.
34. Zutshi A, Reddy YCJ, Thennarasu K, Chandrashekhar CR. Comorbidity of anxiety disorders in patients with remitted bipolar disorder. European Archives Of Psychiatry And Clinical Neuroscience. 2006; 256(7): 428-36.
35. Simon NM, Zalta AK, Otto MW, Ostacher MJ, Fischmann D, Chow CW, et al. The association of comorbid anxiety disorders with suicide attempts and suicidal ideation in outpatients with bipolar disorder. J Psychiatr Res. 2007; 41(3-4): 255-64.

36. Simon NM, Smoller JW, Fava M, Sachs G, Racette SR, Perlis R, et al. Comparing anxiety disorders and anxiety-related traits in bipolar disorder and unipolar depression. J Psychiatr Res. 2003; 37(3): 187-92.
37. Azorin J-M, Kaladjian A, Adida M, Hantouche EG, Hameg A, Lancrenon S, et al. Psychopathological correlates of lifetime anxiety comorbidity in bipolar I patients: findings from a French national cohort. Psychopathology. 2009; 42(6): 380-6.
38. Coryell W, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. The American Journal Of Psychiatry. 2009; 166(11): 1238-43.
39. Goldstein BI, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. Bipolar Disorders. 2008; 10(1): 67-78.
40. Grabski B, Dudek D, Datka W, Mączka G, Zięba A. Lifetime anxiety and substance use disorder comorbidity in bipolar disorder and its relationship to selected variables. Gender and bipolar subtype differences in comorbidity. Arch Psychiatry Psychother. 2008; 3: 5-15.
41. Kessler RC, Rubinow DR, Holmes C, Abelson JM, Zhao S. The epidemiology of DSM-III-R bipolar I disorder in a general population survey. Psychological Medicine. 1997; 27(5): 1079-89.
42. Mantere O, Isometsa E, Ketokivi M, Kiviruusu O, Suominen K, Valtonen HM, et al. A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. Bipolar Disord. 2010; 12(3): 271-84.
43. Nakagawa A, Grunebaum MF, Sullivan GM, Currier D, Ellis SP, Burke AK, et al. Comorbid anxiety in bipolar disorder: does it have an independent effect on suicidality? Bipolar Disorders. 2008; 10(4): 530-8.
44. Nery-Fernandes F, Quarantini LC, Galvao-De-Almeida A, Rocha MV, Kapczinski F, Miranda-Scippa A. Lower rates of comorbidities in euthymic bipolar patients. World J Biol Psychiatry. 2009; 10(4 Pt 2): 474-9.
45. Pini S, Cassano GB, Simonini E, Savino M, Russo A, Montgomery SA. Prevalence of anxiety disorders comorbidity in bipolar depression, unipolar depression and dysthymia. Journal Of Affective Disorders. 1997; 42(2-3): 145-53.
46. Rihmer Z, Szádóczky E, Füredi J, Kiss K, Papp Z. Anxiety disorders comorbidity in bipolar I, bipolar II and unipolar major depression: results from a population-based study in Hungary. Journal Of Affective Disorders. 2001; 67(1-3): 175-9.
47. Slama F, Bellivier F, Henry C, Rousseva A, Etain B, Rouillon F, et al. Bipolar patients with suicidal behavior: toward the identification of a clinical subgroup. The Journal Of Clinical Psychiatry. 2004; 65(8): 1035-9.
48. Szádóczky E, Papp Zs, Vitrai J, Ríhmer Z, Füredi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. Journal Of Affective Disorders. 1998; 50(2-3): 153-62.
49. Tsai HC, Lu MK, Yang YK, Huang MC, Yeh TL, Chen WJ, et al. Empirically derived subgroups of bipolar I patients with different comorbidity patterns of anxiety and substance use disorders in Han Chinese population. J Affect Disord. 2012; 136(1-2): 81-9.
50. Yerevanian BI, Koek RJ, Ramdev S. Anxiety disorders comorbidity in mood disorder subgroups: data from a mood disorders clinic. Journal Of Affective Disorders. 2001; 67(1-3): 167-73.

51. Young LT, Cooke RG, Robb JC, Levitt AJ, Joffe RT. Anxious and non-anxious bipolar disorder. Journal Of Affective Disorders. 1993; 29(1): 49-52.