Iran J Psychiatry Behav Sci. 2016 September; 10(3):e3604. doi: 10.17795/ijpbs-3604.

Published online 2016 August 17. **Review Article**

Bipolar I and II Disorders; A Systematic Review and Meta-Analysis on Differences in Comorbid Obsessive-Compulsive Disorder

Andrea Amerio,[1,2,*] Brendon Stubbs,[3] Anna Odone,[4,5] Matteo Tonna,[6] Carlo Marchesi,[6] and S. Nassir Ghaemi[2,7]

[1]Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy
[2]Mood Disorders Program, Tufts Medical Center, Boston, MA, USA
[3]Institute of Psychiatry, Kings College London, London, UK
[4]School of Medicine-Public Health Unit, University of Parma, Parma, Italy
[5]Department of Global Health and Social Medicine, Harvard Medical School, Boston, MA, USA
[6]Department of Mental Health, Local Health Service, Parma, Italy
[7]Tufts University Medical School, Department of Psychiatry and Pharmacology, Boston, MA, USA

[*]*Corresponding author*: Andrea Amerio, Department of Clinical and Experimental Medicine, University of Parma, Parma, Italy. Tel: +39-0521903594, Fax: +39-0521347047, E-mail: andrea.amerio@studenti.unipr.it

Received 2015 July 21; **Revised** 2016 January 31; **Accepted** 2016 July 23.

Abstract

Context: More than half of the bipolar disorder (BD) cases have an additional diagnosis; one of the most difficult to manage is obsessive-compulsive disorder (OCD). Although some authors recently investigated the co-occurrence of anxiety and BD, the topic remains insufficiently studied. The current study aimed to investigate differences in comorbid OCD between BD-I and BD-II.
Evidence Acquisition: A systematic review and meta-analysis was conducted on the prevalence and predictors of comorbid BD-I/BD-II and OCD. Relevant papers published until June 30, 2015 were identified searching the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Library.
Results: Fourteen articles met the inclusion criteria. The pooled prevalence of BD-I in OCD was 3.9% (95% confidence interval (CI), 2.4 to 6.4, I2 = 83%, Q = 56) while that of BD-II in OCD was 13.5% (95% CI, 9.3 to 19.3, I2 = 89%, Q = 91). The pooled prevalence of OCD in BD-I was 21.7 (95% CI, 4.8 to 60.3, I2 = 84%, Q = 95). With regard to OCD-BD predictors, mean age and rate of males did not predict the prevalence of BD-I (β = 0.0731, 95% CI, -0.1097 to 0.256, z = 0.78; β = 0.035, 95% CI, -0.2356 to 0.1656, z = 0.34) and BD-II (β = 0.0577, 95% CI, -0.1942 to 0.0788, z = 0.83; β = -0.0317, 95% CI, -0.1483 to 0.085, z = 0.53) in OCD. The mean age explained some of the observed heterogeneity (R2 = 0.13; R2 = 0.08).
Conclusions: This first systematic review and meta-analysis of the prevalence and predictors of comorbid BD-I/BD-II and OCD suggests that BD-OCD comorbidity is a common condition in psychiatry. However, the available evidence does not allow to assess whether BD-I or BD-II are more common in patients with OCD.

Keywords: Bipolar I, Bipolar II, Obsessive-Compulsive: Comorbidity

1. Context

In a classic 1970 publication, the famous epidemiologist Alvan R. Feinstein defined comorbidity regarding a specific index condition, as any distinct additional entity that exists or may occur during the clinical course of a patient with the index disease under study (1). In the Feinstein formula, the implication was a different and independent disease occurred at the same time as another disease.

On the contrary, the diagnostic and statistical manual of mental disorders (DSM) explicitly produces overlapping clinical criteria for many diagnoses, especially mood and anxiety disorders, guaranteeing comorbidity in a quite different sense than in the medical meaning of the term as co-occurrence of independent diseases.

Psychiatric comorbidity is extremely common in bipolar disorder (BD). More than half of patients with BD have an additional disorders (2), one of the most difficult to manage is obsessive-compulsive disorder (OCD) (3-5).

However, although some authors recently investigated the co-occurrence of anxiety and BD, no meta-analysis regarding the prevalence or sub-group analyses specific to BD-I and BD-II were performed (6).

The present paper is the first systematic review and meta-analysis on the prevalence and predictors of comorbid BD-I/BD-II and OCD.

2. Objectives

The current review upgraded a previous systematic review and performed a meta-analysis to define the prevalence and predictors of comorbid BD-I/BD-II and OCD.

3. Data Sources

As done before (7), the review was conducted according to the methods recommended by the Cochrane collaboration (8) and the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (9), and documented the process and results in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (10).

3.1. Information Sources and Search Strategy

Studies were identified searching the electronic databases MEDLINE, Embase, PsycINFO and the Cochrane Library. Authors combined the search strategy of free text terms and exploded MESH headings for the topics of bipolar disorder and obsessive-compulsive disorder combined as follows: bipolar disorderor (BD), bipolar or manic depressive disorder, manic depressive, manic and obsessive-compulsive disorder (OCD), obsessive-compulsive. The strategy was first developed in MEDLINE and then adaptedto the other databases (appendix 1. in supplementary file). Studies published in English untill June 30, 2015 were included. In addition, further studies were retrieved from reference listing of relevant articles and consultation with experts in the field.

3.2. Inclusion Criteria

3.2.1. Study Population and Study Design

The studies that included subjects with BD and OCD with specified diagnostic criteria were considered. Studies that considered subjects with bipolar and obsessive-compulsive spectrums with specified diagnostic criteria were also included (11, 12). Participants of both genders older than six years were considered. Studies conducted on subjects with physical comorbidities were excluded as non-representative of the study population (13, 14).

Both population- and hospital-based studies were included. Among hospital-based studies, inpatients, day-hospital and outpatient subjects were included while emergency care records were excluded as non-representative. All experimental and observational study designs were included apart from case reports. Narrative and systematic reviews, letters to the editor and book chapters were excluded.

3.2.2. Outcome Measures

Primary outcomes were i) lifetime prevalence of comorbid OCD in patients with BD-I/BD-II and ii) lifetime prevalence of comorbid BD-I/BD-II in patients with OCD. Studies that reported data only about the current prevalence were excluded (15). Secondary outcomes were potential predictors of comorbidity between BD-I/BD-II and OCD.

4. Study Selection and Data Extraction

Identified studies were independently reviewed for eligibility by two authors in a two-step process; a first screening was performed based on title and abstract while full texts were retrieved for the second screening. At both stages disagreements by reviewers were resolved by consensus. Data were extracted by one author and supervised by a second one using an ad-hoc developed data extraction spreadsheet. The data extraction spreadsheet was piloted on 10 randomly selected papers and modified accordingly.

4.1. Quality Assessment

The same authors who performed data extraction independently assessed the quality of selected studies using the checklist developed by Downs and Black, both for randomised and non-randomised studies (16). Disagreements by reviewers were resolved by consensus. Table 1 shows the quality assessment total score assigned to each study.

4.2. Meta-Analysis

Individual study data were pooled using DerSimonian-Laird method (29) with comprehensive Meta-Analysis software ver. 3. Due to the anticipated heterogeneity, a random effects meta-analysis was employed. First, the data on the prevalence of BD-I and BD-II in patients with OCD were pooled separately; next the data on the prevalence of OCD in patients with BD-I and BD-II were pooled separately. Heterogeneity was assessed with the I2 and Q statistic for each analysis. Further, meta-regression analyses were conducted to investigate potential moderators if available data included (mean age, rate of males and duration of illness) with comprehensive Meta-Analysis ver. 3. Publication bias was assessed with a visual inspection of funnel plots (8), the Begg-Mazumdar Kendall's tau (30) and the Egger test (31).

5. Results

One thousand and two hundred eighty-two potential studies were identified by searching the selected databases and listing references of relevant articles. After removing duplicates, 894 articles were retrieved. Studies were

Table 1. Studies Met the Inclusion Criteria for Systematic Review

References	Study Design	Country	Study Population	Sample Size	Diagnosis Assessment	Quality [a]
Population-Based Studies						
Angst, J. et al. 2004 (11)	Prospective cohort study	Switzerland	591 subjects recruited at age 19/20 and assessed over 20 years: OCD (n = 30)	30	Broad definition for BD and OCD; DSM-IV	26/31
Hospital-Based Studies: Adults						
Bogetto, F. et al. 1999 (16)	Case-control study	Italy	OCD (n = 160, mean age: males 32.1 ± 13.0, females 36.9 ± 11.4 years)	160	NS; DSM-IV	21/31
Dilsaver, S.C. et al. 2008 (17)	Case-control study	USA	187 Latino pt. enrolled consecutively from 2001 to 2003: BD-I (n = 69, mean age = 34.9 ± 11.8 years)	69	SCID-CV; DSM-IV	20/31
Hantouche, E.G. et al. 2003 (18)	Case-control study	France	OCD (n = 628, mean age CYC-OCD = 35 ± 12, mean age NC-OCD = 36 ± 14 years)	628	NS; DSM-IV	24/31
Kim, S.W. et al. 2014 (19)	Cross-sectional study	South Korea	BD-I (n = 174, age > 18 years)	174	SCID; DSM-IV	22/31
Lensi, P. et al. 1996 (20)	Case-control study	Italy	OCD (n = 263, mean age = 33.1 years)	263	NS; DSM-III-R	21/31
Maina, G. et al. 2007 (21)	Case-control study	Italy	OCD (n = 204, mean age = 34.7 ± 12.1 years)	204	SCID; DSM-IV	21/31
Marazziti, D. et al. 2002 (22)	Cross-sectional study	Italy	OCD (n = 117, mean age=30 ± 9.3 years)	117	SCID-P; DSM-IV	21/31
Perugi, G. et al. 1997 (23)	Case-control study	Italy	OCD (n = 315, mean age: BD-OCD = 32.8 ± 12.2, OCD = 32.5 ± 12.6 years)	345	NS; DSM-III-R	22/31
Perugi, G. et al. 1998 (24)	Case-control study	Italy	OCD (n = 135, mean age = 38.4 ± 13.3 years)	135	NS; DSM-III-R	21/31
Perugi, G. et al. 1999 (25)	Case-control study	Italy	269 pt. enrolled consecutively from 1993 to 1995: OCD (n = 79, mean age = 30.4 ± 11.8 years)	79	SCID-Up-R; DSM-III-R	20/31
Perugi, G. et al. 2002 (26)	Case-control study	Italy	OCD-MDE (n = 68, mean age = 34.2 ± 12.5 years); BD-OCD (n = 38, mean age=35.9 ± 12.2 years)	68	SCID; DSM-IV	20/31
Shashidhara, M. et al. 2015 (27)	Cross-sectional study	India	BD-I (n = 396, age > 18 years)	396	SCID; DSM-IV	23/31
Timpano, K.R. et al. 2012 (28)	Case-control study	USA	OCD (n = 605, mean age = 39.2 years)	605	SCID-P; DSM-IV	20/31

Abbreviations: BD: bipolar disorder; BD-I: bipolar disorder type I; OCD: obsessive-compulsive disorder; MDE: major depressive episode; NS: not specified; Pt.: patients; DSM: diagnostic and statistical manual of mental disorders; SCID: structured clinical interview; SCID-P: structured clinical interview patient version; SCID-CV: structured clinical interview clinical version; SCID-Up-R: structured clinical interview Upjohn version.
[a] Checklist for measuring study quality developed by Downs and Black.

screened and selected on the basis of pre-specified inclusion and exclusion criteria (Figure 1). The search identified 14 articles appropriate to be included in the systematic review: three articles about comorbid OCD in BD-I (8, 22, 31) and eleven articles about comorbid BD-I/BD-II in OCD (12, 17, 19, 21-27, 32).

5.1. Comorbid BD in OCD

5.1.1. Study Characteristics

The characteristics of included studies are reported in Table 1. Nine of the eleven studies were case-control studies, one cross-sectional study and one prospective cohort study. One study (9%) was population-based while the majority (n = 10, 91%) were hospital-based. Totally, 2,634 pa-

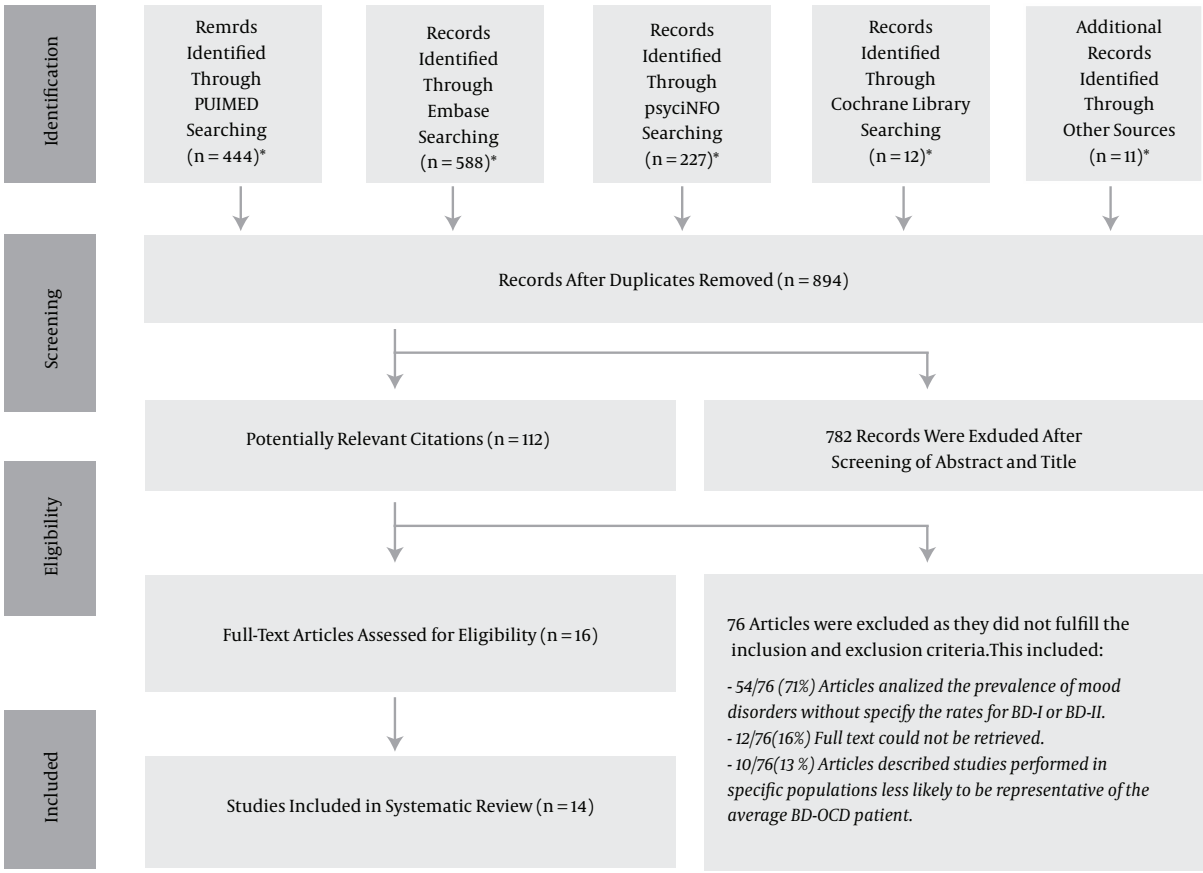

Figure 1. Flow Diagram of Selected Articles. *Search strategy limited to June 2015, English language and human subjects older than six years old

tients with OCD were represented among the eleven included studies. The mean age of patients with OCD was 34.7 ± 2.96 years and 43.8% were male (36.6%-50%). The majority of the studies were conducted in Europe (n = 9, 82%). In all the considered studies, diagnosis of BD-I/BD-II and OCD were based on the DSM criteria and they were established using validated assessment scales.

5.2. Meta-analysis of the pooled prevalence of BD-I/BD-II in patients with OCD

It was possible to pool data from 2,444 patients with OCD across 10 studies to found the prevalence of BD-I as 3.9% (95% CI, 2.4 to 6.4, I2 = 83%, Q = 56) (Figure 2A). Begg (tau = 1, P = 0.4) or Egger (intercept = -2.9, P = 0.19) did not indicate any evidence of publication bias.

It was possible to pool data from 2,634 patients with OCD across 12 studies to found the prevalence of BD-II as 13.5% (95% CI, 9.3 to 19.3, I2 = 89, Q = 91) (Figure 2B). There was no evidence of publication bias (Begg = 1.7, P = 0.2; Egger = 4.8, P = 0.15).

5.3. Predictors of the Prevalence of BD-I/BD-II in Patients with OCD

Mean age did not predict the prevalence of BD-I in OCD (β = 0.0731, 95% CI, -0.1097 to 0.256, z = 0.78), but it did explain some of the observed heterogeneity (R2 = 0.13). The rate of males did not moderate the prevalence of BD-I (β = 0.035, 95% CI, 0.2356 to 0.1656, z = -0.34). Mean age did not moderate the prevalence of BD-II (β = -0.0577, 95% CI, -0.1942 to 0.0788, z = -0.83), but it did explain a small amount of the observed heterogeneity (R2 = 0.08). Moreover, the rate of males was not related to the prevalence of BD-II (β = -0.0317, 95% CI, -0.1483 to 0.085, z =-0.53).

5.4. Comorbid OCD in BD

5.4.1. Study Characteristics

The characteristics of the included studies are reported in Table 1. Two studies were cross-sectional and one case-control. All the studies were hospital-based and conducted in non-European countries. Totally, 639 patients with BD-I were evaluated in the three included studies. The mean

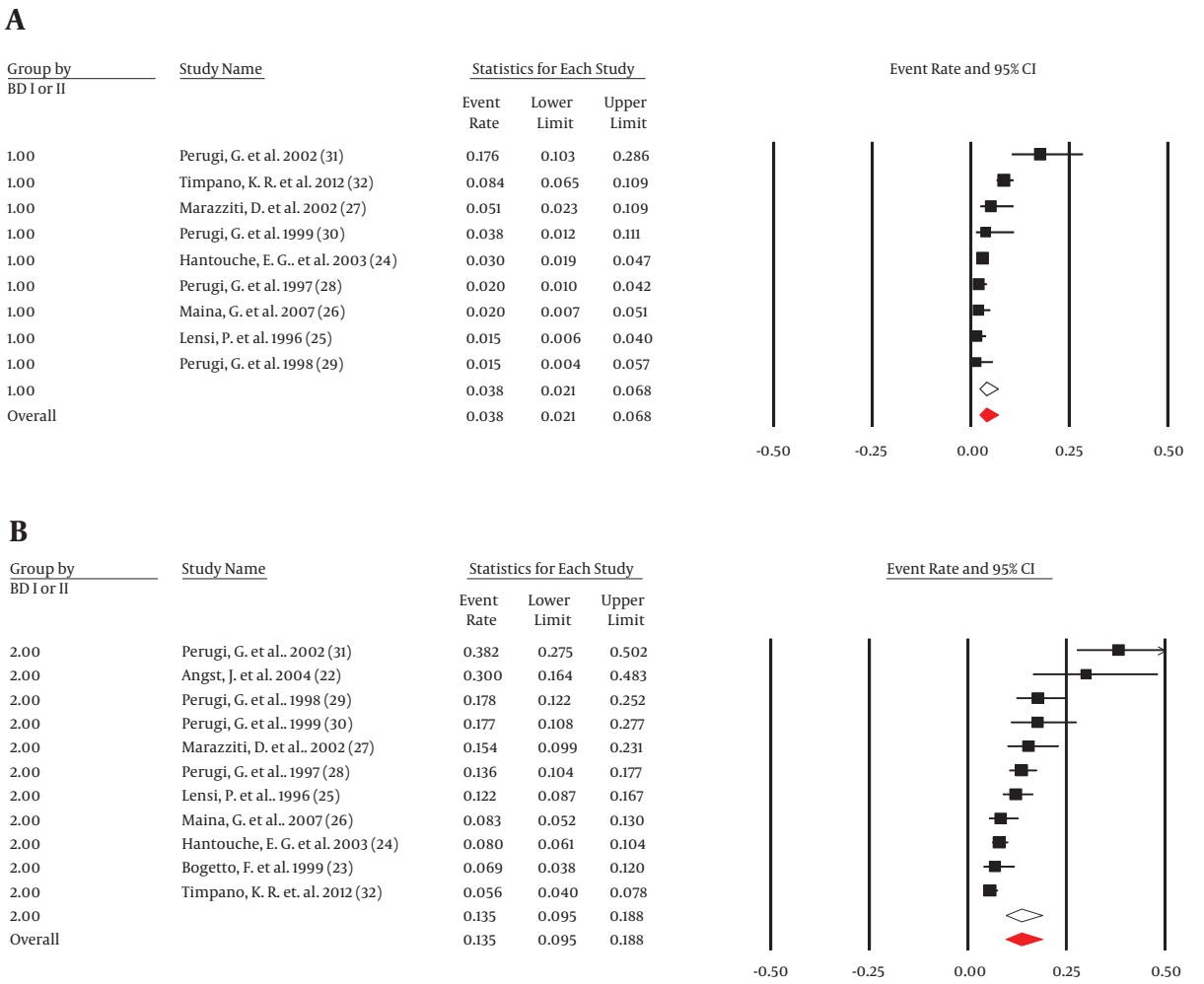

Figure 2. A, Pooled prevalence of bipolar disorder type-I in patients with obsessive-compulsive disorder; B, Pooled prevalence of bipolar disorder type-II in Patients with obsessive-compulsive disorder.

age of patients with BD was 36.8 ± 5.8 years and 45% were male (36% - 60.5%). In all the considered studies, diagnosis of BD-I and OCD were based on the DSM criteria and were established using validated assessment scales.

5.5. Meta-analysis of the pooled prevalence of OCD in patients with BD-I

It was possible to pool data from three studies with 639 patients with BD-I, establishing a pooled prevalence of OCD at 21.7% (95% CI, 4.8 to 60.3, Q = 95, I2 = 84%) (Figure 3). Egger (intercept = 48, P = 0.2) and Begg (tau = 0.66, P = 0.29) did not indicate any publication bias.

6. Discussion

The entire question of comorbidity deserves attention, provided separately (33-36). In a standard 1969 psychiatry textbook, Mayer-Gross et al., mostly considering the course of illness, included patients with BD-OCD in the manic-depressive disorders (37). Although recent studies investigated the co-occurrence of anxiety and bipolar disorders, the topic is insufficiently studied and the relationship between BD and OCD remains unclear. However, given the available scientific evidence, some observations can be made.

Apparent BD-OCD comorbidity is a common condition in psychiatry. In the authors' recent meta-analysis, the pooled prevalence of OCD in BD was 17.0% (95% CI, 12.7 to 22.4), which was comparable to the results reported by the

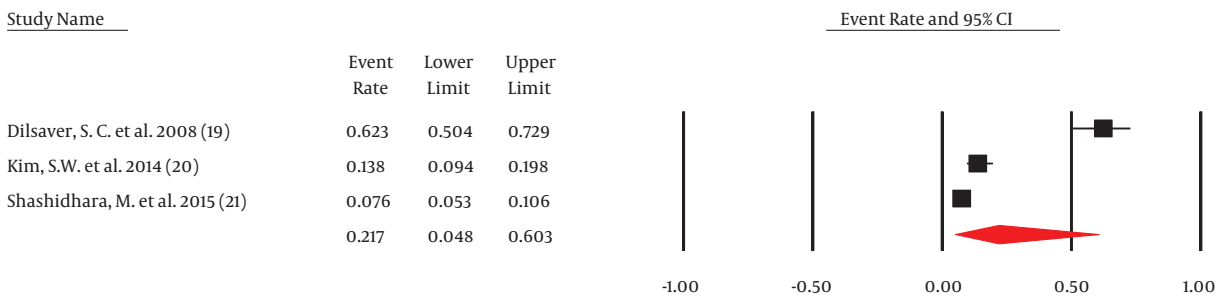

Figure 3. Pooled Prevalence of Obsessive-Compulsive Disorder in Patients with Bipolar Disorder Type-I

pooled prevalence of BD in OCD (18.35%, 95% CI, 13.2 to 24.8) (33). Although limited by the retrospective study design, small sample size, different thresholds for BD diagnosis and a different accuracy in diagnosing OCD, these results suggest the relevance of comorbid BD-OCD.

The current meta-analysis found that the pooled prevalence of BD-I in OCD was 3.9% (95% CI, 2.4 to 6.4, I2 = 83%, Q = 56); while the pooled prevalence of BD-II in OCD was 13.5% (95% CI, 9.3 to 19.3, I2 = 89%, Q = 91). The pooled prevalence of OCD in BD-I was 21.7% (95% CI, 4.8 to 60.3, I2 = 84%, Q = 95). With regard to OCD-BD predictors, mean age and rate of males did not predict the prevalence of BD-I (β = 0.0731, 95% CI, -0.1097 to 0.256, z = 0.78; β = 0.035, 95% CI, -0.2356 to 0.1656, z = -0.34) and BD-II (β = -0.0577, 95% CI, -0.1942 to 0.0788, z = -0.83; β = -0.0317, 95% CI, -0.1483 to 0.085, z =-0.53) in OCD. Mean age explained some of the observed heterogeneity (R2 = 0.13; R2 = 0.08).

From the nosological perspective, considering the course of illness as a key diagnostic validator, especially among patients with a primary diagnosis of BD, the majority of cases with comorbid OCD appeared to be related to mood episodes (34). OC symptoms in patients with comorbid OCD appeared more often - and sometimes exclusively - during depressive episodes, and comorbid BD and OCD cycled together, with OC symptoms often remitting during manic/hypomanic episodes. On the contrary, especially among patients with a primary diagnosis of OCD, there was a substantial minority of comorbid BD-OCD that may represent true OCD separate from BD with OC symptoms that improve or worsen during mood episodes without being related to them.

Results of the authors recent meta-analysis showed higher comorbidity rates in youths (24.2%, 95% CI, 10.36 to 41.60, n = 345, z =-9.5) compared to adults (13.56%, 95% CI, 10.4 to 16.25, n = 4,539) (33). In other words, OC symptoms would initially coexist with BD symptoms and they would gradually tend to decrease in the adulthood (38, 39).

From a neurobiological perspective, BD mostly showed hypoactivity in orbitofrontal cortex (OFC) (i e, decision making, impulse control) and in dorsolateral prefrontal cortex (DLPFC) (i e, planning, attentional set shifting) with grey matter volume reduction associated to manic episodes (40), while OCD mainly presented hyperactivity of OFC with deficit in emotional processing (41). The overlap of similar cortical-subcortical circuits may partially explain the clinical features of patients with comorbid BD-OCD during the course of illness.

The clinical features of patients with comorbid BD-OCD would explain why OCD and BD symptoms respond to adequate mood stabilizer treatment (4, 6). Only in a minority of patients with persistent comorbid OCD, despite improvement in mood episodes, addition of low doses of antidepressants could be considered while strictly monitoring emerging symptoms of mania or mixed states (4). Benefit with neuroleptics was also observed, although a few reports of exacerbation of OC symptoms with neuroleptic agents existed (4). Deep brain stimulation also seems to carry risks of manic worsening, and thus may not be a useful intervention in BD-OCD (4).

Further original studies are needed to clarify BD-OCD comorbidity. In particular, considering the growing interest over the last decades in shared pathophysiologies across psychiatric disorders (42), studies addressing neurobiological substrates are essential to illuminate pathogenetic mechanisms that underlie comorbid BD-OCD.

6.1. Limitations

The main limitation of this systematic review is linked to the study design and analysis strategy of the included studies, as documented in the quality assessment scale used. Most studies were observational and based on retrospective assessments. The use of retrospective assessment scales with low sensitivity in discriminating true ego-dystonic obsessions from depressive ruminations may have biased results towards an overestimation of obsessive symptom prevalence. Some of them did not include

a control group. Small sample size and enrollment of subjects mainly from BD-OCD outpatient units may limit generalizability of these results. Potential confounding factors in these studies include demographic and historical illness variables, which often were not appropriately analyzed through multivariate modelling. In particular, some analyses contained few studies (e g, OCD in BD I, three studies), and in such instances, the publication bias tests used may be insensitive to potential publication bias.

The main strength of this review is being systematic and including the entire scientific evidence published so far in the main medical databases. The strength of the selected studies was that the diagnosis of BD and OCD were consistently based on the DSM criteria and were established by trained investigators using validated assessment scales mainly with inter-rater reliability (IRR).

Supplementary Material

Supplementary material(s) is available here.

Footnotes

Authors' Contribution: Andrea Amerio, Anna Odone, Matteo Tonna, Carlo Marchesi and S. Nassir Ghaemi: study design and writing the protocol; Andrea Amerio and Matteo Tonna: identifying the studies and independently reviewing for eligibility; Andrea Amerio: data collection; S. Nassir Ghaemi: study supervision; Andrea Amerio, S. Nassir Ghaemi: data collection, assessing the quality of selected studies; Brendon Stubbs: performing the meta-analysis and meta-regression of data; Andrea Amerio, Anna Odone and Brendon Stubbs: writing the first draft of the manuscript. All authors approved the final manuscript.

Declaration of interest: None declared.

Funding/Support: This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

References

1. Amerio A, Odone A, Tonna M, Stubbs B, Ghaemi SN. Bipolar disorder and its comorbidities between Feinstein and the Diagnostic and Statistical Manual of Mental Disorders. *Aust N Z J Psychiatry.* 2015;**49**(11):1073. doi: 10.1177/0004867415610201. [PubMed: 26450938].
2. Krishnan KR. Psychiatric and medical comorbidities of bipolar disorder. *Psychosom Med.* 2005;**67**(1):1–8. doi: 10.1097/01.psy.0000151489.36347.18. [PubMed: 15673617].
3. Amerio A, Odone A, Marchesi C, Ghaemi SN. Treatment of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. *J Affect Disord.* 2014;**166**:258–63. doi: 10.1016/j.jad.2014.05.026. [PubMed: 25012439].
4. Amerio A, Odone A, Marchesi C, Ghaemi SN. Do antidepressant-induced manic episodes in obsessive-compulsive disorder patients represent the clinical expression of an underlying bipolarity?. *Aust N Z J Psychiatry.* 2014;**48**(10):957. doi: 10.1177/0004867414530006. [PubMed: 24711576].
5. Amerio A, Tonna M, Odone A, Stubbs B, Ghaemi SN. Treatment of comorbid bipolar disorder and anxiety disorders: A great challenge to modern psychiatry. *Aust N Z J Psychiatry.* 2016 Jul;**50**(7):699–700. doi: 10.1177/0004867415617839. [PubMed: 26619897].
6. Vazquez GH, Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. *Depress Anxiety.* 2014;**31**(3):196–206. doi: 10.1002/da.22248. [PubMed: 24610817].
7. Odone A, Amadasi S, White RG, Cohen T, Grant AD, Houben RM. The impact of antiretroviral therapy on mortality in HIV positive people during tuberculosis treatment: a systematic review and meta-analysis. *PloS one.* 2014;**9**(11) doi: 10.1371/journal.pone.0112017. [PubMed: 25391135].
8. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions. The Cochrane Collaboration; 2011.
9. Amerio A, Tonna M, Odone A, Stubbs B, Ghaemi SN. Treatment of comorbid bipolar disorder and anxiety disorders: A great challenge to modern psychiatry. *Aust N Z J Psychiatry.* 2016 Jul;**50**(7):699–700. doi: 10.1177/0004867415617839. [PubMed: 26619897].
10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ.* 2009;**339**:b2700. doi: 10.1136/bmj.b2700. [PubMed: 19622552].
11. Adam Y, Meinlschmidt G, Gloster AT, Lieb R. Obsessive-compulsive disorder in the community: 12-month prevalence, comorbidity and impairment. *Soc Psychiatry Psychiatr Epidemiol.* 2012;**47**(3):339–49. doi: 10.1007/s00127-010-0337-5. [PubMed: 21287144].
12. Angst J, Gamma A, Endrass J, Goodwin R, Ajdacic V, Eich D, et al. Obsessive-compulsive severity spectrum in the community: prevalence, comorbidity, and course. *Eur Arch Psychiatry Clin Neurosci.* 2004;**254**(3):156–64. doi: 10.1007/s00406-004-0459-4. [PubMed: 15205969].
13. Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. *Arthritis Rheum.* 2009;**61**(6):822–9. doi: 10.1002/art.24519. [PubMed: 19479699].
14. Vinceti M, Fiore M, Signorelli C, Odone A, Tesauro M, Consonni M, et al. Environmental risk factors for amyotrophic lateral sclerosis: methodological issues in epidemiologic studies. *Ann Ig.* 2012;**24**(5):407–15. [PubMed: 23193897].
15. 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. doi: 10.1016/j.jad.2010.10.008. [PubMed: 21074273].
16. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;**52**(6):377–84. [PubMed: 9764259].
17. Bogetto F, Venturello S, Albert U, Maina G, Ravizza L. Gender-related clinical differences in obsessive-compulsive disorder. *Eur Psychiatry.* 1999;**14**(8):434–41. [PubMed: 10683629].
18. Dilsaver SC, Benazzi F, Akiskal KK, Akiskal HS. Differential patterns of lifetime multiple anxiety disorder comorbidity between Latino adults with bipolar I and major depressive disorders. *Bull Menninger Clin.* 2008;**72**(2):130–48. doi: 10.1521/bumc.2008.72.2.130. [PubMed: 18637749].
19. Hantouche EG, Angst J, Demonfaucon C, Perugi G, Lancrenon S, Akiskal HS. Cyclothymic OCD: a distinct form?. *J Affect Disord.* 2003;**75**(1):1–10. [PubMed: 12781344].
20. Kim SW, Berk L, Kulkarni J, Dodd S, de Castella A, Fitzgerald PB, et al. Impact of comorbid anxiety disorders and obsessive-compulsive disorder on 24-month clinical outcomes of bipolar I disorder. *J Affect Disord.* 2014;**166**:243–8. doi: 10.1016/j.jad.2014.05.017. [PubMed: 25012437].

21. Lensi P, Cassano GB, Correddu G, Ravagli S, Kunovac JL, Akiskal HS. Obsessive-compulsive disorder. Familial-developmental history, symptomatology, comorbidity and course with special reference to gender-related differences. *Br J Psychiatry.* 1996;**169**(1):101–7. [PubMed: 8818377].
22. Maina G, Albert U, Pessina E, Bogetto F. Bipolar obsessive-compulsive disorder and personality disorders. *Bipolar Disord.* 2007;**9**(7):722–9. doi: 10.1111/j.1399-5618.2007.00508.x. [PubMed: 17988362].
23. Marazziti D, Dell'Osso L, Di Nasso E, Pfanner C, Presta S, Mungai F, et al. Insight in obsessive-compulsive disorder: a study of an Italian sample. *Eur Psychiatry.* 2002;**17**(7):407–10. [PubMed: 12547307].
24. Perugi G, Akiskal HS, Pfanner C, Presta S, Gemignani A, Milanfranchi A, et al. The clinical impact of bipolar and unipolar affective comorbidity on obsessive-compulsive disorder. *J Affect Disord.* 1997;**46**(1):15–23. [PubMed: 9387083].
25. Perugi G, Akiskal HS, Gemignani A, Pfanner C, Presta S, Milanfranchi A, et al. Episodic course in obsessive-compulsive disorder. *Eur Arch Psychiatry Clin Neurosci.* 1998;**248**(5):240–4. [PubMed: 9840370].
26. Perugi G, Akiskal HS, Ramacciotti S, Nassini S, Toni C, Milanfranchi A, et al. Depressive comorbidity of panic, social phobic, and obsessive-compulsive disorders re-examined: is there a bipolar II connection?. *J Psychiatr Res.* 1999;**33**(1):53–61. [PubMed: 10094240].
27. Perugi G, Toni C, Frare F, Travierso MC, Hantouche E, Akiskal HS. Obsessive-compulsive-bipolar comorbidity: a systematic exploration of clinical features and treatment outcome. *J Clin Psychiatry.* 2002;**63**(12):1129–34. [PubMed: 12523872].
28. Shashidhara M, Sushma BR, Viswanath B, Math SB, Janardhan Reddy YC. Comorbid obsessive compulsive disorder in patients with bipolar-I disorder. *J Affect Disord.* 2015;**174**:367–71. doi: 10.1016/j.jad.2014.12.019. [PubMed: 25545603].
29. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;**7**(3):177–88. [PubMed: 3802833].
30. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;**50**(4):1088–101. [PubMed: 7786990].
31. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;**315**(7109):629–34. [PubMed: 9310563].
32. Timpano KR, Rubenstein LM, Murphy DL. Phenomenological features and clinical impact of affective disorders in OCD: a focus on the bipolar disorder and OCD connection. *Depress Anxiety.* 2012;**29**(3):226–33. doi: 10.1002/da.20908. [PubMed: 22109969].
33. Amerio A, Stubbs B, Odone A, Tonna M, Marchesi C, Ghaemi SN. The prevalence and predictors of comorbid bipolar disorder and obsessive-compulsive disorder: A systematic review and meta-analysis. *J Affect Disord.* 2015;**186**:99–109. doi: 10.1016/j.jad.2015.06.005. [PubMed: 26233320].
34. Amerio A, Odone A, Liapis CC, Ghaemi SN. Diagnostic validity of comorbid bipolar disorder and obsessive-compulsive disorder: a systematic review. *Acta Psychiatr Scand.* 2014;**129**(5):343–58. doi: 10.1111/acps.12250. [PubMed: 24506190].
35. Tonna M, Amerio A, Ottoni R, Paglia F, Odone A, Ossola P, et al. The clinical meaning of obsessive-compulsive symptoms in bipolar disorder and schizophrenia. *Aust N Z J Psychiatry.* 2015;**49**(6):578–9. doi: 10.1177/0004867415572010. [PubMed: 25688121].
36. Tonna M, Amerio A, Odone A, Ossola P, Marchesi C, Ghaemi SN. Are obsessive-compulsive symptoms expression of vulnerability to bipolar disorder?. *Acta Psychiatr Scand.* 2015;**132**(5):411–2. doi: 10.1111/acps.12481. [PubMed: 26366745].
37. Mayer-Gross W, Slater E, Roth M. Clinical Psychiatry. third ed. London: Elsevier Health Sciences; 1969.
38. Tonna M, Amerio A, Stubbs B, Odone A, Ghaemi SN. Comorbid bipolar disorder and obsessive-compulsive disorder: A child and adolescent perspective. *Aust N Z J Psychiatry.* 2015;**49**(11):1066–7. doi: 10.1177/0004867415605642. [PubMed: 26399870].
39. Amerio A, Tonna M, Odone A, Stubbs B, Ghaemi SN. Comorbid bipolar disorder and obsessive-compulsive disorder in children and adolescents: Treatment implications. *Aust N Z J Psychiatry.* 2016;**50**(6):594–6. doi: 10.1177/0004867415611235. [PubMed: 26480937].
40. Ekman CJ, Lind J, Ryden E, Ingvar M, Landen M. Manic episodes are associated with grey matter volume reduction - a voxel-based morphometry brain analysis. *Acta Psychiatr Scand.* 2010;**122**(6):507–15. doi: 10.1111/j.1600-0447.2010.01586.x. [PubMed: 20712826].
41. Casado Y, Cobos P, Godoy A, Machado-Pinheiro W, Vila J. Emotional processing in obsessive-compulsive disorder. *J Anxiety Disord.* 2011;**25**(8):1068–71. doi: 10.1016/j.janxdis.2011.07.003. [PubMed: 21820853].
42. Mostafavi Abdolmaleky H. Horizons of psychiatric genetics and epigenetics: where are we and where are we heading?. *Iran J Psychiatry Behav Sci.* 2014;**8**(3):1–10. [PubMed: 25780369].