

World Journal of *Psychiatry*

World J Psychiatr 2019 January 4; 9(1): 1-29



EDITORIAL

- 1 Electroconvulsive therapy: 80 years old and still going strong
Gazdag G, Ungvari GS

REVIEW

- 7 Comorbidity of bipolar and anxiety disorders: An overview of trends in research
Spoorthy MS, Chakrabarti S, Grover S

ABOUT COVER

Editor-in-Chief of *World Journal of Psychiatry*, Rajesh R Tampi, MD, Chairman, Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Yale School of Medicine, New Haven, CT 06511, United States

AIMS AND SCOPE

World Journal of Psychiatry (*World J Psychiatr*, *WJP*, online ISSN 2220-3206, DOI: 10.5498) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJP covers topics concerning behavior and behavior mechanisms, psychological phenomena and processes, mental disorders, behavioral disciplines and activities, adjustment disorders, anxiety disorders, delirium, etc. Priority publication will be given to articles concerning diagnosis and treatment of psychiatric diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, etc.

We encourage authors to submit their manuscripts to *WJP*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Psychiatry is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Ying-Na Bian*

Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Continuous

EDITORS-IN-CHIEF

Rajesh R Tampi

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2220-3206/editorialboard.htm>

EDITORIAL OFFICE

Jin-Lei Wang, Director

PUBLICATION DATE

January 4, 2019

COPYRIGHT

© 2019 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>



Comorbidity of bipolar and anxiety disorders: An overview of trends in research

Mamidipalli Sai Spoorthy, Subho Chakrabarti, Sandeep Grover

ORCID number: Mamidipalli Sai Spoorthy (0000-0001-6059-9199); Subho Chakrabarti (0000-0001-6023-2194); Sandeep Grover (0000-0002-2714-2055).

Author contributions: All authors equally contributed to this paper with conception and design of the literature review and analysis, drafting, critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: No potential conflicts of interest.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: September 30, 2018

Peer-review started: September 30, 2018

First decision: October 17, 2018

Revised: November 4, 2018

Accepted: December 5, 2018

Article in press: December 5, 2018

Published online: January 4, 2019

Mamidipalli Sai Spoorthy, Subho Chakrabarti, Sandeep Grover, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

Corresponding author: Subho Chakrabarti, MD, Professor, Department of Psychiatry, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India. subhochohd@yahoo.com

Telephone: +91-172-2756808

Fax: +91-172-2744401

Abstract

Over the last three decades burgeoning research has shown that anxiety disorder comorbidity is not only highly prevalent in bipolar disorder (BD), but it also adversely impacts the course, outcome, and treatment of BD. The present review provides an overview of the current trends in research on comorbid anxiety and BDs based on prior reviews and meta-analyses ($n = 103$), epidemiological surveys, and large-scale clinical studies. The results reiterated the fact that at least half of those with BD are likely to develop an anxiety disorder in their lifetimes and a third of them will manifest an anxiety disorder at any point of time. All types of anxiety disorders were equally common in BD. However, there was a wide variation in rates across different sources, with most of this discrepancy being accounted for by methodological differences between reports. Comorbid anxiety disorders negatively impacted the presentation and course of BD. This unfavourable clinical profile led to poorer outcome and functioning and impeded treatment of BD. Despite the extensive body of research there was paucity of data on aetiology and treatment of anxiety disorder comorbidity in BD. Nevertheless, the substantial burden and unique characteristics of this comorbidity has important clinical and research implications.

Key words: Comorbidity; Bipolar disorder; Anxiety disorders; Correlates; Impact; Aetiology; Treatment

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: This review of existing research shows that about half of those with bipolar disorder (BD) are likely to develop anxiety disorders in their lifetimes and a third of them will manifest these disorders at any point of time. Anxiety disorder comorbidity negatively impacts almost all aspects of the presentation and course of BD and makes for a much poorer treatment-response and outcome. Though research data on aetiology and management of such comorbidity is limited, clinicians need to screen patients with BD

for anxiety disorders and provide comprehensive and on-going treatment to prevent the deleterious consequences of anxiety disorder comorbidity in BD.

Citation: Spoorthy MS, Chakrabarti S, Grover S. Comorbidity of bipolar and anxiety disorders: An overview of trends in research. *World J Psychiatry* 2019; 9(1): 7-29

URL: <https://www.wjgnet.com/2220-3206/full/v9/i1/7.htm>

DOI: <https://dx.doi.org/10.5498/wjp.v9.i1.7>

INTRODUCTION

Comorbidity is defined as the ‘presence of more than one disorder in a person in a defined period of time’^[1]. Prior to the 1990s the focus was mostly on the link between anxiety disorders and unipolar depression, while substance-use disorders (SUDs) were the focus of research on comorbidity in bipolar disorder (BD). However, accumulated evidence over the last three decades has conclusively established that comorbidity with anxiety disorders is the rule rather than the exception among patients with BD^[2-5]. In general, about a half to two thirds or even more of the patients with BD have a comorbid psychiatric condition. Anxiety disorders, SUDs, and behavioural disorders are the most common comorbid psychiatric disorders associated with BD. Very high lifetime and current rates of anxiety disorder comorbidity have been found in both epidemiological^[5-9] and clinical studies of BD^[5,6,8,10,11]. Additionally, multiple anxiety disorder comorbidity has been reported in a third of the patients with BD^[12-16]. Despite differing widely across studies, rates of individual anxiety disorders comorbid with BD appear to be largely similar^[11,17-20]. The presence of comorbid anxiety disorders in patients with BD has several adverse consequences including a negative impact on almost all aspects of the presentation and course of BD^[10,15,21-23]. This unfavourable clinical profile leads to poorer outcome and functioning and impedes treatment of BD^[16,17,20,24,25].

The increased awareness of the substantial burden of comorbid bipolar and anxiety disorders over the years has propelled research in this area^[5,26]. Moreover, it gave rise to the hope that examination of anxiety disorder comorbidity in BD could provide clues to underlying etiopathogenetic mechanisms of BD^[3,6,9]. Consequently, the existing literature now contains a sizeable body of research evidence on the subject^[6,8,16,18]. However, there are several unresolved issues as well. This review intends to highlight both the well-known facts and the deficiencies in research concerning anxiety disorder comorbidity in BD. A major problem hampering research in this area has been the widely varying methodology of individual studies^[20,26,27]. To obviate these methodological concerns to whatever extent possible, the current review is based on three of the relatively more reliable sources of evidence including prior reviews and meta-analyses, as well as epidemiological surveys and large-scale clinical studies of comorbid anxiety disorders and BD.

OBJECTIVES

The principal objective of this review was to provide an overview of the current trends in research on comorbidity of bipolar and anxiety disorders. The main areas examined included rates of anxiety disorder comorbidity in BD, its demographic and clinical correlates, the impact of such comorbidity on the course and outcome of BD, and research on management and aetiological mechanisms of comorbid anxiety and BDs.

LITERATURE SEARCH

A comprehensive literature search was undertaken using six English-language databases: MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane, and Google to identify published articles on anxiety disorders comorbid with BD from inception until August 2018. Search terms included BD, or bipolar depression, or mania AND comorbid, or comorbidity AND anxiety, or generalized anxiety disorder (GAD), or panic disorder, or phobia, or phobic disorder, or social anxiety disorder, or obsessive-compulsive disorder (OCD), or post-traumatic stress disorder (PTSD). Reviews,

editorials and original research articles were examined for their relevance to the subject. Reference lists of these articles were searched manually to locate other relevant reports.

SELECTION OF ARTICLES

All articles that provided information on prevalence, clinical features, aetiology, and treatment of anxiety disorder comorbidity in BD were chosen initially. However, for the purposes of the current review only three sources of evidence including earlier reviews (meta-analytic, systematic, and open), epidemiological investigations, and large-scale (usually multi-centric) clinical studies were included. Other original research articles were considered only when they provided additional information not present in these three principal sources.

DATA EXTRACTION AND SYNTHESIS

Data on different aspects of anxiety disorder comorbidity in BD were extracted from each source. Results were organized by identifying common patterns and trends so that logical conclusions could be drawn from the findings of the articles included.

EVIDENCE-BASE FOR THE CURRENT REVIEW

The electronic search yielded 1294 articles, 249 of which were reviews about anxiety disorder comorbidity in BD. Relevant reviews were extracted from this initial list of 249 articles. A manual search was also conducted to identify any other reviews on the topic. After excluding duplicate publications, 103 reviews on the subject were finally included. The final selection contained 14 meta-analytic reviews, 29 systematic reviews, and 60 open (non-systematic) reviews. Incidentally, the literature search also yielded over 350 relevant studies on comorbid bipolar and anxiety disorders. However, only a selected list of articles pertaining to epidemiological and large-scale clinical studies was included in this review.

OVERALL PREVALENCE OF ANXIETY DISORDERS IN BD

Data from meta-analytic and systematic reviews are included in Table 1, while Table 2 depicts the rates obtained as a part of non-systematic reviews. Prevalence rates from epidemiological studies are shown in Table 3 and from selected large-scale clinical studies in Table 4.

The first notable finding across all sources included in this review was the wide variation in prevalence rates between different reviews, epidemiological surveys, and clinical studies. The obvious reason for this discrepancy was differences in designs and methodologies of reviews and individual studies. However, despite these differences there appeared to be some consistency in the rates reported from different sources.

Reviews

Four meta-analyses of lifetime prevalence rates of anxiety disorders among adult patients with BD yielded very similar rates of 41% to 47% from both community and clinical populations^[11,18-20]. Current rates of anxiety disorder comorbidity among adult patients ranged from 35% to 38% in two meta-analyses of epidemiological and clinical studies of BD^[20,35]. Mean prevalence rates in children/adolescents were found to be 27% (range 15% to 43%) in one meta-analysis^[29] and 44% in another^[34], which was in keeping with the adult rates. There was a greater variation in rates (11% to 93%) derived from systematic reviews depending on the number and type of studies included in each review. Nevertheless, systematic reviews among adult patients have also reported lifetime anxiety comorbidity in about half and current comorbidity in about a third of those with BD. Incidentally, the systematic review with the largest number of studies ($n = 167$) has been conducted among those with child/adolescent BD^[43]. The mean prevalence rate of any anxiety disorder in BD was found to be 54% in this review (range 41% to 80%). A much greater disparity in rates was found in the non-systematic reviews, but even in these reviews the average lifetime prevalence was close to 50% and the average current prevalence was about 30% for anxiety disorders in BD. Rates for prevalence among the elderly appeared to be lower (mean

Table 1 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from meta-analytic and systematic reviews

Details	Any anxiety disorder	Individual anxiety disorders
Meta-analytic reviews		
Kowatch <i>et al</i> ^[29] , 2005. 7 studies of child and adolescent BD (<i>n</i> = 362)	Mean prevalence of any anxiety disorder in BD 27% (range 14%-43%)	
Vázquez <i>et al</i> ^[18] , 2014. 46 studies of anxiety comorbidity in BD	Lifetime prevalence in epidemiological and clinical studies - mean 47% (range 24%-88%)	Mean prevalence: PD 22% (1%-40%), PHOBIAS 22% (2%-59%), GAD 20% (7%-42%), PTSD 16% (3%-39%), OCD 13% (5%-48%)
Amerio <i>et al</i> ^[30] , 2015. 46 studies of comorbid BD and OCD		Pooled prevalence of OCD in BD 17.0%; pooled prevalence of BD in OCD 18.0%
Nabavi <i>et al</i> ^[11] , 2015. 52 interview-based studies of outpatients and inpatients	Lifetime prevalence of any anxiety disorder in BD 43%	Lifetime prevalence of: PD 17%, GAD 14%, SAD 13%, PTSD 11%, SP PHOBIA 11%, OCD 11%, AGORA 8%
Pavlova <i>et al</i> ^[19] , 2015. 40 studies (<i>n</i> = 14914) of community and clinical population	Lifetime prevalence of anxiety disorder in BD 45%	Lifetime prevalence of: GAD 20%, SOC PHOBIA 20%, PD 19%, PTSD 17%; no differences between BP I and BP II
Tonna <i>et al</i> ^[31] , 2015. 4 studies of adolescent BD-OCD (<i>n</i> = 345)		Pooled prevalence of comorbid OCD in BD among adolescents 23%; greater than adults (14%)
Amerio <i>et al</i> ^[32] , 2016. 14 studies of comorbid BD and OCD in BP I and BP II		Pooled prevalence of OCD in BP I 22%; pooled prevalence of BP I in OCD 4% and of BP II in OCD 13.5%
Preti <i>et al</i> ^[33] , 2016. 28 studies of comorbid BD and GAD (<i>n</i> = 7894)		Current prevalence 12% and lifetime prevalence 15% of GAD in BD
Taskiran <i>et al</i> ^[34] , 2016. 33 studies of child and adolescent BD	Prevalence of any anxiety disorder in BD 44%	Prevalence of: GAD 25%, SEP ANX 22%, OCD 17%, SOC PHOBIA 15%, PD 10%
Pavlova <i>et al</i> ^[35] , 2017. 10 studies of euthymic BD (<i>n</i> = 2120)	Current prevalence of any anxiety disorder in BD 35%	Current prevalence of: GAD 12%, SAD 10%, SP PHOBIA 10%, OCD 7%
Yapici Eser <i>et al</i> ^[20] , 2018. 135 studies of comorbid BD and anxiety disorders	Lifetime prevalence 41% and current prevalence 38% of anxiety disorder in BD; lifetime prevalence 38% in BD I and 34% in BD II; current prevalence 31% in BD I and 37% in BD II	Lifetime prevalence: PD 18%, GAD 13%, SAD 13%, OCD 10%; current prevalence: GAD 15%, PD 13%, SAD 12%, OCD 10%; prevalence PD and SAD significantly affected by proportion of BD I patients
Preti <i>et al</i> ^[36] , 2018. 15 studies of comorbid BD and PD (<i>n</i> = 3391)		Lifetime prevalence: PD 16%; current prevalence: PD 13%; no difference between BP I and BP II
Systematic reviews		
Strakowski <i>et al</i> ^[37] , 1994. 4 studies of anxiety comorbidity in BD		Mean prevalence: PD 7%-16%, OCD 8%-13%
Krishnan ^[38] , 2005. 10 studies of anxiety comorbidity in BD	Mean rate 71% (range 49%-92%)	Mean rates: SOC PHOBIA 47%, PTSD 39%, PD 11%, OCD 10%
McIntyre <i>et al</i> ^[8] , 2006. 17 studies of anxiety comorbidity in BD	Lifetime rates 16%-79% in 11 studies; usually 30%-50%; current prevalence 15%-56% in 8 studies	AGORA lifetime 22%-62%; current 6%-7%; SP PHOBIA lifetime 2%-67%; current 8% SOC PHOBIA lifetime 4%-47%; current 13%-19% GAD lifetime 3%-43%; current 2%-25% PTSD lifetime 7%-37%; current 4%-40% PD lifetime 2%-38%; current 8%-26% OCD lifetime 2%-31%; current 6%-8%
Tamam ^[9] , 2007. 15 studies of anxiety comorbidity in BD	Lifetime prevalence in epidemiological and clinical studies 24%-93%	Lifetime prevalence of: SOC PHOBIA 5%-47%, PD 6%-43%, OCD 7%-39%, GAD 3%-43%, PTSD 7%-21%
Kauer-Sant'Anna <i>et al</i> ^[15] , 2009. 9 studies of anxiety comorbidity in BD	Lifetime prevalence in epidemiological studies 48%-93%	SP PHOBIA 10%-67%, SOC PHOBIA 8%-47%, PTSD 7%-39%, GAD 3%-42%, PD 5%-33%
Quarantini <i>et al</i> ^[39] , 2009. PTSD prevalence in BD		Lifetime rates of PTSD in BD 16%-39%
Maina <i>et al</i> ^[16] , 2011. 11 studies of anxiety comorbidity in BD	Lifetime prevalence in epidemiological studies 63%-89%; in clinical samples 11%-79%	PD 4%-39%, OCD 3%-35%, GAD 3%-32%, SOC PHOBIA 2%-31%, PTSD 5%-29%
Pallanti <i>et al</i> ^[40] , 2011. 10 studies of comorbid BD and OCD		Lifetime prevalence in epidemiological and clinical studies 15%-35%
Lala <i>et al</i> ^[41] , 2012. 7 studies of elderly patients		PTSD 5%-11%, PD -current 22%, GAD-current 16%, OTHERS 10%-11%
Schaffer <i>et al</i> ^[10] , 2012. 9 studies of anxiety comorbidity in BD	Lifetime prevalence in epidemiological studies 52%-75%	Lifetime prevalence: OCD 10%-25%, PD 14%-27%, PTSD 16%-39%
Latalova <i>et al</i> ^[22] , 2013. 12 studies of anxiety comorbidity in BD	Lifetime prevalence in epidemiological studies 75%; in clinical samples 27%-56%	Lifetime prevalence: SOC PHOBIA 47%-52%, SAD 38%, SP PHOBIA 35%, GAD 30%, PTSD 24% (16%-39%), PD 20%, OCD 14% (3%-35%)
Amerio <i>et al</i> ^[42] , 2014. 64 articles of comorbid BD and OCD		Lifetime prevalence of OCD in BD 11%-21% (mean BP I 15%, BP II 13%); lifetime prevalence of BD in OCD 6%-10% (mean BP I 4%, BP II 9%)

Frias <i>et al</i> ^[43] , 2015. 167 studies of child and adolescent BD	Mean prevalence of any anxiety disorder in BD 54% (range 41%-80%)	GAD and SEP ANX rates higher than other disorders; OCD 36%-39%, PD 18%-23%, PTSD 8%
Sharma ^[44] , 2017. 8 studies of post-partum BD comorbidity		Anecdotal reports of simultaneous onset of comorbid BD-OCD in the postpartum period

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; AGORA: Agoraphobia; GAD: Generalized anxiety disorder; OCD: Obsessive compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; SEP ANX: Separation anxiety disorder; SOC PHOBIA: Social phobia; SP PHOBIA: Specific phobia.

23%)^[54], while average rates among children/adolescents seemed to be higher (range 14% to 77%) than adult rates^[56,58,59].

Epidemiological and clinical studies

Some of the highest rates of anxiety disorder comorbidity in BD have been reported in epidemiological surveys. In these studies, a minimum of one third of the patients with BD appeared to have a lifetime comorbid anxiety disorder^[88], with some epidemiological studies reporting exceptionally high lifetime rates of 89% to 100%^[76,78,90]. However, most epidemiological investigations have found lifetime rates of about 50% to 60% in those with BD. Current rates were lower and ranged from 7% to 52% in three studies^[97-99]. The high rates obtained in epidemiological studies could be explained by the large number of patients examined, many of whom may have never sought treatment. Alternatively, they could be due to the high rates of false positive diagnoses made by lay interviewers who are usually employed to carry out these population surveys^[26]. In contrast, while diagnostic ascertainment may be more reliable in clinical settings, clinical samples are also more likely to include severely ill patients with higher chances of having comorbid disorders (the so called Berkson's bias)^[8,16,26]. Still, lifetime rates of anxiety comorbidity in BD were about 40% to 50%, while current rates were about 30% across several large-scale clinical studies. Thus, though rates in community samples were somewhat higher than clinical populations^[26], these differences were not significant as indicated by two meta-analytic reviews^[19,35].

Remitted patients

Although some evidence suggested that anxiety disorder comorbidity was higher during acute, particularly depressive episodes^[8,35], reviews of studies of remitted patients with BD have found that about a third to half of such patients (range 7% to 61%) have a comorbid anxiety disorder^[16,35,119]. A recent meta-analysis of remitted BD found that the current prevalence rate for any anxiety disorder was 35%, thus confirming that anxiety disorder comorbidity extends beyond the acute to the inter-episodic period^[35].

Multiple comorbidity

About a third of the patients with BD also develop more than one anxiety disorder during their lifetimes^[8,10,27,60]. Rates of such multiple anxiety disorder comorbidity have ranged from 10% to 47% in different studies of BD^[9,13-16].

BD in anxiety disorders

The prevalence of BD in anxiety disorders has been examined less often. Though some reviews have reported low rates of BD in primary anxiety disorders^[18,40], the majority of reviews and studies have found that the prevalence of BD in anxiety disorders is equivalent to the rates of anxiety disorders in patients with BD^[7,8,66,80,128]. This appears to be mainly true for OCD^[30,32,128,129], but a similar trend has also been found for social phobia and panic disorder^[7,8,46,66,128].

PREVALENCE OF INDIVIDUAL ANXIETY DISORDERS IN BD

Not surprisingly, the greatest discrepancy was found in the prevalence of individual anxiety disorders in BD. Nonetheless, some uniform trends were evident from the three different sources of evidence of this review.

The four meta-analytic reviews among adults have reported highest lifetime rates for panic disorder (17% to 22%), GAD (13% to 20%), and social phobia (20%), followed by PTSD (11% to 17%), social anxiety disorder (13%), OCD (10% to 13%), specific phobias (11%), and agoraphobia (8%)^[11,18-20]. A similar trend was also apparent in a meta-analysis of remitted patients^[35]. Among children/adolescents the mean prevalence of GAD (25%) was very high, as were the rates of separation anxiety disorder (22%), OCD (17%), and social phobia (15%)^[34]. Reviews of individual

Table 2 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from open reviews

Ref.	Any anxiety disorder	Individual anxiety disorders
Himmelhoch ^[45] , 1998		Lifetime prevalence of PD in BD 21%; prevalence of BD in PD 14%-34%
Hantouche <i>et al</i> ^[46] , 2002		Prevalence of BD in OCD 11%-16%, cyclothymia 50%-56%
Freeman <i>et al</i> ^[6] , 2002	Lifetime and current rates 32%-79%	SOC PHOBIA lifetime 8%-47%; PTSD lifetime 39%; current 40%-43%; PD lifetime 11%-21%; current 2%-9%; OCD lifetime 9%-21%; current 35%
McIntyre <i>et al</i> ^[47] , 2003	Lifetime rate 92%	Lifetime rates SP PHOBIA 67%, SOC PHOBIA 47%, GAD 42%, PTSD 39%, PD 33%
Sasson <i>et al</i> ^[12] , 2003	Lifetime rate 60%-65%	SOC PHOBIA 10%-40%, OCD 7%-35%, SP PHOBIA 10%, PTSD 7%, GAD 3%
Ghaemi ^[48] , 2004	Lifetime rate > 90%	GAD 50%, PD 20%, OCD 20%
Goldberg <i>et al</i> ^[2] , 2004	Epidemiological studies > 90%; clinical 4%-50%	
Issler <i>et al</i> ^[13] , 2004	Lifetime rate 24% to 79%	
McIntyre <i>et al</i> ^[49] , 2004	Lifetime rate 42%-90%; current rate 30%	PD 9%-20%, SOC PHOBIA 13%-16%, SP PHOBIA 8%-10%, GAD 3%, OCD 8%-9%, PTSD 4%-7%
Otto <i>et al</i> ^[50] , 2004		Mean prevalence of PTSD in BD 16%
Bauer <i>et al</i> ^[14] , 2005	Lifetime rate 16%-42% and current rate 30%-31% in clinical studies	PTSD lifetime 7%-50%; current 4%-40% PD lifetime 4%-38%; current 8% OCD lifetime 3%-35%; current 6%-8% GAD lifetime 3%-32%; current 2%-3%; SOC PHOBIA lifetime 0%-31%; current 13% SP PHOBIA lifetime 10%-20%; current 8%
Hirschfeld <i>et al</i> ^[24] , 2005	Lifetime rate 42%-92%	PD 21% OCD 21%
Simon <i>et al</i> ^[51] , 2005	Lifetime rate 50%; current rate 30%	PD lifetime rates 14%-38%; PD current rates 4%-9%
Baldassano ^[52] , 2006	Lifetime rate 51%-65%; current rate 7%	
Keller ^[27] , 2006	Lifetime rates 51%-65%	
MacKinnon <i>et al</i> ^[53] , 2006		Prevalence PD - community studies 12%-35%; clinical studies 5%-63%; family studies 11%-21%
Sajatovic <i>et al</i> ^[54] , 2006	Prevalence 23% among elderly patients	Prevalence PTSD 44%, others 43%, GAD 23%, PD 6%, OCD 5%, AGORA 3%, SOC PHOBIA 0.5%, SP PHOBIA 0.2%
Singh <i>et al</i> ^[55] , 2006	Mean prevalence 55%	Mean prevalence SOC PHOBIA 47%, PTSD 16%, PD 11%, OCD 10%
Dineen Wagner ^[56] , 2006	Prevalence in community studies 29%-50% and clinical samples 14%-76% of anxiety comorbidity in child and adolescent BD	Prevalence: OCD 9%-49%, SOC PHOBIA 3%-33%, GAD 19%-20%, SEP ANX 13%-57%, AGORA 15%-27%, PD 6%-11%, PTSD 18%
Bhagwagar ^[21] , 2007	Lifetime rate > 50%	
MacKinnon ^[57] , 2007		Prevalence PD 15%-20%
Mantere ^[28] , 2007	Lifetime rate 42%-56%; current rate 30%	
El-Mallakh <i>et al</i> ^[17] , 2008	Lifetime rate 87%-92% in epidemiological studies	Lifetime rates: SAD 5%-52%, GAD 30%-42%, PTSD 16%-39%, OCD 17%-21%, PD 21%
Jolin <i>et al</i> ^[58] , 2008	Mean prevalence 14%-77% in childhood and adolescent BD	Mean prevalence: SEP ANX 18%-22%, PHOBIA 4%-11%, PD 3%-11%, OCD 3%
Joshi <i>et al</i> ^[59] , 2009	Prevalence in adults and children 12%-76%	Prevalence OCD 15%-35%
Sagman <i>et al</i> ^[60] , 2009	Lifetime rate 50%-65%; current rate 30%	
Simon ^[61] , 2009	Lifetime rate 51%	Lifetime rate GAD 18%
Bowden ^[62] , 2010	Lifetime rate 92%	
Saunders <i>et al</i> ^[4] , 2010	Lifetime rate 65%	Lifetime rate OCD 21%
Andrade-Nascimento <i>et al</i> ^[63] , 2012		Current 15% and lifetime prevalence 16% of GAD in euthymic patients
Jana <i>et al</i> ^[64] , 2012		Mean prevalence of OCD 0%-54% in childhood and adolescent BD
McIntyre <i>et al</i> ^[65] , 2012	Lifetime rate 63%-87%	
Perugi <i>et al</i> ^[66] , 2012	Lifetime rate 30%-93%; current rate 30%	Lifetime rate SP PHOBIA 67%, PD 33%
Cazard <i>et al</i> ^[67] , 2013	Mean prevalence 5%-33%	Mean prevalence: SOC PHOBIA 0.5%-47%, PTSD 2%-44%, GAD 3%-42%, OCD 1%-14%
Amerio <i>et al</i> ^[68] , 2015	Mean prevalence 50%	OCD 17%-18%
Chang <i>et al</i> ^[69] , 2016	Lifetime rate 51%-90%; current rate 31%	
Ketter ^[23] , 2015	Lifetime prevalence mean 48% (range 17%-79%)	

Shi ^[70] , 2015	Prevalence rate of OCD in BD 11%-21%
Tonna <i>et al</i> ^[71] , 2015	Prevalence rate of OCD in BD 21%

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; AGORA: Agoraphobia; GAD: Generalized anxiety disorder; OCD: Obsessive compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; SEP ANX: Separation anxiety disorder; SOC PHOBIA: Social phobia; SP PHOBIA: Specific phobia.

disorders have usually confirmed these rates. The prevalence of OCD in BD was about 17% (range 11% to 23%) among adults and children/adolescents in three meta-analyses and one systematic review^[30-32,42]. The lifetime prevalence of GAD was found to be 15% and that of panic disorder 16% in two separate meta-analyses^[36], while a systematic review estimated the lifetime rates of PTSD to vary from 16% to 39%^[39].

Epidemiological studies, on the other hand have found very high lifetime rates of comorbid phobias in BD including specific phobias, agoraphobia, social phobia, and social anxiety disorder. This is understandable given that phobic disorders are among the most common disorders found in general population surveys^[131-134]. Lifetime rates of GAD were also very high while rates of other disorders were more variable. Consequently, most systematic as well as non-systematic reviews based on both epidemiological and clinical studies have found a similar pattern of prevalence of individual anxiety disorders in BD^[8-10,22]. While some clinical studies have also found a comparable distribution of anxiety disorders, the more usual finding has been that panic disorder, PTSD, and OCD are about as common as phobic disorders and GAD.

DEMOGRAPHIC CORRELATES OF ANXIETY DISORDER COMORBIDITY IN BD

Correlates of anxiety disorders among patients with BD are depicted in Table 5. Few studies have examined demographic correlates of comorbid bipolar and anxiety disorders. The association with age has yielded conflicting results^[8,9,40,70], except for OCD comorbidity in BD, where younger patients have been found to have higher rates in a series of meta-analyses and systematic reviews^[20,30,32,40,42]. In contrast, gender seemed to make a significant difference to the prevalence of comorbid anxiety disorders in BD in some studies. Higher prevalence of anxiety disorders has been reported among women, particularly from large-scale clinical studies such as those conducted by the Stanley Foundation^[104]. However, the Systematic Treatment Enhancement Program for Bipolar Disorder and other studies have not been able to reproduce these gender differences^[52]. There was similar inconsistency among epidemiological studies with some reporting higher prevalence of anxiety disorders in women with BD^[74,85] and others finding equivalent rates between the two genders^[76,99]. One meta-analysis found a significant excess of anxiety disorders among women with BD based on pooled prevalence rates from several studies^[18], but many other meta-analyses and reviews have concluded that there are no gender differences in rates of anxiety disorder comorbidity in BD. The association of anxiety disorders with other demographic variables such as marital status, education, or socioeconomic class has been similarly characterized by inconsistent and contradictory results. On the other hand, there was some preliminary evidence of cross-national and ethnic differences in the prevalence of anxiety disorder comorbidity in BD. Geographical variations in rates of anxiety disorders have been found in several meta-analyses and systematic reviews^[11,19,30,42]. Ethnic differences have also been noted in epidemiological studies^[74]. Notably, some reviews have found lower rates of anxiety disorders among Asian patients with BD; genetic differences have been proposed to account for this finding^[69,122,135].

CLINICAL CORRELATES OF ANXIETY DISORDER COMORBIDITY IN BD

Unlike demographic variables, there appeared to be considerably more uniformity regarding clinical correlates of anxiety comorbidity in BD.

Age of onset

Joslyn *et al*^[136] examined the effects of age of onset of BD on the clinical profile and outcome of BD in a meta-analysis of 15 studies including 7370 patients. An earlier age of onset was found to be significantly associated with comorbid bipolar and anxiety

Table 3 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from epidemiological studies

	Any anxiety disorder	Individual anxiety disorders
Lifetime prevalence rates		
ECA ^[72-74]		OCD 21%, PD 21%
NCS ^[75-77]	BD 93%	SP PHOBIA 67%, AGORA 62%, SOC PHOBIA 47%, GAD 43%, PTSD 39%, PD 33%, OCD 21%
NCS-R ^[78-80]	ANY BD 75%, BP I 87%, BP II 83%-89%, ST-BD 63%-72%	SOC PHOBIA 38%, SP PHOBIA 35%, SAD 35%, GAD 30%, PTSD 24%, PD 20%, OCD 14%-23%, AGORA 6%
WMH ^[81]	Bipolar spectrum 63%, BP I 77%, BP II 75%, ST-BD 53%	¹ SP PHOBIA 30%, ¹ SAD 29%, SOC PHOBIA 26%, GAD 20%, PTSD 19%, OCD 12%, PD 11%, AGORA 6%
NESARC ^{[82-84]2}	BD 60%, BP I 65%, BP II 45%	PD 53%, GAD 51%, SAD 48%, SP PHOBIA 21%-34%, PD 19%-33%, GAD 18%-32%, SOC PHOBIA 18%-26%, AGORA 0.2%-1%
Edmonton, Alberta, Canada ^[87]		PHOBIA 54%, PD 18%, OCD 15%
OADP study ^[88]	33% among adolescents with BD	SEP ANX 18%-22%, PHOBIA 4%-11%, PD 3%-11%, OCD 3%
Zurich Cohort Study ^[89]	Hypomania - any anxiety disorders 46%-78%	SOC PHOBIA 10%-36%, AGORA 7%-29%, SP PHOBIA 10%-23%, PD 12%-22%, OCD 5%-6%
National Epidemiologic Survey, Hungary ^[90]	BD 39%	GAD 14%, SP PHOBIA 13%, PD 11%, AGORA 9%, SOC PHOBIA 8%, OCD 3%
Population-based study from Hungary ^[91]	BP I 54%, BP II 100%	AGORA 22%-37%, GAD 10%-21%, SP PHOBIA 9%-17%, PD 7%-12%, SOC PHOBIA 4%-12%
Sesto Fiorentino Study, Italy ^[92]		In BD and ST-BD: GAD 28%-39%, SOC PHOBIA 13%-20%, OCD 16%-17%, PD 6%-16%, SP PHOBIA 4%
EDSP study ^[93]	BP I 55%, BP II 59%, ST-BD 53% (in 14-24-year-olds with BD)	SP PHOBIA 19%-38%, GAD 10%-18%, SOC PHOBIA 14%-16%, AGORA 5%-16%, OCD 3%-16%, PD 3%-12%, PTSD 9%-11%
Canadian Community Health Survey ^[94,95]	BD 52%-61%	
Singapore Mental Health Study ^[96]		In BD: OCD 26%, GAD 18%
Current prevalence rates		
Australian National Survey ^[97]	BD 52%	PD 26%, GAD 25%, SOC PHOBIA 19%, PTSD 11%, OCD 9%, AGORA 6%
Australian National Survey ^[98]	BD 7%-9%	SOC PHOBIA 5%-7%, PTSD 4%-7%, GAD 4%-6%, PD 4%-5%, OCD 4%-5%, AGORA 2%-3%
Canadian Community Health Survey ^[99]	BD 29%	SOC PHOBIA 17%, PD 13%, AGORA 3%

¹Only for bipolar spectrum disorders; ²National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) prevalence among elderly-generalized anxiety disorder (GAD): lifetime 2.5%; current 1%, and panic disorder (PD)-lifetime 2.5%; current 2%-NESARC prevalence among youth-lifetime anxiety disorder 15%; GAD 29%-PD 22%-Social phobia 14%^[85,86]. BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; ST-BD: Sub-threshold bipolar disorder; ECA: Epidemiologic Catchment Area Study; NCS: National Comorbidity Survey; NCS-R: National Comorbidity Survey-Replication study; WMH: World Mental Health surveys; NESARC: National Epidemiologic Survey on Alcohol and Related Conditions; OADP: Oregon Adolescent Depression Project; EDSP: Early Developmental Stages of Psychopathology study; AGORA: Agoraphobia; GAD: Generalized anxiety disorder; OCD: Obsessive compulsive disorder; PD: Panic disorder; PTSD: Post-traumatic stress disorder; SAD: Social anxiety disorder; SEP ANX: Separation anxiety disorder; SOC PHOBIA: Social phobia; SP PHOBIA: Specific phobia.

disorders with an odds ratio of more than two. The association with early onset has been replicated by other meta-analytic reviews of total anxiety disorder comorbidity and meta-analyses of individual anxiety disorders including comorbid GAD, OCD, and panic disorders^[18,20,30,33,36]. This relationship has been further endorsed by several systematic reviews of comorbid anxiety disorders in BD^[9,10,16,17,22]. Higher prevalence of anxiety disorders among those with a younger age of onset has also been found in epidemiological surveys^[73,80,86,93,132] as well as large-scale clinical studies of BD^[100,106,107,110,113]. Moreover, earlier age of onset has been associated with poorer outcome in patients with BD and comorbid anxiety disorders^[8,17].

Predominance of depression

A depressive onset, *i.e.* the first lifetime episode being a depressive one, has been reported more commonly among those with anxiety disorder comorbidity. Comorbid anxiety disorders have also been linked to more frequent and severe episodes of depression in BD. Impaired functioning, poor quality of life, and higher risk of suicide have been attributed to the predominance depressive pathology in comorbid anxiety disorders and BD^[15,16,18,36,42]. In contrast, the relationship of this comorbidity with mania

Table 4 Prevalence of anxiety disorder comorbidity in bipolar disorder: Evidence from selected large-scale clinical studies

	Any anxiety disorder	Individual anxiety disorders
Stanley foundation studies		
McElroy <i>et al</i> ^[100] , 2001 (<i>n</i> = 288)	Lifetime rate 42%; Current rate 30%	PD lifetime 20%, current 9%; SOC PHOBIA lifetime 16%, current 13%; SP PHOBIA lifetime 10%, current 8%; OCD lifetime 9%, current 8%; PTSD lifetime 7%, current 4%; GAD lifetime 3%, current 3%
Suppes <i>et al</i> ^[101] , 2001 (<i>n</i> = 261)	Lifetime rate 44%	
Dittmann <i>et al</i> ^[102] , 2002 (<i>n</i> = 152)	Lifetime rate 12%	
Levander <i>et al</i> ^[103] , 2007 (<i>n</i> = 350)	Lifetime rate BD 46%; BP I 45%-48%; BP II 38%-58%	
Altshuler <i>et al</i> ^[104] , 2010 (<i>n</i> = 711)	Lifetime rate: women 46%, men 29%	Lifetime rates: PD women 21%, men 14%; SOC PHOBIA women 12%, men 10%; SP PHOBIA women 12%, men 4%; OCD women 12%, men 7%; PTSD women 11%, men 3%; AGORA women 3%, men 2%
STEP-BD		
Kogan <i>et al</i> ^[105] , 2004 (<i>n</i> = 1000)	Lifetime rate 47%	
Perlis <i>et al</i> ^[106] , 2004 (<i>n</i> = 983)	Prevalence rate 38%-69%	SOC PHOBIA 13%-31%, GAD 13%-29%, PD 14%-27%, PTSD 11%-27%, OCD 8%-13%, AGORA 5%-11%
Simon <i>et al</i> ^[107] , 2004 (<i>n</i> = 475)	Lifetime rate BD 51%; BP I/BP II 53%/46%; Current BD 30%; BP I/BP II 34%/19%;	Lifetime BD: SAD 22%, GAD 18%, PD 17%, PTSD 17%, OCD 10%, AGORA 8%; current BD: SAD 13%, PD 8%, OCD 6%, PTSD 5%, AGORA 4%, GAD 2%
Simon <i>et al</i> ^[108] , 2004 (<i>n</i> = 919)	Current rate 32%	GAD 13%, SAD 13%, PD 8%, OCD 7%, PTSD 5%, AGORA 4%
Otto <i>et al</i> ^[109] , 2006 (<i>n</i> = 1000)	Current rate 32%	Current rates: SAD 13%, GAD 13%, PD 8%, OCD 7%, PTSD 5%, AGORA 4%
Simon <i>et al</i> ^[110] , 2007 (<i>n</i> = 120)	Lifetime rate 62%; current rate 29%	GAD lifetime 31%, current 13%; SAD lifetime 27%, current 14%; PD lifetime 22%, current 5%; PTSD lifetime 27%, current 11%; OCD lifetime 11%, current 6%; AGORA lifetime 9%, current 2%
Other studies		
Vieta <i>et al</i> ^[111] , 2001 (<i>n</i> = 129)		PD 2%, SOC PHOBIA 2%, SP PHOBIA 2%, OCD 2%
MacKinnon <i>et al</i> ^[112] , 2002 (<i>n</i> = 192)		Prevalence PD 14%
Henry <i>et al</i> ^[113] , 2003 (<i>n</i> = 318)	Lifetime rates 24%	Lifetime rates: PD 16%, PHOBIA 11%, OCD 3%
Boylan <i>et al</i> ^[114] , 2004 (<i>n</i> = 138)	Prevalence 56%	
Bauer <i>et al</i> ^[114] , 2005 (<i>n</i> = 328)	Lifetime rate 43%; current rate 38%	PTSD lifetime 28%, current 25%; PD lifetime 20%, current 17%; OCD lifetime 11%, current 8%
Mantere ^[28] , 2007 (<i>n</i> = 191)	Lifetime rate: BD 53%, BP I 46%, BP II 60%; current rate: BD 45%, BP I 36%, BP II 52%	PD lifetime 32%, current 24%; SOC PHOBIA lifetime 26%, current 18%; PTSD lifetime 16%, current 10%; GAD lifetime 15%; SP PHOBIA lifetime 8%, current 8%; OCD lifetime 5%, current 2%; AGORA lifetime 3%, current 2%
Azorin <i>et al</i> ^[115] , 2009 (<i>n</i> = 1090)	Lifetime rate 27%	Lifetime rates: GAD 20%, PD 5%, AGORA 4%, SOC PHOBIA 2%, PTSD 2%, OCD 1.5%
Coryell <i>et al</i> ^[116] , 2009 (<i>n</i> = 259)		Lifetime rates: PHOBIA 3%-6%, GAD 1%-5%, PD 1%-4%, OCD 2%
Gao <i>et al</i> ^[117] , 2010 (<i>n</i> = 564)	Prevalence in RCBD 46%	
Guo <i>et al</i> ^[118] , 2010 (<i>n</i> = 136763)	Prevalence 36%-37%	
Mantere <i>et al</i> ^[119] , 2010 (<i>n</i> = 191)	Current rate 31%-44%	
Fracalanza <i>et al</i> ^[120] , 2011 (<i>n</i> = 186)	Current rate 33%	Current rates: SAD 39%, PD 31%, OCD 16%, GAD 10%, PTSD 3%
Goes <i>et al</i> ^[121] , 2012 (<i>n</i> = 1416)		Prevalence: PD 23%, SP PHOBIA 10%, SOC PHOBIA 8%, OCD 6%
Chang <i>et al</i> ^[122] , 2012 (<i>n</i> = 325)	Lifetime rates: BP I 27%, BP II 39%	Lifetime rates (BP I/BP II): GAD 10%/29%, PD 5%/9%, SOC PHOBIA 4%/5%, PTSD 3%/2%, OCD 2%/4%, SP PHOBIA 1%/4%
Angst <i>et al</i> ^[123] , 2013 (<i>n</i> = 903)	Mean prevalence: BP I 17%; BP II 27%	Mean prevalence (BP I/BP II): GAD 6%/12%, PD 12%/18%, SOC PHOBIA 5%/8%, OCD 6%/11%
Castilla-Puentes <i>et al</i> ^[124] , 2013 (<i>n</i> = 8129 youth)	Prevalence: Non RCBD 51%; RCBD 65%; BP I 41%-65%; BP II 69%-75%;	Prevalence (RCBD): GAD 55%, SAD 44%, OCD 11%, PTSD 9%, PD 9%, SP PHOBIA 8%

Young <i>et al</i> ^[125] , 2013 (<i>n</i> = 304)	Lifetime rate 22%	PD 40%, SP PHOBIA 24%, OCD 15%, GAD 13%, SAD 10%, AGORA 8%
Asaad <i>et al</i> ^[126] , 2014 (<i>n</i> = 350)	Prevalence 2.3%	
Baek <i>et al</i> ^[127] , 2014 (<i>n</i> = 417)	Lifetime rate 30%	Lifetime rates: PD 13%, SP PHOBIA 13%, OCD 13%, SOC PHOBIA 9%

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; RCBD: Rapid cycling bipolar disorder; STEP-BD: Systematic Treatment Enhancement Program for Bipolar Disorder.

was much less evident^[8,14,16,18,36].

Other clinical features

Rapid cycling, mixed states or features, and psychotic symptoms are other clinical characteristics frequently associated with anxiety disorder comorbidity in BD^[8,9,16,17,22].

Additional comorbidities

Among all comorbid conditions associated with anxiety disorder comorbidity in BD, the most common was substance use comorbidity. Patients with comorbid anxiety disorders and BD were twice as likely to have an additional diagnosis of SUD^[9]. The high prevalence of comorbid SUDs in those with anxiety disorders and BD has been noted by a number of meta-analyses and systematic reviews^[8,18,20,22,42]. It has been repeatedly documented by almost all major epidemiological studies^[74,87,150,152,153], and by the Systematic Treatment Enhancement Program for Bipolar Disorder and Stanley Foundation studies, as well as other large-scale clinical studies of anxiety disorder comorbidity^[14,52,100,114,117]. Conversely, only a few studies have been unable to find this relationship between anxiety disorders and SUDs in BD^[9,28,113]. The presence of a combination of anxiety disorders and SUDs in BD not only complicates the diagnosis, but also impairs treatment response and can lead to a more severe course of illness and increased suicidal risk^[10,17,27,69,154]. Apart from associated SUD comorbidity, anxiety disorders in BD have also been linked with other comorbid conditions such as attention deficit hyperkinetic disorders, eating disorders, and a range of personality disorders^[9,14,18,22,42]. Rates of medical comorbidity were also greater in those with comorbid anxiety disorders and BD^[155,156].

Bipolar subtypes

In contrast to other clinical correlates, findings regarding the association of anxiety disorder comorbidity with bipolar subtypes I and II have been equivocal and contradictory. While one meta-analysis found somewhat greater rates in patients with bipolar subtype II^[20], others have either found a higher prevalence of anxiety disorders in bipolar subtype I^[30,33], or more commonly, no significant differences between the two subtypes^[18,19,32,36]. This inconsistent association between anxiety disorders and bipolar subtypes has also been found in other reviews^[8,10,15-17], in epidemiological studies^[78,81,82,84,91], and in clinical samples of patients with BD^[52,100,120]. On the other hand, more than a few reviews have reported a considerably higher prevalence of bipolar spectrum disorders^[7,42,46,66,128], sub-threshold BD, or subsyndromal bipolar symptoms^[7,14,66,69,139] among comorbid anxiety and BDs.

IMPACT OF ANXIETY DISORDER COMORBIDITY IN BD

As is evident from Table 5, existing literature has been fairly consistent in reporting the widespread negative impact of anxiety disorder comorbidity among patients with BD on almost all aspects of the course and outcome of the illness.

Increased symptom-burden

The presence of anxiety disorders in BD has been linked with a marked increase in symptom-burden including increased psychological distress, increased irritability, greater severity of acute episodes, and greater burden of both manic and depressive symptoms.

Longer episodes

The greater severity of mood episodes in individuals with comorbid anxiety disorders is also reflected by the longer duration of these episodes, particularly depressive ones, and the higher rates of chronicity in BD with anxiety disorders.

Poorer remission and recovery

Patients with comorbid bipolar and anxiety disorders have been found to have

Table 5 Correlates and impact of anxiety disorder comorbidity in bipolar disorder

	Principal findings	Ref.
Demographic correlates		
Age	Higher prevalence in younger patients with BD	[8,20,30,32,40,42]
	No differences in rates according to age	[9,33,36,70]
Gender	Higher prevalence among women	[8-10,14,16-18,24, 40]
	No gender differences	[30,32,33,36,42,52,69,70]
Marital status	No differences according to marital status	[20,70]
Education	Higher levels more comorbidity	[20]
	Lower levels greater comorbidity	[8,9,14,66]
	No effect of education	[33,36,70]
Socioeconomic status	Greater comorbidity among those with lower socioeconomic status	[8,9,14,74]
	No effect of socioeconomic status	[33,36]
Ethnic and cross-national differences	Differences in comorbidity across nations and ethnicities	[11,16,19,30,69,74,135]
Clinical correlates		
Age of onset	Lower age of onset is associated with higher levels of comorbidity	[8-10,14,16-18,20,21-24,27,30,31,33,36,40,42,49,52,56,57,60,66,70,136-142]
BP I vs BP II	Greater comorbidity in BP I	[15,17,30,33,49,60,84]
	Greater comorbidity in BP II	[4,9,20,128]
	No clear differences in comorbidity between BP I and BP II	[7,8,10,16,18,19,28,32,36,42,50,52,66,69,78-81,93,137]
Depression	Anxiety comorbidity is associated with more frequent and severe depressive episodes	[8,10,14-17,26,36,42,49,52,57,66,69,137-139,143]
	No clear evidence of predominance of depressive pathology	[19,28,70]
Mania	Anxiety comorbidity is associated with more frequent and severe manic episodes	[8,16,19]
	No clear evidence of association with mania	[14,18,28,36,40,49,70]
Euthymia	Anxiety comorbidity is associated with shorter durations of euthymia	[8,9,14,16,17,21,22,50,52,66,67,69]
Rapid cycling and mixed features	Anxiety comorbidity is associated with rapid cycling and mixed states	[8-10,13,15-18,40,49,52,67,69,141,142]
	No association with rapid cycling and mixed features	[19,28,66,70,144]
Psychotic symptoms	Anxiety comorbidity is associated with psychotic symptoms	[5,8,16,20,22,25,40]
	No association with psychotic symptoms	[70]
Insight	Anxiety comorbidity is associated with greater insight	[9]
Cognitive impairment	Anxiety comorbidity is associated with greater cognitive impairment	[15, 66]
Bipolar spectrum	Anxiety comorbidity is associated with bipolar spectrum disorders	[7,8,40,42,45,46,66,128]
Subsyndromal symptoms	Anxiety comorbidity is associated with subsyndromal symptoms	[14,66,69,139]
Substance-use disorders	Anxiety comorbidity is associated with greater prevalence of substance use and substance use disorders	[5,8-10,12-14,16-18,20,22-25,27,40,42,50,57,60,66,67,69,70,139,141-143]
Other comorbidity	Anxiety comorbidity is associated with greater prevalence of ADHD, eating disorders, personality disorders.	[9,12,14,20,22,42,139,145]
Impact		
Course of illness	Anxiety comorbidity is associated with poorer course and outcome in BD in terms of greater illness severity, frequent episodes, and greater risk of hospitalization	[5,8-10,13-18,20,22,23,26,27,33,36,40,42,49,52,56,57,60,70,128,137-139,141-143,146]
Treatment response	Anxiety comorbidity is associated with poorer treatment response in BD	[4-6,8-10,12-14,16-18,22-27,40,49,57,60,66,67,69,137-139,141,142,146,147]

Suicide	Anxiety comorbidity is associated with increased risk of suicidality in BD	[4,5,8-10,13,14-18,21-27,33,36,40,42,49,50,52,57,60,66,67,69,128, 136-139,141,142,148,149]
Functioning	Anxiety comorbidity is associated with impaired functioning in BD	[8-10,14-18,21,22,25,27,33,36,40,42,49,50,66,67,69,128,139]
Quality of life	Anxiety comorbidity is associated with impaired quality of life in BD	[8-10,14-17,21,22,25,27,36,39,42,50,66,67,138,139]
Outcome of BD	Anxiety comorbidity is associated with incomplete remission and recovery in BD	[5,8,10,14,16,17,21,22,26,36,50,66,69,128,138]
Adherence	Anxiety comorbidity is associated with irregular treatment-adherence in BD	[10,16]
Delayed diagnosis-costs-service utilization	Anxiety comorbidity is associated with delayed diagnosis increased health-care utilization and costs in BD	[24,27,41,49 69,137]

BD: Bipolar disorder; BP I: Bipolar disorder subtype I; BP II: Bipolar disorder subtype II; ADHD: Attention deficit hyperactivity disorder.

significantly longer times to remission, less likelihood of achieving complete remission or recovery, persistence of subsyndromal symptoms, shorter durations of remission, greater risk of developing an early relapse or recurrence, and higher risk for hospitalizations.

Impaired functioning and quality of life

Patients with comorbid anxiety disorders and BD have greater functional impairment and poorer quality of life than those without this comorbidity.

Inadequate treatment response

Many reviews and studies on anxiety disorder comorbidity in BD have also reported poorer treatment response, delayed diagnosis and institution of treatment, more severe medication side-effects, non-adherence with treatment, increased health-care utilization, and increased costs of care.

Elevated suicidal risk

A large meta-analysis of suicidal risk in BD found that comorbid anxiety disorders were strongly associated with suicide attempts with an odds ratio of two derived from eight studies^[148]. Another systematic review also found an increased risk of suicidal behaviour among patients with comorbid panic disorders^[149]. Similar increases in suicide risk have been reported among other comorbid anxiety disorders including GAD, PTSD, OCD, and social phobia^[33,36,42,45,50]. The elevated risk of suicide has been proposed to be the result of increased illness severity, greater depressive symptom-burden, additional SUD comorbidity, the presence of comorbid personality disorders, and several maladaptive traits such as impulsivity or neuroticism^[18,26,33,46,148].

TREATMENT OF ANXIETY DISORDER COMORBIDITY IN BD

In contrast to the substantial data on rates, correlates, and impact of anxiety disorder comorbidity in BD, research on the efficacy of different modalities of treatment for comorbid anxiety disorders in BD has been rather scarce. **Table 6** provides a brief summary of this research.

Treatment of anxiety comorbidity in BD is challenging because of inherent difficulties in diagnosing comorbid bipolar and anxiety disorders and the high prevalence of inadequate response to treatment^[6,10,17,18,172]. Treatment options include both pharmacotherapy and psychotherapy. Only two randomized-controlled trials of medication treatment have been conducted in comorbid BD and anxiety disorders. One showed some efficacy for olanzapine and lamotrigine in treating anxiety symptoms^[173], while the other failed to show similar efficacy for risperidone^[174]. Therefore, findings from treatment of bipolar depression have been extrapolated to provide the necessary evidence-base for pharmacotherapy of anxiety comorbidity in BD^[10,26,15,17,162]. However, despite the lack of evidence there appeared to be considerable consensus that the primary aim of treatment is mood stabilization, although there was little agreement about the mood stabilizer of choice^[6,7,9,10,162]. Following mood stabilization, treatment with other specific medications might be considered. Options include second-generation antipsychotics, specific serotonergic reuptake inhibitors, anticonvulsants, and benzodiazepines, though each medication group appears to have its advantages and disadvantages^[6,10,15,17,162]. Although psychotherapy, particularly cognitive behavioural treatment is also recommended as a first-line

Table 6 Treatment of anxiety disorder comorbidity in bipolar disorder

	Findings	Ref.
Pharmacotherapy		
Evidence base	Few RCTs of treatment of comorbid anxiety disorders in BD	[7-10,15,22,26,49,55,60,141,142,157-162]
	RCTs of treatment of BD reporting change in anxiety symptoms as secondary outcomes	[6,10,26,15,16,25,33,49,162]
Principles of treatment	Mood stabilization is the first priority	[3,6,7,9,10,12,15,48,49,55,128,157-159,162]
Add-on treatments	SGAs <i>e.g.</i> , quetiapine and olanzapine first line choices	[6,7,9,10,12,15,17,22,26,33,48,55,128,141,142,158-162]
	SSRIs <i>e.g.</i> , paroxetine but risk of mood destabilization	[6,7,9,10,12,15-17,22,25,26,33,48,55,128,157-159,162]
	Anticonvulsants <i>e.g.</i> , valproate, lamotrigine and gabapentin but no strong evidence	[6, 7, 9, 10, 12, 15, 17, 22, 25, 48, 55, 60, 67, 158, 159, 162]
	Benzodiazepines only for short-term treatment because of risk of abuse and dependence	[6,7,9,10,15-17,22,33,48,162,163]
Psychotherapy		
Evidence base	Psychotherapy such as CBT may be effective in promoting recovery in those with comorbid anxiety and BD but there are only a few RCTs	[10,22,25,26,162,164-171]
Principles of treatment	Psychotherapy such as CBT is a first-line add-on treatment option	[6,7,9,12,10,15,17,22,25,26,67,128,157-159,162,164,165]

BD: Bipolar disorder; RCTs: Randomized controlled trials; SGAs: Second generation antipsychotics; SSRIs: Specific serotonergic reuptake inhibitors; CBT: Cognitive behavioural treatment.

treatment option, the evidence base for cognitive behavioural treatment was meagre until recently^[164]. However, lately several new randomized-controlled trials of cognitive behavioural treatment have demonstrated its efficacy in treating anxiety symptoms in BD, making it a legitimate option for concomitant treatment of anxiety disorders in BD^[165,168-171].

AETIOLOGY OF ANXIETY DISORDER COMORBIDITY IN BD

Though there is no clarity regarding the aetiology of anxiety disorder comorbidity in BD, several lines of evidence have suggested that family genetics, neurobiology, trauma, and other psychosocial factors may be involved in the genesis of anxiety disorders in BD^[6,20]. Different conceptual models have been proposed to explain the co-occurrence of anxiety disorders and BD^[3,6,9,13,16]. The first model suggests that comorbid bipolar and anxiety disorders occur together simply by chance. However, the high rates of anxiety disorders in BD negate the possibility of a chance association. The second model suggests that a pathophysiological link between anxiety disorders and BD explains the high rates of anxiety disorder comorbidity in BD. Two possibilities exist within this conceptual model; either the anxiety disorder predisposes to the development of BD, or BD increases the chance of the anxiety disorder emerging. The first possibility is supported by studies indicating that anxiety disorders serve as prodromal conditions preceding the development of BD^[7,11,45,175,176]. The second possibility of BD contributing to emergence of anxiety disorders is indicated by the evidence suggesting that anxiety symptoms are an integral part of BD^[6,8,16], by the episodic course of anxiety disorders in a subset of patients with BD and anxiety disorders^[177], by familial genetic links between the two disorders^[9,10,17,69,178], and by the benefits of mood stabilization as a primary mode of treatment^[3,6,9,10]. The third model posits that higher-order pathophysiological mechanisms contribute to the onset of both anxiety disorders and BD. The list of such core pathophysiological processes includes familial genetic, neurobiological, and psychosocial factors. There is reasonable evidence suggesting genetic links between anxiety disorders and BD^[69,130,157], particularly for panic disorder^[53,57,112,128,179] and OCD^[40,42,70,176,178]. Neurotransmitter disturbances, structural and functional brain changes, and alterations of synaptic plasticity could also provide the common link^[9,10,20,53,130]. Psychosocial factors such as early childhood adversities, particularly trauma as an aetiological factor for comorbid PTSD, have also been implicated^[9,10,17,39,50]. Finally, a fundamental disturbance in affective regulation, suggested by the presence of abnormal temperamental and personality characteristics among those with BD and

comorbid anxiety disorders, is also a likely underlying mechanism^[9,33,50,180].

UNIQUE FEATURES OF ANXIETY DISORDER COMORBIDITY IN BD

In their review of publication trends on the subject, Provencher *et al*^[5] concluded that research on anxiety disorder comorbidity in BD, which had been expanding since the 1990s had almost stopped 20 years later. They also noted that the bulk of the publications were non-specific or descriptive in nature, with little research on causal mechanisms or management of this comorbidity. Similar apprehensions have been expressed by a number of other researchers^[6,9,18,70,137]. The results of the current review, however, suggested that such concerns might only be partly true. The present review identified more than 100 prior reviews and over 350 studies on the subject. Therefore, the volume of extant research on this comorbidity was by no means inadequate and interest in the topic does not appear to be diminishing. Then again, the findings of the current review also showed that the majority of the research pertains to rates, correlates, and impact of comorbid anxiety disorders in BD, while research on treatment and aetiological processes is relatively limited.

The principal findings of this review were consonant with prior research in profiling the unique features of anxiety comorbidity in BD. The results reiterated the fact that at least half of those with BD are likely to develop an anxiety disorder in their lifetimes and a third of them will manifest an anxiety disorder at any point of time. The markedly elevated rates of anxiety disorders in BD were not only several fold higher than general population rates of anxiety disorders^[18-20,23,35], but also higher than those found in unipolar disorders^[6,13,15,20,43] and schizophrenia^[181,182]. There was also some evidence, particularly from epidemiological studies, to indicate that anxiety disorders may be the most common comorbid conditions in BD and even more prevalent than comorbid SUDs^[8,15,20,60,183]. Other notable characteristics included the coexistence of multiple anxiety disorders and additional comorbidities, especially the link with SUDs. The adverse clinical profile of comorbid bipolar and anxiety disorders as well as its association with poorer course and outcome, including the strong association with increased suicidality were additional distinctive features of anxiety disorder comorbidity in BD. Although these aspects of comorbid anxiety and BDs have been documented earlier, by collating findings from a larger and updated database the present review re-emphasized the significance and uniformity of these findings across multiple types of reports. Moreover, being based on more reliable sources of evidence it provided stronger endorsement for these unique attributes of comorbid anxiety disorders in BD.

LACUNAE IN EXISTING RESEARCH

Treatment and aetiological research

Although concomitant anxiety disorders have important implications for management of BD, evidence on this aspect was scarce. Additionally, the lack of research on aetiology of comorbid bipolar and anxiety disorders was also evident. The expectation that examination of this comorbidity would reveal the etiopathogenetic processes underlying BD has thus not been fully realized.

Methodological issues

Despite the sizeable body of evidence on anxiety disorder comorbidity in BD, meta-analytic reviews have indicated that only 50 studies or less are of sufficient methodological rigor^[11,18,19,30,34]. The same meta-analyses have revealed significant heterogeneity in rates of anxiety disorders, while almost all the other reviews have also noted the wide variation in rates. Many potential sources of bias could account for this discrepancy across studies including the method of diagnostic ascertainment, the type of investigators employed, the source and nature of patient samples, study designs, and the type of rates used^[11,15,16,26,27]. Notwithstanding these numerous methodological confounders, two meta-analyses have concluded that all these methodological variables did not fully explain the heterogeneity in rates across studies, suggesting that unknown and unexplored factors were possibly the chief sources of the differences found^[19,35].

Conceptual issues

Although there is substantial evidence that anxiety disorder comorbidity is commonplace in BD, critics have proposed that some of this apparent comorbidity

could be an artefact of current nosological systems and diagnostic practices^[3,13,157,184,185]. In medicine (from where the term comorbidity originates), Feinstein's definition specified that the two co-occurring disorders should be independent and distinct, presumably based on aetiological differences between the disorders^[186]. This concept cannot be easily transposed to psychiatry because of the lack of knowledge about the causes of most psychiatric disorders and because of overlap in diagnostic criteria sets in current classifications^[26,28,139,184]. Therefore, it remains uncertain whether this comorbidity is a product of two independent disorders, or of additive interactions between two coexisting disorders, or simply a part of the range of symptomatic expression of BD^[11,18,22,26]. True comorbidity presupposes that the comorbid conditions will be fully diagnosable axis I or axis II disorders with minimal overlap in the content of their symptoms^[1,3]. However, certain studies have moved beyond these precise definitions by including sub-threshold anxiety disorders or anxiety symptoms as a part of the anxiety disorder comorbidity of BD. This often leads to over-diagnosis and over-inflated rates of comorbidity^[3,13]. Finally, a series of meta-analyses, systematic reviews, and studies of comorbid OCD in BD have found that spurious comorbidity, in which OCD was confined to the depressive episodes and disappeared during mania or remission, was present in nearly 50% to 75% of patients with BD-OCD comorbidity^[30,32,42,68,177]. Truly comorbid OCD, where OC symptoms were not confined exclusively to mood episodes was less common. Unfortunately, there are very few longitudinal studies of BD, which could allow an accurate estimation of the rates of such true anxiety disorder comorbidity in BD.

LIMITATIONS OF THE PRESENT REVIEW

Though the current review was based on a reasonably comprehensive literature search, some sources especially those not in English may have been missed. Additionally, the present review relied mainly on results of prior meta-analyses and reviews, while it only included selected epidemiological and clinical studies. Thus, some findings from smaller studies might have been ignored. Moreover, it was difficult to know which source to trust when findings from the three sources were in conflict. However, an attempt was always made to present a balanced perspective by considering both the more dependable findings from research as well as the controversial ones.

CONCLUSIONS

Despite the deficiencies of research and limitations of the present review, it is quite clear that clinicians need to be fully aware of the substantial nature of anxiety disorder comorbidity in BD and its deleterious consequences, especially because it often goes unrecognized in routine clinical practice^[9,12,33,46]. Such awareness is necessary for proper identification and accurate diagnosis of both BD and the anxiety disorder^[3,6,9,15,19]. Firstly, patients with BD will need to be routinely screened for the presence of anxiety disorders; when detected a comprehensive and systematic assessment of the anxiety disorder comorbidity should be performed. Similarly, clinicians should examine patients presenting with anxiety disorders for the presence of comorbid BD^[3,7,8,30,45]. Secondly, while managing anxiety disorder comorbidity in BD precedence is almost always given to adequate mood stabilization as the first step in treatment^[3,6,7,9,10]. Following this, clinicians can either adopt a sequential or a hierarchical approach to treatment^[3,10]. The hierarchical approach involves determining the primary condition and comprehensively managing it before focusing on the treatment of the secondary condition^[3]. In the more commonly used sequential approach, after initial mood stabilization a stepped-care strategy may be employed in which pharmacological and psychosocial interventions can be added sequentially depending on the patient's treatment needs^[3,10,164]. In either approach utmost caution must be exercised to prevent the treatment of one condition from adversely affecting the outcome of the other. The final component of management is regular monitoring and on-going treatment to prevent the long-term adverse consequences of this comorbidity^[48].

For researchers there are many unresolved questions to answer including the significance of anxiety disorder comorbidity in BD, the nature of its underlying mechanisms, and the best possible ways to effectively manage this comorbidity^[5,13,18,20,26]. The current investigative methodology needs to be improved by examining truly representative samples of patients, focusing on individual disorders as well as overall anxiety disorder comorbidity, and by longitudinal and more in-

depth analyses of comorbid anxiety and BDs. However, since added efforts on the part of both clinicians as well as researchers are likely to alleviate the burden of anxiety comorbidity on patients with BD, they are worth pursuing.

REFERENCES

- 1 **Wittchen HU.** Critical issues in the evaluation of comorbidity of psychiatric disorders. *Br J Psychiatry Suppl* 1996; 9-16 [PMID: 8864144 DOI: 10.1192/S000712500029836X]
- 2 **Goldberg JF,** Fagin-Jones S. Diagnosing and treating anxiety comorbidity in bipolar disorders. *Psychiatr Ann* 2004; **34**: 874-884 [DOI: 10.3928/0048-5713-20041101-16]
- 3 **Parker GB.** Comorbidities in bipolar disorder: models and management. *Med J Aust* 2010; **193**: S18-S20 [PMID: 20712555]
- 4 **Saunders KEA,** Goodwin GM. The course of bipolar disorder. *Adv Psychiatr Treat* 2010; **16**: 318-330 [DOI: 10.1192/apt.bp.107.004903]
- 5 **Provencher MD,** Guimond AJ, Hawke LD. Comorbid anxiety in bipolar spectrum disorders: a neglected research and treatment issue? *J Affect Disord* 2012; **137**: 161-164 [PMID: 22209124 DOI: 10.1016/j.jad.2011.12.001]
- 6 **Freeman MP,** Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. *J Affect Disord* 2002; **68**: 1-23 [PMID: 11869778 DOI: 10.1016/S0165-0327(00)00299-8]
- 7 **Perugi G,** Toni C. Bipolarity presenting as anxiety disorders. *Prim Psychiatry* 2004; **11**: 31-35
- 8 **McIntyre RS,** Soczynska JK, Bottas A, Bordbar K, Konarski JZ, Kennedy SH. Anxiety disorders and bipolar disorder: a review. *Bipolar Disord* 2006; **8**: 665-676 [PMID: 17156153 DOI: 10.1111/j.1399-5618.2006.00355.x]
- 9 **Tamam L.** Comorbid anxiety disorders in bipolar disorder patients: a review. *Turk Psikiyatri Derg* 2007; **18**: 59-71 [PMID: 17364269]
- 10 **Schaffer A,** McIntosh D, Goldstein BI, Rector NA, McIntyre RS, Beaulieu S, Swinson R, Yatham LN; Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force. The CANMAT task force recommendations for the management of patients with mood disorders and comorbid anxiety disorders. *Ann Clin Psychiatry* 2012; **24**: 6-22 [PMID: 22303519]
- 11 **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**: 1405-1419 [PMID: 26629535 DOI: 10.1016/j.ebiom.2015.09.006]
- 12 **Sasson Y,** Chopra M, Harrari E, Amitai K, Zohar J. Bipolar comorbidity: from diagnostic dilemmas to therapeutic challenge. *Int J Neuropsychopharmacol* 2003; **6**: 139-144 [PMID: 12890307 DOI: 10.1017/S1461145703003432]
- 13 **Issler CK,** Sant'anna MK, Kapczinski F, Lafer B. [Anxiety disorders comorbidity in bipolar disorder]. *Braz J Psychiatry* 2004; **26** Suppl 3: 31-36 [PMID: 15597137 DOI: 10.1590/S1516-44462004000700008]
- 14 **Bauer MS,** Altshuler L, Evans DR, Beresford T, Williford WO, Hauger R; VA Cooperative Study #430 Team. Prevalence and distinct correlates of anxiety, substance, and combined comorbidity in a multi-site public sector sample with bipolar disorder. *J Affect Disord* 2005; **85**: 301-315 [PMID: 15780700 DOI: 10.1016/j.jad.2004.11.009]
- 15 **Kauer-Sant'Anna M,** Kapczinski F, Vieta E. Epidemiology and management of anxiety in patients with bipolar disorder. *CNS Drugs* 2009; **23**: 953-964 [PMID: 19845416 DOI: 10.2165/11310850-000000000-00000]
- 16 **Maina G,** Rosso G, Aguglia A, Chiodelli DF, Bogetto F. Anxiety and bipolar disorders: epidemiological and clinical aspects. *Giorn Ital Psicopat* 2011; **17**: 365-375
- 17 **El-Mallakh RS,** Hollifield M. Comorbid anxiety in bipolar disorder alters treatment and prognosis. *Psychiatr Q* 2008; **79**: 139-150 [PMID: 18491230 DOI: 10.1007/s11226-008-9071-5]
- 18 **Vázquez GH,** Baldessarini RJ, Tondo L. Co-occurrence of anxiety and bipolar disorders: clinical and therapeutic overview. *Depress Anxiety* 2014; **31**: 196-206 [PMID: 24610817 DOI: 10.1002/da.22248]
- 19 **Pavlova B,** Perlis RH, Alda M, Uher R. Lifetime prevalence of anxiety disorders in people with bipolar disorder: a systematic review and meta-analysis. *Lancet Psychiatry* 2015; **2**: 710-717 [PMID: 26249302 DOI: 10.1016/S2215-0366(15)00112-1]
- 20 **Yapici Eser H,** Kacar AS, Kilciksiz CM, Yalçınay-Inan M, Ongur D. Prevalence and associated features of anxiety disorder comorbidity in bipolar disorder: a meta-analysis and meta-regression study. *Front Psychiatry* 2018; **9**: 229 [PMID: 29997527 DOI: 10.3389/fpsyt.2018.00229]
- 21 **Bhagwagar Z.** Bipolar disorder and its comorbidities. *Medscape Psychiatry* 2007
- 22 **Latalova K,** Prasko J, Grambal A, Havlikova P, Jelenova D, Mainerova B, Kamaradova D, Ociskova M, Sedlackova Z, Sandoval A. Bipolar disorder and anxiety disorders. *Neuro Endocrinol Lett* 2013; **34**: 738-744 [PMID: 24522015]
- 23 **Ketter TA.** Recognizing the extent of overlap between bipolar disorder and anxiety disorders. *EBioMedicine* 2015; **2**: 1284-1285 [PMID: 26629510 DOI: 10.1016/j.ebiom.2015.09.022]
- 24 **Hirschfeld RM,** Vornik LA. Bipolar disorder--costs and comorbidity. *Am J Manag Care* 2005; **11**: S85-S90 [PMID: 16097719]
- 25 **Lohano K,** El-Mallakh RS. The anxious bipolar patient. *Psychiatric Times* 2011; **28**: 1-4
- 26 **Goes FS.** The importance of anxiety states in bipolar disorder. *Curr Psychiatry Rep* 2015; **17**: 3 [PMID: 25617037 DOI: 10.1007/s11920-014-0540-2]
- 27 **Keller MB.** Prevalence and impact of comorbid anxiety and bipolar disorder. *J Clin Psychiatry* 2006; **67** Suppl 1: 5-7 [PMID: 16426110]
- 28 **Mantere O.** Recognition, comorbidity, and outcome of DSM-IV bipolar I and II disorders in psychiatric care. . Helsinki: National Public Health Institute; 2007; 1-110
- 29 **Kowatch RA,** Youngstrom EA, Danielyan A, Findling RL. Review and meta-analysis of the phenomenology and clinical characteristics of mania in children and adolescents. *Bipolar Disord* 2005; **7**: 483-496 [PMID: 16403174 DOI: 10.1111/j.1399-5618.2005.00261.x]
- 30 **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 [PMID: [26233320](#) DOI: [10.1016/j.jad.2015.06.005](#)]
- 31 **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**: 1066-1067 [PMID: [26399870](#) DOI: [10.1177/0004867415605642](#)]
- 32 **Amerio A**, Stubbs B, Odone A, Tonna M, Marchesi C, Nassir Ghaemi S. Bipolar I and II disorders; a systematic review and meta-analysis on differences in comorbid obsessive-compulsive disorder. *Iran J Psychiatry Behav Sci* 2016; **10**: e3604 [PMID: [27826323](#) DOI: [10.17795/ijpbs-3604](#)]
- 33 **Preti A**, Vrublevska J, Veroniki AA, Huedo-Medina TB, Fountoulakis KN. Prevalence, impact and treatment of generalised anxiety disorder in bipolar disorder: a systematic review and meta-analysis. *Evid Based Ment Health* 2016; **19**: 73-81 [PMID: [27405742](#) DOI: [10.1136/eb-2016-102412](#)]
- 34 **Taskiran S**, Fakultesi T, Yapici-Eser H, Mutluer T, Kilic O, Ozcan A, Nefci I, Yalcinay M, Ongur D. A meta-analysis of anxiety disorder comorbidity in pediatric bipolar disorder. *J Am Acad Child Adolesc Psychiatry* 2016; **55**: S213 [DOI: [10.1016/j.jaac.2016.09.350](#)]
- 35 **Pavlova B**, Perlis RH, Mantere O, Sellgren CM, Isometsä E, Mitchell PB, Alda M, Uher R. Prevalence of current anxiety disorders in people with bipolar disorder during euthymia: a meta-analysis. *Psychol Med* 2017; **47**: 1107-1115 [PMID: [27995827](#) DOI: [10.1017/S0033291716003135](#)]
- 36 **Preti A**, Vrublevska J, Veroniki AA, Huedo-Medina TB, Kyriazis O, Fountoulakis KN. Prevalence and treatment of panic disorder in bipolar disorder: systematic review and meta-analysis. *Evid Based Ment Health* 2018; **21**: 53-60 [PMID: [29636354](#) DOI: [10.1136/eb-2017-102858](#)]
- 37 **Strakowski SM**, McElroy SL, Keck PW Jr, West SA. The co-occurrence of mania with medical and other psychiatric disorders. *Int J Psychiatry Med* 1994; **24**: 305-328 [PMID: [7737787](#) DOI: [10.2190/CM8E-46R5-9AJL-03FN](#)]
- 38 **Krishnan KR**. Psychiatric and medical comorbidities of bipolar disorder. *Psychosom Med* 2005; **67**: 1-8 [PMID: [15673617](#) DOI: [10.1097/01.psy.0000151489.36347.18](#)]
- 39 **Quarantini LC**, Netto LR, Andrade-Nascimento M, Almeida AG, Sampaio AS, Miranda-Scippa A, Bressan RA, Koenen KC. [Comorbid mood and anxiety disorders in victims of violence with posttraumatic stress disorder]. *Braz J Psychiatry* 2009; **31** Suppl 2: S66-S76 [PMID: [19967202](#) DOI: [10.1590/S1516-44462009000600005](#)]
- 40 **Pallanti S**, Grassi G, Sarrecchia ED, Cantisani A, Pellegrini M. Obsessive-compulsive disorder comorbidity: clinical assessment and therapeutic implications. *Front Psychiatry* 2011; **2**: 70 [PMID: [22203806](#) DOI: [10.3389/fpsy.2011.00070](#)]
- 41 **Lala SV**, Sajatovic M. Medical and psychiatric comorbidities among elderly individuals with bipolar disorder: a literature review. *J Geriatr Psychiatry Neurol* 2012; **25**: 20-25 [PMID: [22467842](#) DOI: [10.1177/0891988712436683](#)]
- 42 **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**: 343-358 [PMID: [24506190](#) DOI: [10.1111/acps.12250](#)]
- 43 **Frias Á**, Palma C, Farriols N. Comorbidity in pediatric bipolar disorder: prevalence, clinical impact, etiology and treatment. *J Affect Disord* 2015; **174**: 378-389 [PMID: [25545605](#) DOI: [10.1016/j.jad.2014.12.008](#)]
- 44 **Sharma V**. Relationship of bipolar disorder with psychiatric comorbidity in the postpartum period-a scoping review. *Arch Womens Ment Health* 2018; **21**: 141-147 [PMID: [29067549](#) DOI: [10.1007/s00737-017-0782-1](#)]
- 45 **Himmelhoch JM**. Social anxiety, hypomania and the bipolar spectrum: data, theory and clinical issues. *J Affect Disord* 1998; **50**: 203-213 [PMID: [9858079](#) DOI: [10.1016/S0165-0327\(98\)00139-6](#)]
- 46 **Hantouche EG**, Kochman F, Demonfaucon C, Barrot I, Millet B, Lancrenon S, Akiskal HS. [Bipolar obsessive-compulsive disorder: confirmation of results of the "ABC-OCD" survey in 2 populations of patient members versus non-members of an association]. *Encephale* 2002; **28**: 21-28 [PMID: [11963340](#)]
- 47 **McIntyre R**, Katzman M. The role of atypical antipsychotics in bipolar depression and anxiety disorders. *Bipolar Disord* 2003; **5** Suppl 2: 20-35 [PMID: [14700010](#)]
- 48 **Ghaemi NS**. Anxiety and bipolar disorder. *Medscape Psychiatry* 2004
- 49 **McIntyre RS**, Konarski JZ, Yatham LN. Comorbidity in bipolar disorder: a framework for rational treatment selection. *Hum Psychopharmacol* 2004; **19**: 369-386 [PMID: [15303241](#)]
- 50 **Otto MW**, Perlman CA, Wernicke R, Reese HE, Bauer MS, Pollack MH. Posttraumatic stress disorder in patients with bipolar disorder: a review of prevalence, correlates, and treatment strategies. *Bipolar Disord* 2004; **6**: 470-479 [PMID: [15541062](#) DOI: [10.1111/j.1399-5618.2004.00151.x](#)]
- 51 **Simon NM**, Fischmann D. The implications of medical and psychiatric comorbidity with panic disorder. *J Clin Psychiatry* 2005; **66** Suppl 4: 8-15 [PMID: [15842182](#)]
- 52 **Baldassano CF**. Illness course, comorbidity, gender, and suicidality in patients with bipolar disorder. *J Clin Psychiatry* 2006; **67** Suppl 11: 8-11 [PMID: [17029490](#)]
- 53 **MacKinnon DF**, Zamoiski R. Panic comorbidity with bipolar disorder: what is the manic-panic connection? *Bipolar Disord* 2006; **8**: 648-664 [PMID: [17156152](#) DOI: [10.1111/j.1399-5618.2006.00356.x](#)]
- 54 **Sajatovic M**, Kales HC. Diagnosis and management of bipolar disorder with comorbid anxiety in the elderly. *J Clin Psychiatry* 2006; **67** Suppl 1: 21-27 [PMID: [16426113](#)]
- 55 **Singh JB**, Zarate CA Jr. Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials. *Bipolar Disord* 2006; **8**: 696-709 [PMID: [17156156](#) DOI: [10.1111/j.1399-5618.2006.00371.x](#)]
- 56 **Dineen Wagner K**. Bipolar disorder and comorbid anxiety disorders in children and adolescents. *J Clin Psychiatry* 2006; **67** Suppl 1: 16-20 [PMID: [16426112](#)]
- 57 **Mackinnon DF**. Comorbidity of bipolar and panic disorders and its consequences. *Psychiatric times* 2007; **24**: 2
- 58 **Jolin EM**, Weller EB, Weller RA. Anxiety symptoms and syndromes in bipolar children and adolescents. *Curr Psychiatry Rep* 2008; **10**: 123-129 [PMID: [18474202](#) DOI: [10.1007/s11920-008-0022-5](#)]
- 59 **Joshi G**, Wilens T. Comorbidity in pediatric bipolar disorder. *Child Adolesc Psychiatr Clin N Am* 2009; **18**: 291-319, vii-viii [PMID: [19264265](#) DOI: [10.1016/j.chc.2008.12.005](#)]

- 60 **Sagman D**, Tohen M. Comorbidity in bipolar disorder. *Psychiatric times* 2009; **26**: 4
- 61 **Simon NM**. Generalized anxiety disorder and psychiatric comorbidities such as depression, bipolar disorder, and substance abuse. *J Clin Psychiatry* 2009; **70** Suppl 2: 10-14 [PMID: [19371501](#) DOI: [10.4088/JCP.s.7002.02](#)]
- 62 **Bowden CL**. Comorbidities with bipolar disorders: significance, recognition, and management. *CNS Spectr* 2010; **15**: 8-9; discussion 17 [PMID: [20414159](#) DOI: [10.1017/S1092852900027760](#)]
- 63 **Andrade-Nascimento M**, Miranda-Scippa A, Nery-Fernandes F, Rocha M, Quarantini LC. Comorbid generalized anxiety disorder in bipolar disorder: a possible diagnosis? *Rev Psiq Clin* 2012; **39**: 149-152 [DOI: [10.1590/S0101-60832012000400006](#)]
- 64 **Jana AK**, Praharaj SK, Sinha VK. Comorbid bipolar affective disorder and obsessive compulsive disorder in childhood: a case study and brief review. *Indian J Psychol Med* 2012; **34**: 279-282 [PMID: [23440037](#) DOI: [10.4103/0253-7176.106036](#)]
- 65 **McIntyre RS**, Rosenbluth M, Ramasubbu R, Bond DJ, Taylor VH, Beaulieu S, Schaffer A; Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force. Managing medical and psychiatric comorbidity in individuals with major depressive disorder and bipolar disorder. *Ann Clin Psychiatry* 2012; **24**: 163-169 [PMID: [22563572](#)]
- 66 **Perugi G**, Toni C. Comorbidity between panic-disorder and bipolar disorder. *J Psychopathology* 2012; **18**: 75-81
- 67 **Cazard F**, Ferreri F. [Bipolar disorders and comorbid anxiety: prognostic impact and therapeutic challenges]. *Encephale* 2013; **39**: 66-74 [PMID: [23095585](#) DOI: [10.1016/j.encep.2012.04.005](#)]
- 68 **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**: 1073 [PMID: [26450938](#) DOI: [10.1177/0004867415610201](#)]
- 69 **Chang HY**, Lee SY, Lu RB. Comorbid mental disorders in anxiety disorders: genetic aspects of bipolar disorders and of ethnicity. In: Durbano F, Marchesi B, eds. *New developments in anxiety disorders*. London: IntechOpen; 2016; 65-87 [DOI: [10.5772/66117](#)]
- 70 **Shi S**. Obsessive compulsive symptoms in bipolar disorder patients: a comorbid disorder or a subtype of bipolar disorder? *Shanghai Arch Psychiatry* 2015; **27**: 249-251 [PMID: [26549962](#) DOI: [10.11919/j.issn.1002-0829.215091](#)]
- 71 **Tonna M**, Amerio A, Ottoni R, Paglia F, Odone A, Ossola P, De Panfilis C, Ghaemi SN, Marchesi C. The clinical meaning of obsessive-compulsive symptoms in bipolar disorder and schizophrenia. *Aust N Z J Psychiatry* 2015; **49**: 578-579 [PMID: [25688121](#) DOI: [10.1177/0004867415572010](#)]
- 72 **Robins LN**, Locke BZ, Regier DA. An overview of psychiatric disorders in America. In: Robins LN, Regier DA, eds. *Psychiatric disorders in America: the Epidemiologic Catchment Area Study*. New York: Free Press; 1991; 328-366
- 73 **Chen YW**, Dilsaver SC. Comorbidity of panic disorder in bipolar illness: evidence from the Epidemiologic Catchment Area Survey. *Am J Psychiatry* 1995; **152**: 280-282 [PMID: [7840367](#) DOI: [10.1176/ajp.152.2.280](#)]
- 74 **Chen YW**, Dilsaver SC. Comorbidity for obsessive-compulsive disorder in bipolar and unipolar disorders. *Psychiatry Res* 1995; **59**: 57-64 [PMID: [8771221](#) DOI: [10.1016/0165-1781\(95\)02752-1](#)]
- 75 **Kessler RC**, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry* 1994; **51**: 8-19 [PMID: [8279933](#) DOI: [10.1001/archpsyc.1994.03950010008002](#)]
- 76 **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**: 1079-1089 [PMID: [9300513](#) DOI: [10.1017/S0033291797005333](#)]
- 77 **Kessler RC**, Stang P, Wittchen HU, Stein M, Walters EE. Lifetime co-morbidities between social phobia and mood disorders in the US National Comorbidity Survey. *Psychol Med* 1999; **29**: 555-567 [PMID: [10405077](#) DOI: [10.1017/S0033291799008375](#)]
- 78 **Merikangas KR**, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RM, Petukhova M, Kessler RC. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. *Arch Gen Psychiatry* 2007; **64**: 543-552 [PMID: [17485606](#) DOI: [10.1001/archpsyc.64.5.543](#)]
- 79 **Angst J**, Cui L, Joel Swendsen J, Rothen S, Cravchik A, Kessler R, Merikangas K. Major depressive disorder with sub-threshold bipolarity in the national comorbidity survey replication. *Am J Psychiatry* 2010; **167**: 1194-1201 [DOI: [10.1176/appi.ajp.2010.09071011](#)]
- 80 **Ruscio AM**, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry* 2010; **15**: 53-63 [PMID: [18725912](#) DOI: [10.1038/mp.2008.94](#)]
- 81 **Merikangas KR**, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M, Medina-Mora ME, Ono Y, Posada-Villa J, Sagar R, Wells JE, Zarkov Z. Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Arch Gen Psychiatry* 2011; **68**: 241-251 [PMID: [21383262](#) DOI: [10.1001/archgenpsychiatry.2011.12](#)]
- 82 **Grant BF**, Stinson FS, Hasin DS, Dawson DA, Chou SP, Ruan WJ, Huang B. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2005; **66**: 1205-1215 [PMID: [16259532](#) DOI: [10.4088/JCP.v66n1001](#)]
- 83 **Sala R**, Goldstein BI, Morcillo C, Liu SM, Castellanos M, Blanco C. Course of comorbid anxiety disorders among adults with bipolar disorder in the U.S. population. *J Psychiatr Res* 2012; **46**: 865-872 [PMID: [22534180](#) DOI: [10.1016/j.jpsychires.2012.03.024](#)]
- 84 **Bega S**, Schaffer A, Goldstein B, Levitt A. Differentiating between bipolar disorder types I and II: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Affect Disord* 2012; **138**: 46-53 [PMID: [22284021](#) DOI: [10.1016/j.jad.2011.12.032](#)]
- 85 **Goldstein BI**, Herrmann N, Shulman KI. Comorbidity in bipolar disorder among the elderly: results from an epidemiological community sample. *Am J Psychiatry* 2006; **163**: 319-321 [PMID: [16449489](#) DOI: [10.1176/appi.ajp.163.2.319](#)]
- 86 **Goldstein BI**, Levitt AJ. Prevalence and correlates of bipolar I disorder among adults with primary youth-onset anxiety disorders. *J Affect Disord* 2007; **103**: 187-195 [PMID: [17328960](#) DOI: [10.1016/j.jad.2007.03.001](#)]

- 10.1016/j.jad.2007.01.029]
- 87 **Chrysant SG**, Frohlich ED. Comparison of the antihypertensive effectiveness of guanadrel and guanethidine. *Curr Ther Res Clin Exp* 1976; **19**: 379-385 [PMID: 817868 DOI: 10.1111/j.1600-0447.1994.tb05787.x]
- 88 **Lewinsohn PM**, Klein DN, Seeley JR. Bipolar disorders in a community sample of older adolescents: prevalence, phenomenology, comorbidity, and course. *J Am Acad Child Adolesc Psychiatry* 1995; **34**: 454-463 [PMID: 7751259 DOI: 10.1097/00004583-199504000-00012]
- 89 **Angst J**. The emerging epidemiology of hypomania and bipolar II disorder. *J Affect Disord* 1998; **50**: 143-151 [PMID: 9858074 DOI: 10.1016/S0165-0327(98)00142-6]
- 90 **Szádóczky E**, Papp Zs, Vitrai J, Rihmer Z, Füredi J. The prevalence of major depressive and bipolar disorders in Hungary. Results from a national epidemiologic survey. *J Affect Disord* 1998; **50**: 153-162 [PMID: 9858075 DOI: 10.1016/S0165-0327(98)00056-1]
- 91 **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. *J Affect Disord* 2001; **67**: 175-179 [PMID: 11869765 DOI: 10.1016/S0165-0327(01)00309-3]
- 92 **Faravelli C**, Rosi S, Alessandra Scarpato M, Lampronti L, Amedei SG, Rana N. Threshold and subthreshold bipolar disorders in the Sesto Fiorentino Study. *J Affect Disord* 2006; **94**: 111-119 [PMID: 16701902 DOI: 10.1016/j.jad.2006.01.031]
- 93 **Zimmermann P**, Brückl T, Nocon A, Pfister H, Lieb R, Wittchen HU, Holsboer F, Angst J. Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. *Arch Gen Psychiatry* 2009; **66**: 1341-1352 [PMID: 19996039 DOI: 10.1001/archgenpsyc.2009.158]
- 94 **Schaffer A**, Cairney J, Cheung A, Veldhuizen S, Levitt A. Community survey of bipolar disorder in Canada: lifetime prevalence and illness characteristics. *Can J Psychiatry* 2006; **51**: 9-16 [PMID: 16491979 DOI: 10.1177/070674370605100104]
- 95 **Schaffer A**, Cairney J, Veldhuizen S, Kurdyak P, Cheung A, Levitt A. A population-based analysis of distinguishers of bipolar disorder from major depressive disorder. *J Affect Disord* 2010; **125**: 103-110 [PMID: 20223522 DOI: 10.1016/j.jad.2010.02.118]
- 96 **Subramaniam M**, Abidin E, Vaingankar JA, Chong SA. Prevalence, correlates, comorbidity and severity of bipolar disorder: results from the Singapore Mental Health Study. *J Affect Disord* 2013; **146**: 189-196 [PMID: 23017543 DOI: 10.1016/j.jad.2012.09.002]
- 97 **Mitchell PB**, Slade T, Andrews G. Twelve-month prevalence and disability of DSM-IV bipolar disorder in an Australian general population survey. *Psychol Med* 2004; **34**: 777-785 [PMID: 15500298 DOI: 10.1017/S0033291703001636]
- 98 **Mitchell PB**, Johnston AK, Frankland A, Slade T, Green MJ, Roberts G, Wright A, Corry J, Hadzi-Pavlovic D. Bipolar disorder in a national survey using the World Mental Health Version of the Composite International Diagnostic Interview: the impact of differing diagnostic algorithms. *Acta Psychiatr Scand* 2013; **127**: 381-393 [PMID: 22906117 DOI: 10.1111/acps.12005]
- 99 **Hawke LD**, Provencher MD, Parikh SV, Zagorski B. Comorbid anxiety disorders in Canadians with bipolar disorder: clinical characteristics and service use. *Can J Psychiatry* 2013; **58**: 393-401 [PMID: 23870721 DOI: 10.1177/070674371305800704]
- 100 **McElroy SL**, Altshuler LL, Suppes T, Keck PE Jr, Frye MA, Denicoff KD, Nolen WA, Kupka RW, Leverich GS, Rochussen JR, Rush AJ, Post RM. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. *Am J Psychiatry* 2001; **158**: 420-426 [PMID: 11229983 DOI: 10.1176/appi.ajp.158.3.420]
- 101 **Suppes T**, Leverich GS, Keck PE, Nolen WA, Denicoff KD, Altshuler LL, McElroy SL, Rush AJ, Kupka R, Frye MA, Bickel M, Post RM. The Stanley Foundation Bipolar Treatment Outcome Network. II. Demographics and illness characteristics of the first 261 patients. *J Affect Disord* 2001; **67**: 45-59 [PMID: 11869752 DOI: 10.1016/S0165-0327(01)00432-3]
- 102 **Dittmann S**, Biedermann NC, Grunze H, Hummel B, Schärer LO, Kleindienst N, Forstthoff A, Matzner N, Walser S, Walden J. The Stanley Foundation Bipolar Network: results of the naturalistic follow-up study after 2.5 years of follow-up in the German centres. *Neuropsychobiology* 2002; **46** Suppl 1: 2-9 [PMID: 12571425 DOI: 10.1159/000068018]
- 103 **Levander E**, Frye MA, McElroy S, Suppes T, Grunze H, Nolen WA, Kupka R, Keck PE Jr, Leverich GS, Altshuler LL, Hwang S, Mintz J, Post RM. Alcoholism and anxiety in bipolar illness: differential lifetime anxiety comorbidity in bipolar I women with and without alcoholism. *J Affect Disord* 2007; **101**: 211-217 [PMID: 17254638 DOI: 10.1016/j.jad.2006.11.023]
- 104 **Altshuler LL**, Kupka RW, Helleman G, Frye MA, Sugar CA, McElroy SL, Nolen WA, Grunze H, Leverich GS, Keck PE, Zerneno M, Post RM, Suppes T. Gender and depressive symptoms in 711 patients with bipolar disorder evaluated prospectively in the Stanley Foundation bipolar treatment outcome network. *Am J Psychiatry* 2010; **167**: 708-715 [PMID: 20231325 DOI: 10.1176/appi.ajp.2009.09010105]
- 105 **Kogan JN**, Otto MW, Bauer MS, Dennehy EB, Miklowitz DJ, Zhang HW, Ketter T, Rudorfer MV, Wisniewski SR, Thase ME, Calabrese J, Sachs GS; STEP-BD Investigators. Demographic and diagnostic characteristics of the first 1000 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Bipolar Disord* 2004; **6**: 460-469 [PMID: 15541061 DOI: 10.1111/j.1399-5618.2004.00158.x]
- 106 **Perlis RH**, Miyahara S, Marangell LB, Wisniewski SR, Ostacher M, DelBello MP, Bowden CL, Sachs GS, Nierenberg AA; STEP-BD Investigators. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Biol Psychiatry* 2004; **55**: 875-881 [PMID: 15110730 DOI: 10.1016/j.biopsych.2004.01.022]
- 107 **Simon NM**, Otto MW, Wisniewski SR, Fossey M, Sagduyu K, Frank E, Sachs GS, Nierenberg AA, Thase ME, Pollack MH. 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**: 2222-2229 [PMID: 15569893 DOI: 10.1176/appi.ajp.161.12.2222]
- 108 **Simon NM**, Otto MW, Weiss RD, Bauer MS, Miyahara S, Wisniewski SR, Thase ME, Kogan J, Frank E, Nierenberg AA, Calabrese JR, Sachs GS, Pollack MH; STEP-BD Investigators. Pharmacotherapy for bipolar disorder and comorbid conditions: baseline data from STEP-BD. *J Clin Psychopharmacol* 2004; **24**: 512-520 [PMID: 15349007 DOI: 10.1016/j.jad.2007.01.029]

- 10.1097/01.jcp.0000138772.40515.70]
- 109 **Otto MW**, Simon NM, Wisniewski SR, Miklowitz DJ, Kogan JN, Reilly-Harrington NA, Frank E, Nierenberg AA, Marangell LB, Sagduyu K, Weiss RD, Miyahara S, Thas ME, Sachs GS, Pollack MH; STEP-BD Investigators. Prospective 12-month course of bipolar disorder in out-patients with and without comorbid anxiety disorders. *Br J Psychiatry* 2006; **189**: 20-25 [PMID: 16816301 DOI: 10.1192/bjp.bp.104.007773]
- 110 **Simon NM**, Pollack MH, Ostacher MJ, Zalta AK, Chow CW, Fischmann D, Demopulos CM, Nierenberg AA, Otto MW. Understanding the link between anxiety symptoms and suicidal ideation and behaviors in outpatients with bipolar disorder. *J Affect Disord* 2007; **97**: 91-99 [PMID: 16820212 DOI: 10.1016/j.jad.2006.05.027]
- 111 **Vieta E**, Colom F, Corbella B, Martínez-Arán A, Reinares M, Benabarre A, Gastó C. Clinical correlates of psychiatric comorbidity in bipolar I patients. *Bipolar Disord* 2001; **3**: 253-258 [PMID: 11903208 DOI: 10.1034/j.1399-5618.2001.30504.x]
- 112 **MacKinnon DF**, Zandi PP, Cooper J, Potash JB, Simpson SG, Gershon E, Nurnberger J, Reich T, DePaulo JR. Comorbid bipolar disorder and panic disorder in families with a high prevalence of bipolar disorder. *Am J Psychiatry* 2002; **159**: 30-35 [PMID: 11772686 DOI: 10.1176/appi.ajp.159.1.30]
- 113 **Henry C**, Van den Bulke D, Bellivier F, Etain B, Rouillon F, Leboyer M. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. *J Clin Psychiatry* 2003; **64**: 331-335 [PMID: 12716276 DOI: 10.4088/JCP.v64n0316]
- 114 **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**: 1106-1113 [PMID: 15323597 DOI: 10.4088/JCP.v65n0813]
- 115 **Azorin JM**, Kaladjian A, Adida M, Hantouche EG, Hameg A, Lancrenon S, Akiskal HS. Psychopathological correlates of lifetime anxiety comorbidity in bipolar I patients: findings from a French national cohort. *Psychopathology* 2009; **42**: 380-386 [PMID: 19776668 DOI: 10.1159/000241193]
- 116 **Coryell W**, Solomon DA, Fiedorowicz JG, Endicott J, Schettler PJ, Judd LL. Anxiety and outcome in bipolar disorder. *Am J Psychiatry* 2009; **166**: 1238-1243 [PMID: 19797434 DOI: 10.1176/appi.ajp.2009.09020218]
- 117 **Gao K**, Chan PK, Verduin ML, Kemp DE, Tolliver BK, Ganocy SJ, Bilali S, Brady KT, Findling RL, Calabrese JR. Independent predictors for lifetime and recent substance use disorders in patients with rapid-cycling bipolar disorder: focus on anxiety disorders. *Am J Addict* 2010; **19**: 440-449 [PMID: 20716307 DOI: 10.1111/j.1521-0391.2010.00060.x]
- 118 **Guo JJ**, Patel NC, Li H, Keck PE Jr. Prevalence of treated bipolar disorders and associated comorbidities in managed care and Medicaid populations. *Am Health Drug Benefits* 2010; **3**: 171-178
- 119 **Mantere O**, Isometsä E, Ketokivi M, Kiviruusu O, Suominen K, Valtonen HM, Arvilommi P, Leppämäki S. A prospective latent analyses study of psychiatric comorbidity of DSM-IV bipolar I and II disorders. *Bipolar Disord* 2010; **12**: 271-284 [PMID: 20565434 DOI: 10.1111/j.1399-5618.2010.00810.x]
- 120 **Fracalanza KA**, McCabe RE, Taylor VH, Antony MM. Bipolar disorder comorbidity in anxiety disorders: relationship to demographic profile, symptom severity, and functional impairment. *Eur J Psychiatry* 2011; **25**: 223-233 [DOI: 10.4321/S0213-61632011000400005]
- 121 **Goes FS**, McCusker MG, Bienvenu OJ, Mackinnon DF, Mondimore FM, Schweizer B; National Institute of Mental Health Genetics Initiative Bipolar Disorder Consortium, Depaulo JR, Potash JB. Co-morbid anxiety disorders in bipolar disorder and major depression: familial aggregation and clinical characteristics of co-morbid panic disorder, social phobia, specific phobia and obsessive-compulsive disorder. *Psychol Med* 2012; **42**: 1449-1459 [PMID: 22099954 DOI: 10.1017/S0033291711002637]
- 122 **Chang YH**, Chen SL, Chen SH, Chu CH, Lee SY, Yang HF, Tzeng NS, Lee IH, Chen PS, Yeh TL, Huang SY, Chou KR, Yang YK, Ko HC, Lu RB, Angst J. Low anxiety disorder comorbidity rate in bipolar disorders in Han Chinese in Taiwan. *Prog Neuropsychopharmacol Biol Psychiatry* 2012; **36**: 194-197 [PMID: 21996277 DOI: 10.1016/j.pnpbp.2011.09.013]
- 123 **Angst J**, Gamma A, Bowden CL, Azorin JM, Perugi G, Vieta E, Young AH. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. *Eur Arch Psychiatry Clin Neurosci* 2013; **263**: 663-673 [PMID: 23370488 DOI: 10.1007/s00406-013-0393-4]
- 124 **Castilla-Puentes R**, Sala R, Ng B, Galvez J, Camacho A. Anxiety disorders and rapid cycling: data from a cohort of 8129 youths with bipolar disorder. *J Nerv Ment Dis* 2013; **201**: 1060-1065 [PMID: 24284641 DOI: 10.1097/NMD.0000000000000052]
- 125 **Young S**, Pfaff D, Lewandowski KE, Ravichandran C, Cohen BM, Öngür D. Anxiety disorder comorbidity in bipolar disorder, schizophrenia and schizoaffective disorder. *Psychopathology* 2013; **46**: 176-185 [PMID: 22906962 DOI: 10.1159/000339556]
- 126 **Asaad T**, Okasha T, Ramy H, Fekry M, Zaki N, Azzam H, Rabie MA, Elghoneimy S, Sultan M, Hamed H, Refaat O, Shorab I, Elhabiby M, Elgweily T, ElShinnawy H, Nasr M, Fathy H, Meguid MA, Nader D, Elserafi D, Enaba D, Ibrahim D, Elmissiry M, Mohsen N, Ahmed S. Correlates of psychiatric co-morbidity in a sample of Egyptian patients with bipolar disorder. *J Affect Disord* 2014; **166**: 347-352 [PMID: 24981131 DOI: 10.1016/j.jad.2014.04.050]
- 127 **Baek JH**, Cha B, Moon E, Ha TH, Chang JS, Kim JH, Choi JE, Kang BJ, Hong KS, Ha K. The effects of ethnic, social and cultural factors on axis I comorbidity of bipolar disorder: results from the clinical setting in Korea. *J Affect Disord* 2014; **166**: 264-269 [PMID: 25012440 DOI: 10.1016/j.jad.2014.05.027]
- 128 **Perugi G**, Toni C, Akiskal HS. Anxious-bipolar comorbidity. Diagnostic and treatment challenges. *Psychiatr Clin North Am* 1999; **22**: 565-583, viii [PMID: 10550856]
- 129 **Wiegartz SP**, Rasminsky S. Treating OCD in patients with psychiatric comorbidity. *Curr Psychiatry* 2005; **4**: 57-68
- 130 **Murphy DL**, Moya PR, Fox MA, Rubenstein LM, Wendland JR, Timpano KR. Anxiety and affective disorder comorbidity related to serotonin and other neurotransmitter systems: obsessive-compulsive disorder as an example of overlapping clinical and genetic heterogeneity. *Philos Trans R Soc Lond B Biol Sci* 2013; **368**: 20120435 [PMID: 23440468 DOI: 10.1098/rstb.2012.0145]

- 10.1098/rstb.2012.0435]
- 131 **Bourdon KH**, Rae DS, Locke BZ, Narrow WE, Regier DA. Estimating the prevalence of mental disorders in U.S. adults from the Epidemiologic Catchment Area Survey. *Public Health Rep* 1992; **107**: 663-668 [PMID: [1454978](#)]
- 132 **Kessler RC**, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; **62**: 593-602 [PMID: [15939837](#) DOI: [10.1001/archpsyc.62.6.617](#)]
- 133 **Kessler RC**, Aguilar-Gaxiola S, Alonso J, Chatterji S, Lee S, Üstün TB. The WHO World Mental Health (WMH) Surveys. *Psychiatrie (Stuttg)* 2009; **6**: 5-9 [PMID: [21132091](#) DOI: [10.1055/s-0038-1671923](#)]
- 134 **Hasin DS**, Grant BF. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Waves 1 and 2: review and summary of findings. *Soc Psychiatry Psychiatr Epidemiol* 2015; **50**: 1609-1640 [PMID: [26210739](#) DOI: [10.1007/s00127-015-1088-0](#)]
- 135 **Subramanian K**, Sarkar S, Kattimani S. Bipolar disorder in Asia: Illness course and contributing factors. *Asian J Psychiatr* 2017; **29**: 16-29 [PMID: [29061417](#) DOI: [10.1016/j.ajp.2017.04.009](#)]
- 136 **Joslyn C**, Hawes DJ, Hunt C, Mitchell PB. Is age of onset associated with severity, prognosis, and clinical features in bipolar disorder? A meta-analytic review. *Bipolar Disord* 2016; **18**: 389-403 [PMID: [27530107](#) DOI: [10.1111/bdi.12419](#)]
- 137 **Mitchell PB**. Bipolar disorder and anxiety: a comorbidity needing better treatments. *Lancet Psychiatry* 2015; **2**: 671-672 [PMID: [26249280](#) DOI: [10.1016/S2215-0366\(15\)00209-6](#)]
- 138 **Grande I**, Kunz M, Potter W, Balanzá-Martínez V, Vieta E, Kapczinski F. Should bipolar disorder be considered a systemic illness? *Neuropsychiatry* 2011; **1**: 45-54 [DOI: [10.2217/NPY.10.7](#)]
- 139 **Keck PE Jr**, Strawn JR, McElroy SL. Pharmacologic treatment considerations in co-occurring bipolar and anxiety disorders. *J Clin Psychiatry* 2006; **67** Suppl 1: 8-15 [PMID: [16426111](#)]
- 140 **Tonna M**, Amerio A, Odone A, Stubbs B, Ghaemi SN. Comorbid bipolar disorder and obsessive-compulsive disorder: state of the art in pediatric patients. *Shanghai Arch Psychiatry* 2015; **27**: 386-387 [PMID: [27199533](#) DOI: [10.11919/j.issn.1002-0829.215128](#)]
- 141 **Gao K**, Muzina D, Gajwani P, Calabrese JR. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review. *J Clin Psychiatry* 2006; **67**: 1327-1340 [PMID: [17017818](#) DOI: [10.4088/JCP.v67n0902](#)]
- 142 **Gao K**. Antipsychotics in the treatment of comorbid anxiety in bipolar disorder. *Psychiatric Times* 2007; **24**: 5
- 143 **Peng D**, Jiang K. Comorbid bipolar disorder and obsessive-compulsive disorder. *Shanghai Arch Psychiatry* 2015; **27**: 246-248 [PMID: [26549961](#) DOI: [10.11919/j.issn.1002-0829.215009](#)]
- 144 **Brieger P**. Do comorbidity studies support the idea that mixed states and rapid cycling are distinct categories of bipolar disorder? *Clin Neuropsychiatry* 2004; **1**: 175-181
- 145 **Amerio A**, Tonna M, Odone A, Stubbs B, Ghaemi SN. Psychiatric comorbidities in comorbid bipolar disorder and obsessive-compulsive disorder patients. *Asian J Psychiatr* 2016; **21**: 23-24 [PMID: [27208451](#) DOI: [10.1016/j.ajp.2016.02.009](#)]
- 146 **Myers JE**, Thase ME. Anxiety in the patient with bipolar disorder: recognition, significance, and approaches to treatment. *Psychiatr Ann* 2000; **30**: 456-464 [DOI: [10.3928/0048-5713-20000701-06](#)]
- 147 **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**: 258-263 [PMID: [25012439](#) DOI: [10.1016/j.jad.2014.05.026](#)]
- 148 **Schaffer A**, Isometsä ET, Tondo L, H Moreno D, Turecki G, Reis C, Cassidy F, Sinyor M, Azorin JM, Kessing LV, Ha K, Goldstein T, Weizman A, Beautrais A, Chou YH, Diazgranados N, Levitt AJ, Zarate CA Jr, Rihmer Z, Yatham LN. International Society for Bipolar Disorders Task Force on Suicide: meta-analyses and meta-regression of correlates of suicide attempts and suicide deaths in bipolar disorder. *Bipolar Disord* 2015; **17**: 1-16 [PMID: [25329791](#) DOI: [10.1111/bdi.12271](#)]
- 149 **Kilbane EJ**, Gokbayrak NS, Galynker I, Cohen L, Tross S. A review of panic and suicide in bipolar disorder: does comorbidity increase risk? *J Affect Disord* 2009; **115**: 1-10 [PMID: [19000640](#) DOI: [10.1016/j.jad.2008.09.014](#)]
- 150 **Goodwin RD**, Hoven CW. Bipolar-panic comorbidity in the general population: prevalence and associated morbidity. *J Affect Disord* 2002; **70**: 27-33 [PMID: [12113917](#) DOI: [10.1016/S0165-0327\(01\)00398-6](#)]
- 151 **Goodwin RD**, Stein DJ. Anxiety disorders and drug dependence: evidence on sequence and specificity among adults. *Psychiatry Clin Neurosci* 2013; **67**: 167-173 [PMID: [23581868](#) DOI: [10.1111/pcn.12030](#)]
- 152 **Goldstein BI**, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. *Bipolar Disord* 2008; **10**: 67-78 [PMID: [18199243](#) DOI: [10.1111/j.1399-5618.2008.00461.x](#)]
- 153 **Conway KP**, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2006; **67**: 247-257 [PMID: [16566620](#) DOI: [10.4088/JCP.v67n0211](#)]
- 154 **Oquendo MA**, Currier D, Liu SM, Hasin DS, Grant BF, Blanco C. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry* 2010; **71**: 902-909 [PMID: [20667292](#) DOI: [10.4088/JCP.09m05198gry](#)]
- 155 **Druss BG**, Walker ER. Mental disorders and medical comorbidity. *Synth Proj Res Synth Rep* 2011; **1**-26 [PMID: [21675009](#)]
- 156 **Perron BE**, Howard MO, Nienhuis JK, Bauer MS, Woodward AT, Kilbourne AM. Prevalence and burden of general medical conditions among adults with bipolar I disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry* 2009; **70**: 1407-1415 [PMID: [19906344](#) DOI: [10.4088/JCP.08m04586yel](#)]
- 157 **Agius M**, Aquilina FF. Comorbidities and psychotic illness. Part 1: Philosophy and clinical consequences. *Psychiatr Danub* 2014; **26** Suppl 1: 246-249 [PMID: [25413548](#)]
- 158 **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**: 594-596 [PMID: [26480937](#) DOI: [10.1177/0004867415611235](#)]
- 159 **Wagner KD**. Diagnosis and treatment of bipolar disorder in children and adolescents. *J Clin*

- Psychiatry* 2004; **65** Suppl 15: 30-34 [PMID: [15554794](#)]
- 160 **Gao K**, Sheehan DV, Calabrese JR. Atypical antipsychotics in primary generalized anxiety disorder or comorbid with mood disorders. *Expert Rev Neurother* 2009; **9**: 1147-1158 [PMID: [19673604](#) DOI: [10.1586/ern.09.37](#)]
- 161 **Coplan JD**, Aaronson CJ, Panthangi V, Kim Y. Treating comorbid anxiety and depression: Psychosocial and pharmacological approaches. *World J Psychiatry* 2015; **5**: 366-378 [PMID: [26740928](#) DOI: [10.5498/wjp.v5.i4.366](#)]
- 162 **Rakofsky JJ**, Dunlop BW. Treating nonspecific anxiety and anxiety disorders in patients with bipolar disorder: a review. *J Clin Psychiatry* 2011; **72**: 81-90 [PMID: [21208580](#) DOI: [10.4088/JCP.09r05815gre](#)]
- 163 **Otheman Y**, Kadiri M, Mehsanni J, Zakaria Bichra M. The use of benzodiazepines in bipolar disorders. *Addict Clin Res* 2018; **2**: 1-4
- 164 **Provencher MD**, Hawke LD, Thienot E. Psychotherapies for comorbid anxiety in bipolar spectrum disorders. *J Affect Disord* 2011; **133**: 371-380 [PMID: [21093062](#) DOI: [10.1016/j.jad.2010.10.040](#)]
- 165 **Stratford HJ**, Cooper MJ, Di Simplicio M, Blackwell SE, Holmes EA. Psychological therapy for anxiety in bipolar spectrum disorders: a systematic review. *Clin Psychol Rev* 2015; **35**: 19-34 [PMID: [25462111](#) DOI: [10.1016/j.cpr.2014.11.002](#)]
- 166 **Deckersbach T**, Peters AT, Sylvia L, Urdahl A, Magalhães PV, Otto MW, Frank E, Miklowitz DJ, Berk M, Kinrys G, Nierenberg A. Do comorbid anxiety disorders moderate the effects of psychotherapy for bipolar disorder? Results from STEP-BD. *Am J Psychiatry* 2014; **171**: 178-186 [PMID: [24077657](#) DOI: [10.1176/appi.ajp.2013.13020225](#)]
- 167 **Lembke A**, Miklowitz DJ, Otto MW, Zhang H, Wisniewski SR, Sachs GS, Thase ME, Ketter TA; STEP-BD Investigators. Psychosocial service utilization by patients with bipolar disorders: data from the first 500 participants in the Systematic Treatment Enhancement Program. *J Psychiatr Pract* 2004; **10**: 81-87 [PMID: [15330403](#) DOI: [10.1097/00131746-200403000-00002](#)]
- 168 **Bowen RC**, D'Arcy C. Response of patients with panic disorder and symptoms of hypomania to cognitive behavior therapy for panic. *Bipolar Disord* 2003; **5**: 144-149 [PMID: [12680905](#) DOI: [10.1034/j.1399-5618.2003.00023.x](#)]
- 169 **Ellard KK**, Bernstein EE, Hearing C, Baek JH, Sylvia LG, Nierenberg AA, Barlow DH, Deckersbach T. Transdiagnostic treatment of bipolar disorder and comorbid anxiety using the Unified Protocol for Emotional Disorders: A pilot feasibility and acceptability trial. *J Affect Disord* 2017; **219**: 209-221 [PMID: [28577505](#) DOI: [10.1016/j.jad.2017.05.011](#)]
- 170 **Hawke LD**, Velyvis V, Parikh SV. Bipolar disorder with comorbid anxiety disorders: impact of comorbidity on treatment outcome in cognitive-behavioral therapy and psychoeducation. *Int J Bipolar Disord* 2013; **1**: 15 [PMID: [25505682](#) DOI: [10.1186/2194-7511-1-15](#)]
- 171 **Jones S**, McGrath E, Hampshire K, Owen R, Riste L, Roberts C, Davies L, Mayes D. A randomised controlled trial of time limited CBT informed psychological therapy for anxiety in bipolar disorder. *BMC Psychiatry* 2013; **13**: 54 [PMID: [23414176](#) DOI: [10.1186/1471-244X-13-54](#)]
- 172 **Lee JH**, Dunner DL. The effect of anxiety disorder comorbidity on treatment resistant bipolar disorders. *Depress Anxiety* 2008; **25**: 91-97 [PMID: [17311265](#) DOI: [10.1002/da.20279](#)]
- 173 **Maina G**, Albert U, Rosso G, Bogetto F. Olanzapine or lamotrigine addition to lithium in remitted bipolar disorder patients with anxiety disorder comorbidity: a randomized, single-blind, pilot study. *J Clin Psychiatry* 2008; **69**: 609-616 [PMID: [18294024](#) DOI: [10.4088/JCP.v69n0413](#)]
- 174 **Sheehan DV**, McElroy SL, Harnett-Sheehan K, Keck PE Jr, Janavs J, Rogers J, Gonzalez R, Shivakumar G, Suppes T. Randomized, placebo-controlled trial of risperidone for acute treatment of bipolar anxiety. *J Affect Disord* 2009; **115**: 376-385 [PMID: [19042026](#) DOI: [10.1016/j.jad.2008.10.005](#)]
- 175 **Tonna M**, Amerio A, Odone A, Stubbs B, Ghaemi SN. Comorbid bipolar disorder and obsessive-compulsive disorder: Which came first? *Aust N Z J Psychiatry* 2016; **50**: 695-698 [PMID: [26685183](#) DOI: [10.1177/0004867415621395](#)]
- 176 **Perugi G**, Akiskal HS, Toni C, Simonini E, Gemignani A. The temporal relationship between anxiety disorders and (hypo)mania: a retrospective examination of 63 panic, social phobic and obsessive-compulsive patients with comorbid bipolar disorder. *J Affect Disord* 2001; **67**: 199-206 [PMID: [11869769](#) DOI: [10.1016/S0165-0327\(01\)00433-5](#)]
- 177 **Amerio A**, Tonna M, Odone A, Stubbs B, Ghaemi SN. Course of illness in comorbid bipolar disorder and obsessive-compulsive disorder patients. *Asian J Psychiatry* 2016; **20**: 12-14 [PMID: [27025465](#) DOI: [10.1016/j.ajp.2016.01.009](#)]
- 178 **Amerio A**, Tonna M, Odone A, Stubbs B, Ghaemi SN. Heredity in comorbid bipolar disorder and obsessive-compulsive disorder patients. *Shanghai Arch Psychiatry* 2015; **27**: 307-310 [PMID: [26977128](#) DOI: [10.11919/j.issn.1002-0829.215123](#)]
- 179 **MacKinnon DF**, Xu J, McMahon FJ, Simpson SG, Stine OC, McInnis MG, DePaulo JR. Bipolar disorder and panic disorder in families: an analysis of chromosome 18 data. *Am J Psychiatry* 1998; **155**: 829-831 [PMID: [9619158](#)]
- 180 **Corry J**, Green M, Roberts G, Fullerton JM, Schofield PR, Mitchell PB. Does perfectionism in bipolar disorder pedigrees mediate associations between anxiety/stress and mood symptoms? *Int J Bipolar Disord* 2017; **5**: 34 [PMID: [28983840](#) DOI: [10.1186/s40345-017-0102-8](#)]
- 181 **Somers JM**, Goldner EM, Waraich P, Hsu L. Prevalence and incidence studies of anxiety disorders: a systematic review of the literature. *Can J Psychiatry* 2006; **51**: 100-113 [PMID: [16989109](#) DOI: [10.1177/070674370605100206](#)]
- 182 **Achim AM**, Maziade M, Raymond E, Olivier D, Mérette C, Roy MA. How prevalent are anxiety disorders in schizophrenia? A meta-analysis and critical review on a significant association. *Schizophr Bull* 2011; **37**: 811-821 [PMID: [19959704](#) DOI: [10.1093/schbul/sbp148](#)]
- 183 **Hirschfeld RM**. Introduction: an overview of the issues surrounding the recognition and management of bipolar disorder and comorbid anxiety. *J Clin Psychiatry* 2006; **67** Suppl 1: 3-4 [PMID: [16426109](#)]
- 184 **Maj M**. "Psychiatric comorbidity": an artefact of current diagnostic systems? *Br J Psychiatry* 2005; **186**: 182-184 [PMID: [15738496](#) DOI: [10.1192/bjp.186.3.182](#)]
- 185 **Pincus HA**, Tew JD, First MB. Psychiatric comorbidity: is more less? *World Psychiatry* 2004; **3**: 18-23 [PMID: [16633444](#)]

- 186 **Feinstein AR.** The pre-therapeutic classification of co-morbidity in chronic disease. *J Chronic Dis* 1970; **23**: 455-468 [PMID: [26309916](#) DOI: [10.1016/0021-9681\(70\)90054-8](#)]

P- Reviewer: Seeman MV

S- Editor: Wang JL **L- Editor:** Filipodia **E- Editor:** Bian YN





Published By Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

