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EDITORIAL

Electroconvulsive therapy: 80 years old and still going strong

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Abstract

Electroconvulsive therapy (ECT), which is among the oldest and most controversial treatments in the field of psychiatry, has its 80th birthday this year. In this brief historical overview, the discovery of the therapeutic effects of convulsive therapy by Laszló Meduna, and the circumstances that motivated Ugo Cerletti and Lucio Bini to use electricity as a means of seizure induction are described. Meduna's original theory about the antagonism between epilepsy and schizophrenia has been replaced by hypotheses on the mechanism of action of ECT. The position of ECT in modern psychiatry is also discussed with special attention to its most important clinical indications, including catatonia, and pre- and postpartum affective and psychotic states that are responsive to ECT and in which ECT may even be lifesaving. Adverse effects and comparison of ECT with recently developed brain stimulation methods are also reviewed. The negative media portrayal of ECT and its earlier misuse may have contributed to its negative professional and public perceptions indicated repeatedly in attitude surveys. This negative attitude has played an important role in the decreasing use of ECT in the developed world and a reduction in access to ECT, which constitutes a violation of psychiatric patients' right to an effective treatment.

Key words: Electroconvulsive therapy; History; Indications; Utilization; Attitudes

Core tip: Electroconvulsive therapy (ECT), which is among the most controversial psychiatric treatments, has its 80th birthday this year. The introduction of convulsive therapy to psychiatry and changes in seizure induction from chemical to electrical are

outlined. The place of ECT in contemporary psychiatry, particularly its most important clinical indications, is briefly discussed. Negative media representation and historical misuse are likely to have contributed to negative professional and public attitudes towards ECT and, consequently, it decreased use. Recent limitations of access to effective treatment in many parts of the world constitute a violation of patients' rights.

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INTRODUCTION

Brief historical overview

Electroconvulsive therapy (ECT), one of the oldest treatment methods in the field of psychiatry, was first introduced 80 years ago in Rome when Ugo Cerletti and Lucio Bini used an electric current to elicit an epileptic seizure for therapeutic purposes[1]. However, this was not the first use of an epileptic fit to treat mental illness. The idea of inducing epileptic seizures to treat patients was first proposed by Meduna[2], a Hungarian neuropathologist and psychiatrist.

History of chemical convulsive therapy

The idea that a disease could be cured by inducing another disease was proposed by Wagner-Jauregg, who observed that high fever caused symptomatic improvement in general paresis of the insane and infected syphilitic patients with malaria to induce repeated bouts of high fever. In 1927, Wagner-Jauregg was awarded the Nobel Prize for developing the first effective biological treatment in the field of psychiatry[3]. In the late 1920s, Meduna[4], a researcher at the beginning of his professional career in the psychiatric department of the University in Budapest, was interested in the histopathology of epilepsy. Meduna[4] observed that in the brains of epileptic patients, glial cells occupied the spaces left by lost neurons. In 1931, Hechst *et al*[5], his departmental colleague who studied the histopathology of schizophrenia, described a reduction in the number of glial cells in the brains of schizophrenia patients. This finding strongly contrasted Meduna[4]'s observations in the brains of patients with epilepsy.

Besides these neuropathological findings, clinical observations also appeared to indicate antagonism between epilepsy and schizophrenia. Nyírö *et al*[6] reported that the rate of schizophrenia was significantly lower among patients with epilepsy than in the general population. Meduna[4] was also intrigued by a report about two schizophrenia patients whose conditions remitted following episodic epileptic seizures[7]. A report in which only 8 of 6000 schizophrenia patients suffered from epilepsy also appeared to support the antagonism theory[8]. By then, Meduna[4] had become convinced of an antagonism between schizophrenia and epilepsy, as he concluded in his autobiography: "...if I can stimulate epileptic seizures in schizophrenics then these... will alter the chemical and humoral processes in the body in a way... that the abatement of the disease will be made physiologically possible"[9].

Meduna[10] planned to induce a seizure using a chemical agent and proceeded to test the safety and effectiveness of several epileptogenic compounds for this purpose. Finally, Meduna[10] identified camphor as the compound that satisfied his requirements. On January 2, 1934, he conducted the first human experiment involving intramuscular camphor injections[11]. In the 2 subsequent years, Meduna[12] treated more than 100 patients, of whom half recovered or significantly improved.

Introduction of electrically induced seizures

Although camphor was later replaced with intravenous cardiazol, chemical seizure induction remained somewhat unpredictable, with considerable interpersonal variance. Furthermore, the time interval between the injection and seizure was extremely stressful for the patients. These difficulties led Ugo Cerletti and his colleagues at the university psychiatric clinic in Rome to search for an alternative means of seizure induction.

Prior to his arrival in Rome, Cerletti already had some experience with electricity, as he had used an electric current in animal studies of epilepsy in Genoa[13]. In Rome,

Cerletti continued these studies with the involvement of his assistant, Lucio Bini. The idea of using electricity to induce seizure first occurred to Cerletti and Bini when they witnessed cardiazol therapy in Vienna[14]. After defining the parameters of a safe electric stimulus through animal studies, they performed the first electric seizure induction in a psychotic patient named Enrico X on April 11, 1938. Although the initial stimulation did not result in an epileptic seizure, stimulation at a higher voltage induced an eighty seconds tonic-clonic seizure on April 20. After 11 further treatments, Enrico recovered and was released from the university psychiatry clinic[14]. Although the technical details of electric seizure induction were published shortly after the first treatment[1], their results with electroshock therapy were not summarized until 2 years later, which attests to the careful attitudes of the inventors[15].

MECHANISM OF ACTION

Subsequent research could not confirm Meduna[12]'s hypothesis on antagonism between epilepsy and schizophrenia, and the mechanism of action of ECT remains to be elucidated. In response to frequent criticism regarding the latter point, significant efforts have been made to clarify the mechanism underlying ECT. One theory explains the therapeutic effects of ECT by referring to its effects on neurotransmitters, particularly the serotonin and dopamine systems[16]. Another theory conceptualizes depression as a pro-inflammatory state wherein ECT acts on cytokines, thereby treating the inflammation and normalizing mood[17]. Furthermore, clinical evidence indicates a hypertensive surge during ECT that causes transient blood-brain barrier permeability which may also play a role in its therapeutic effect[18]. Animal studies suggest that electrically induced seizures have epigenetic effects that may also add to the clinical effectiveness of ECT[19]. Finally, the most promising new findings appear to involve ECT-induced changes in structural brain plasticity. Recent studies also identified ECT as a strong stimulator of neurogenesis by promoting the proliferation of stem cells[20].

PLACE OF ELECTROCONVULSIVE THERAPY IN MODERN PSYCHIATRY

Notwithstanding major advances in psychopharmacology and several recently introduced brain stimulation methods, ECT is not a closed chapter in the history of psychiatry but is rather a treatment modality used widely throughout the world[21]. ECT has well-defined indications[22,23] and remains one of the most effective treatment methods in psychiatry[24].

ECT in the treatment of affective disorders

Meduna[12] considered convulsive therapy as a treatment for schizophrenia. However, it was soon found to be even more effective for the treatment of affective disorders[25]. Currently, major depression is the first indication for ECT[22,23,26]. Between the 1960s and 1980s, several studies investigated the efficacy of ECT. The majority of randomized controlled studies confirmed the superiority of ECT relative to sham ECT or antidepressants for the treatment of affective disorders, and these findings were supported by meta-analyses[24,27-29].

Independent of its antidepressant effects, ECT also has a clear anti-suicidal effect[30]. Therefore, ECT is recommended as the first choice of treatment for patients at a high risk of suicide[31].

In pharmacotherapy-resistant patients, maintenance ECT proved to be an effective alternative in relapse prevention[32].

ECT in psychosis and schizophrenia

In several developing countries, including India[33] and China[34], the two most populous nations, schizophrenia remains the first indication for ECT. Although antipsychotics are equally effective for schizophrenia[35], financial reasons may explain the common use of ECT in this patient population[36]. Unmodified ECT is still practiced in the developing world due to limited financial resources[34].

Resistance to pharmacotherapy remains a serious problem in the treatment of schizophrenia[37]. ECT could be an augmentation strategy to enhance the effects of antipsychotic drugs[38]. ECT could also augment clozapine in clozapine-resistant patients[39]. Psychotic conditions that respond well to ECT include catatonia and pre- and postpartum psychotic states[40]. Combining maintenance ECT with antipsychotic

medications is an effective strategy for relapse prevention in schizophrenia[41].

Adverse effects of ECT

From the beginning, psychiatrists' intentions was to make ECT as safe as possible by decreasing its side effects to the minimum. As a result of these efforts, muscle relaxation[42] and anaesthesia[43] were introduced by the early 1950s. The importance of minimizing cognitive side-effects was recognized early and unilateral stimulation technique was introduced as early as 1954[44]. Recent efforts to further reduce cognitive side effects focus on changing from brief to ultra brief pulse stimulation[45]. While a few individual testimonies reported longlasting and severe memory disturbances after ECT[46], extensive psychological tests could not detect significant memory deficits beyond six months following a course of ECT[47].

ATTITUDES TOWARDS ECT

ECT is probably the most controversial form of treatment in medicine. It has been banned in certain parts of the world[48] while remaining widely practiced in other countries[49]. Besides economic and socio-cultural factors, historical contexts, such as the misuse of ECT during the Nazi era[50], might have contributed to the negative perceptions of this form of therapy. Misleading media representations of ECT have contributed further to this negative image. For example, the portrayal of ECT in the film "One Flew over the Cuckoo's Nest" by Milos Forman, has had a huge and long-lasting effect on perceptions, although other movies and social media have also presented a grossly distorted image[51]. Recently, however, a slow tendency towards a more objective depiction of ECT has been observed[52]. In contrast to its negative image in the media and the public misperception[53,54], attitudes towards ECT in patients, relatives and the mental health professionals are mainly positive[55,56].

COMPARISON OF ECT WITH RECENTLY DEVELOPED BRAIN STIMULATION METHODS

In the last two decades several new neurostimulation methods have been introduced in psychiatry mainly from the field of neurology. These include transcranial magnetic stimulation (TMS), vagus nerve stimulation, deep brain stimulation, transcranial direct current stimulation. Most of these new techniques were introduced to treat major depression. To date, only TMS has been compared with ECT in randomized controlled trials, which consistently proved the superior efficacy of ECT in the treatment of major depression[57]. No other neurostimulation technique has a firm place in the treatment algorithm for major depression[58].

CONCLUSION

After 80 years, electroconvulsive therapy remains one of the most effective treatment modalities in psychiatry. However, the popular image of ECT is controversial and mainly negative. This perception can sometimes hinder its use, thereby violating the rights of patients to access to an effective and sometimes lifesaving treatment.

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REVIEW

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

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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

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.

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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 *et al*[29], 2005. 7 studies of child and adolescent BD (n = 362)	Mean prevalence of any anxiety disorder in BD 27% (range 14%-43%)	
Vázquez *et al*[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 *et al*[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 *et al*[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 *et al*[19], 2015. 40 studies (n = 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 *et al*[31], 2015. 4 studies of adolescent BD-OCD (n = 345)		Pooled prevalence of comorbid OCD in BD among adolescents 23%; greater than adults (14%)
Amerio *et al*[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 *et al*[33], 2016. 28 studies of comorbid BD and GAD (n = 7894)		Current prevalence 12% and lifetime prevalence 15% of GAD in BD
Taskiran *et al*[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 *et al*[35], 2017. 10 studies of euthymic BD (n = 2120)	Current prevalence of any anxiety disorder in BD 35%	Current prevalence of: GAD 12%, SAD 10%, SP PHOBIA 10%, OCD 7%
Yapici Eser *et al*[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 *et al*[36], 2018. 15 studies of comorbid BD and PD (n = 3391)		Lifetime prevalence: PD 16%; current prevalence: PD 13%; no difference between BP I and BP II
Systematic reviews		
Strakowski *et al*[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 *et al*[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 *et al*[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 *et al*[39], 2009. PTSD prevalence in BD		Lifetime rates of PTSD in BD 16%-39%
Maina *et al*[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 *et al*[40], 2011. 10 studies of comorbid BD and OCD		Lifetime prevalence in epidemiological and clinical studies 15%-35%
Lala *et al*[41], 2012. 7 studies of elderly patients		PTSD 5%-11%, PD -current 22%, GAD-current 16%, OTHERS 10%-11%
Schaffer *et al*[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 *et al*[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 *et al*[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%)

Frías *et al*[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 *et al*[46], 2002		Prevalence of BD in OCD 11%-16%, cyclothymia 50%-56%
Freeman *et al*[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 *et al*[47], 2003	Lifetime rate 92%	Lifetime rates SP PHOBIA 67%, SOC PHOBIA 47%, GAD 42%, PTSD 39%, PD 33%
Sasson *et al*[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 *et al*[2], 2004	Epidemiological studies > 90%; clinical 4%-50%	
Issler *et al*[13], 2004	Lifetime rate 24% to 79%	
McIntyre *et al*[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 *et al*[50], 2004		Mean prevalence of PTSD in BD 16%
Bauer *et al*[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 *et al*[24], 2005	Lifetime rate 42%-92%	PD 21% OCD 21%
Simon *et al*[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 *et al*[53], 2006		Prevalence PD - community studies 12%-35%; clinical studies 5%-63%; family studies 11%-21%
Sajatovic *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[59], 2009	Prevalence in adults and children 12%-76%	Prevalence OCD 15-35%
Sagman *et al*[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 *et al*[4], 2010	Lifetime rate 65%	Lifetime rate OCD 21%
Andrade-Nascimento *et al*[63], 2012		Current 15% and lifetime prevalence 16% of GAD in euthymic patients
Jana *et al*[64], 2012		Mean prevalence of OCD 0%-54% in childhood and adolescent BD
McIntyre *et al*[65], 2012	Lifetime rate 63%-87%	
Perugi *et al*[66], 2012	Lifetime rate 30%-93%; current rate 30%	Lifetime rate SP PHOBIA 67%, PD 33%
Cazard *et al*[67], 2013	Mean prevalence 5%-33%	Mean prevalence: SOC PHOBIA 0.5%-47%, PTSD 2%-44%, GAD 3%-42%, OCD 1%-14%
Amerio *et al*[68], 2015	Mean prevalence 50%	OCD 17%-18%
Chang *et al*[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 *et al*[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%

[1]Only for bipolar spectrum disorders; [2]National 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 *et al*[100], 2001 (*n* = 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 *et al*[101], 2001 (*n* = 261)	Lifetime rate 44%	
Dittmann *et al*[102], 2002 (*n* = 152)	Lifetime rate 12%	
Levander *et al*[103], 2007 (*n* = 350)	Lifetime rate BD 46%; BP I 45%-48%; BP II 38%-58%	
Altshuler *et al*[104], 2010 (*n* = 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 *et al*[105], 2004 (*n* = 1000)	Lifetime rate 47%	
Perlis *et al*[106], 2004 (*n* = 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 *et al*[107], 2004 (*n* = 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 *et al*[108], 2004 (*n* = 919)	Current rate 32%	GAD 13%, SAD 13%, PD 8%, OCD 7%, PTSD 5%, AGORA 4%
Otto *et al*[109], 2006 (*n* = 1000)	Current rate 32%	Current rates: SAD 13%, GAD13%, PD 8%, OCD 7%, PTSD 5%, AGORA 4%
Simon *et al*[110], 2007 (*n* = 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 *et al*[111], 2001 (*n* =129)		PD 2%, SOC PHOBIA 2%, SP PHOBIA 2%, OCD 2%
MacKinnon *et al*[112], 2002 (*n* = 192)		Prevalence PD 14%
Henry *et al*[113], 2003 (*n* = 318)	Lifetime rates 24%	Lifetime rates: PD 16%, PHOBIAS 11%, OCD 3%
Boylan *et al*[114], 2004 (*n* = 138)	Prevalence 56%	
Bauer *et al*[14], 2005 (*n* = 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 (*n* = 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 *et al*[115], 2009 (*n* = 1090)	Lifetime rate 27%	Lifetime rates: GAD 20%, PD 5%, AGORA 4%, SOC PHOBIA 2%, PTSD 2%, OCD 1.5%
Coryell *et al*[116], 2009 (*n* = 259)		Lifetime rates: PHOBIA 3%-6%, GAD 1%-5%, PD 1%-4%, OCD 2%
Gao *et al*[117], 2010 (*n* = 564)	Prevalence in RCBD 46%	
Guo *et al*[118], 2010 (*n* = 136763)	Prevalence 36%-37%	
Mantere *et al*[119], 2010 (*n* =191)	Current rate 31%-44%	
Fracalanza *et al*[120], 2011 (*n* = 186)	Current rate 33%	Current rates: SAD 39%, PD 31%, OCD 16%, GAD 10%, PTSD 3%
Goes *et al*[121], 2012 (*n* = 1416)		Prevalence: PD 23%, SP PHOBIA 10%, SOC PHOBIA 8%, OCD 6%
Chang *et al*[122], 2012 (*n* = 325)	Lifetime rates: BP I 27%, BP II 39%	Lifetime rates (BPI/BP II): GAD 10%/29%, PD 5%/9%, SOC PHOBIA 4%/5%, PTSD 3%/2%, OCD 2%/4%, SP PHOBIA 1%/4%
Angst *et al*[123], 2013 (*n* = 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 *et al*[124], 2013 (*n* = 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 *et al*[125], 2013 (*n* = 304)	Lifetime rate 22%	PD 40%, SP PHOBIA 24%, OCD 15%, GAD 13%, SAD 10%, AGORA 8%
Asaad *et al*[126], 2014 (*n* = 350)	Prevalence 2.3%	
Baek *et al*[127], 2014 (*n* = 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 *e.g.*, quetiapine and olanzapine first line choices	[6,7,9,10,12,15,17,22,26,33,48,55,128,141,142,158-162]
	SSRIs *e.g.*, paroxetine but risk of mood destabilization	[6,7,9,10,12,15-17,22,25,26,33,48,55,128,157-159,162]
	Anticonvulsants *e.g.*, 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.

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