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by Subho Chakrabarti

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Abstract

BACKGROUND Lifetime psychotic symptoms are present in over half of the patients with bipolar disorder (BD) and have an adverse effect on its course, outcome, and treatment. However, despite the considerable amount of research, the impact of psychotic symptoms on BD remains unclear and there are very few systematic reviews on the subject.

AIM

This systematic review examined the extent of psychotic symptoms in BD and their impact on several aspects of the illness.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed. An electronic literature search of six English-language databases and a manual search was undertaken to identify published articles on psychotic symptoms in BD from January 1940 to December 2021. Combinations of the relevant Medical Subject Headings terms were used to search for these studies. Articles were selected after a screening phase, followed by a review of the full texts of the articles. Assessment of the methodological quality of the studies and the risk of bias was conducted using standard tools.

RESULTS

This systematic review included 339 studies of patients with BD. Lifetime psychosis was found in more than a half to two-thirds of the patients, while

current psychosis was found in a little less than half of them. Delusions were more common than hallucinations in all phases of BD. About a third of the patients reported first-rank symptoms or mood-incongruent psychotic symptoms, particularly during manic episodes. Psychotic symptoms were more frequent in bipolar type I compared to bipolar type II disorder, and in mania or mixed episodes compared to bipolar depression. Although psychotic symptoms were not more severe in BD, the severity of the illness in psychotic BD was consistently greater. Psychosis was usually associated with poor insight and a higher frequency of agitation, anxiety, and hostility, but not with psychiatric comorbidity. Psychosis was consistently linked with increased rates and the duration of hospitalizations, switching among patients with depression, and poorer outcomes with mood-incongruent symptoms. In contrast, psychosis was less likely to be accompanied by a rapid-cycling course, longer illness duration, and heightened suicidal risk. There was no significant impact of psychosis on the other parameters of course and outcome.

CONCLUSION Though psychotic symptoms are very common in BD, they are not always associated with an adverse impact on BD and its course and outcome.

Keywords: Psychotic Symptoms; Bipolar Disorder; Extent; Impact

Core tip: This systematic review examined the extent and impact of psychosis in 339 studies of bipolar disorder (BD). The results endorsed the high rates of all types of psychotic symptoms in BD. However, psychosis was associated with an adverse impact only in a few domains of the illness including the severity of BD, the rate/duration of hospitalizations, switches to BD, and poorer outcomes with mood-incongruent symptoms. No consistent associations were found in other areas, suggesting that psychosis is not always associated with a

negative impact on BD. This finding conformed to the current consensus in the literature on psychotic BD.

INTRODUCTION

Psychosis in bipolar disorder (BD) is characterized by the presence of either delusions or hallucinations or both [1]. It is well known that over half of the patients with BD develop psychotic symptoms during their lifetimes [2, 3]. Psychotic symptoms are more frequent in bipolar than in unipolar depression [3-5]. Rates of psychotic symptoms in BD may be comparable to schizophrenia and there appears to be no qualitative distinction in psychotic symptoms found in BD or schizophrenia [6-8]. Psychotic symptoms are much more frequent during manic than depressive episodes [3, 5, 8]. Their rates are so high in mania that it is often indistinguishable from primary psychotic disorders [9]. All kinds of psychotic symptoms may occur among patients with BD, though grandiose, persecutory, and referential delusions, auditory verbal hallucinations (AVH) or hearing voices, and visual hallucinations are particularly common [2, 8, 10]. Both mood-congruent and mood-incongruent psychotic symptoms as well as Schneiderian first-rank symptoms (FRS) also occur in BD [2, 3, 6, 8].

Given their ubiquity, psychotic symptoms in BD have the potential to adversely affect its course, outcome, and response to treatment. Somewhat surprisingly, the impact of psychosis on the course and outcome of BD remains unclear despite extensive research on the subject. While some reviews regarding the impact of psychosis on BD have indicated that psychotic BD represents a more severe form of the illness with an adverse course and outcome [9, 11, 12], the majority of the others have not been able to find an association between

psychotic symptoms and outcome in BD [2, 3, 5, 8, 13]. Nevertheless, the presence of psychotic symptoms in BD may be of some significance in determining its current nosology [12-14]. Moreover, the similarity of psychotic BD with schizophrenia on genetic, neurobiological, and cognitive aspects indicates common aetiological underpinnings of these disorders [14-16]. In both these aspects, BD seems to lie in an intermediate position between psychotic and non-psychotic disorders, leading to the hypothesis of a continuum of psychosis stretching from major depressive disorders with psychosis, to psychotic BD, and schizophrenia [15-18]. Finally, from the clinical perspective, psychotic symptoms have a considerable influence on the way BD is diagnosed and treated. The high prevalence of psychotic symptoms in BD often results in a mistaken diagnosis of schizophrenia. This can lead to inappropriate treatment and can have negative social and economic consequences for those with BD [2, 6, 8, 19]. Moreover, the best way to manage psychotic BD is not clear, though guidelines emphasize the role of antipsychotics or electroconvulsive therapy, while research on adjunctive psychosocial interventions for psychotic symptoms is limited [8, 14]. Over the years there have been many reviews of psychotic symptoms in BD including the seminal ones by Goodwin and Jamison [3, 5], and by other authors [2, 6, 9, 14, 20]. However, there have been very few systematic reviews on the subject. Only three such systematic reviews could be identified. Two of them were primarily focused on hallucinations in BD, unipolar depression, or other disorders [10, 21]. Only one systematic review had examined the phenomenology of AVH and delusions along with their clinical and cognitive correlates in 32 studies of BD [8].

Aims and objectives of the current systematic review

The current systematic review was specifically intended to address the gaps in the literature regarding psychotic symptoms and their impact on BD. It attempted to comprehensively examine the extent of psychotic symptoms in BD with a particular emphasis on the associations of psychotic symptoms with the course and outcome of BD. For this purpose, it focused on four groups of studies including those of BD (bipolar type I or BPI and bipolar type II or BPII disorders), studies of mania, bipolar depression, and mixed episodes. Four types of psychotic symptoms were examined including delusions, hallucinations, mood-congruent and mood-incongruent symptoms, and FRS. Mood-congruent and incongruent symptoms, and FRS were examined separately because these symptoms usually indicate a more severe form of BD and may have a greater impact on its outcome. The impact of psychotic symptoms was determined by exploring the demographic correlates of psychotic symptoms, their clinical correlates, and the influence of psychotic symptoms on different parameters of the course and outcome of BD.

MATERIALS AND METHODS

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [22]. Supplementary Table 1 includes the PRISMA 2009 Checklist.

Search strategy

The search for the studies was carried out in 2021. A comprehensive literature search was undertaken using six English-language databases—MEDLINE, PubMed, PsycINFO, EMBASE, Cochrane, and Google to identify published articles on psychotic symptoms in BD from January 1940 to December 2021.

The year 1940 was chosen as the inception point because the initial search revealed that very few studies of psychotic symptoms in BD had been conducted before that year. Only two studies from 1931 identified by the manual search were included in the final list of studies.

The following Medical Subject Headings (MESH) search terms or combinations of these terms were used to search for the relevant studies: BD, mania, depression, psychosis, psychotic, delusions, hallucinations, first-rank symptoms, mood-congruent symptoms, mood-incongruent symptoms, prevalence, course, and outcome. Supplementary Table 1 includes a list of the search strings used and the results retrieved from the Pubmed search.

Selection of studies

During the screening phase, all relevant original research articles were identified based on their titles and abstracts. At this stage, articles with no relevant information on the subject, those not in English, reviews, case reports/series, conference abstracts, editorials, and viewpoints were excluded. Full texts of the articles derived from the screening phase were reviewed to determine whether they met the selection criteria. These full texts were also searched manually to identify additional studies.

Inclusion criteria: Studies were included if they: (i) had examined psychotic symptoms in BD; psychosis was defined as the presence of delusions and/or hallucinations (ii) had a patient sample that included adult subjects (> 18 years of age) (iii) had provided information on the relevant aspects of psychotic symptoms in BD including the rates and types of psychotic symptoms, clinical and demographic correlates, or the association with different parameters of outcome

Exclusion criteria: The following were excluded: (i) studies providing only qualitative data (ii) studies where data on psychotic symptoms were not provided separately for BD (iii) studies of child and adolescent subjects with BD (iv) studies conducted exclusively among subjects with schizophrenia, schizoaffective disorder, and unipolar depression (v) studies exclusively reporting neurocognitive outcomes of psychosis in BD. (These studies were excluded because there are already several systematic reviews and meta-analyses on the subject.)

Data extraction

The following data were extracted for each study included in the final list: authors, year of study, sample size, assessment procedures, results related to the areas of interest, and any indices that estimated the strength of associations, e.g., odds or hazard ratios. The mean, median, and range were estimated for the rates of psychosis and different types of psychotic symptoms. The relationship of psychotic symptoms with the clinical and demographic correlates and outcome parameters was determined based on studies reporting either positive or negative associations. Other aspects, such as the difference between BPI and BPII disorders, or between mania, mixed episodes, and depression were also examined.

Assessment of the quality of studies and risk of bias from the review

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Checklist for cohort, case-control, and cross-sectional studies (combined) was used to rate the quality of studies included in this review [23]. Additional considerations included a sample size of 200 patients (determined

by power calculations based on the included studies), the use of standardized interviews to ascertain the diagnosis, the use of validated operational criteria, and the use of validated scales to measure outcomes. Based on these criteria, the studies included in the review were judged to be of good, moderate, or poor quality. The Risk of Bias in Systematic Reviews tool was used to ascertain the risk of bias arising from the quality of included studies, or the methods of this review [24].

To reduce the selection bias arising from included studies as well as the bias in rating the quality of studies, these procedures were initially carried out independently by the two authors. Any discrepancies were resolved by joint consensus following the independent evaluations.

RESULTS

Studies included for the review

The final list of this review included 339 studies [25-363]. The accompanying figure shows how these studies were eventually selected. Supplementary Table 2 includes the complete list of these studies with their methodological details. The largest number of studies provided data on patients with current episodes of mania (n = 121), followed by the studies on lifetime psychosis among patients with BD (n=113), current psychosis in patients with BD (n = 66), bipolar depression (n = 57), and mixed episodes (n = 43). Comparatively fewer studies had provided lifetime data among patients with mania (n = 29), bipolar depression (n = 21), and mixed episodes (n = 8).

Figure here

Ratings of study quality and risk of bias

Supplementary Table 2 also includes the quality ratings for individual studies. According to these ratings, 97 studies were of good quality, 168 were of moderate quality, and 74 were poor-quality studies. Since the majority of studies were of moderate quality, the risk of bias from studies included in this review was moderate to high.

Prevalence of psychosis in bipolar disorder

The lifetime and current rates of psychosis for BD, and manic, depressive, and mixed episodes are shown in Table 1. Supplementary Table 3 includes the complete details of these studies.

More than half of the patients with BD and about two-thirds of those with BPI disorder had psychotic symptoms during their lifetimes. The lifetime rates of psychosis were about 40%-60% in mania and mixed episodes, but only about 20% in the episodes of bipolar depression. The current rates of psychosis were somewhat lower but still in the range of 40%-60% for BD, BPI disorder, mania, and mixed episodes. The current rates of psychosis were less than 20% for bipolar depression. Both the lifetime and current rates of psychosis were about two to three times higher in BPI compared to BPII disorder; this difference was more marked for mixed episodes where the current rates of psychosis in BPI disorder were about five times that of BPII disorder. Lifetime rates of psychosis were about twice as common in mania than in bipolar depression, while the current rates of psychosis were about three times higher in mania compared to

bipolar depression. On the other hand, both the lifetime and current rates of psychosis were similar in mania and mixed episodes. Finally, about 60 studies had compared the rates of psychosis in bipolar and unipolar depression. In all but 12 of them, the rates of psychosis were higher in BD than in unipolar disorder. In contrast, 18 of the 20 studies that had compared BD with schizophrenia found much higher rates among patients with schizophrenia. An obvious problem in obtaining an accurate picture of the rates of psychosis was that the average rates tended to get skewed as the number of available studies declined. Though relying on median rates and excluding outliers resolved the problem to an extent, this did not completely current the imbalance. Thus, the only reliable rates were those for BD, BPI disorder, and the current rates of psychosis in mania.

Table 1 here

Rates of different psychotic symptoms in bipolar disorder

The lifetime and current rates of the different psychotic symptoms for BD, mania, bipolar depression, and mixed episodes are shown in Table-2. Supplementary Table 4 includes the complete details of these studies.

Predictably, there was greater variability in the rates of the four types of psychotic symptoms. The number of studies from which these rates were derived was also smaller, ranging from 1 to 25. However, certain consistent trends could still be made out.

The average rates of delusions ranged from 44%-87% (median - 43%-87%) with the highest rates being obtained for a lifetime and current psychosis in BD, BPI disorder, mania, and mixed episodes. The average rates of psychosis in bipolar depression were much less, ranging from 12%-20% in a lifetime and current episodes. In contrast, hallucinations were reported only in about a third of the patients, except for those with lifetime episodes of mania and mixed states where rates ranged from 55%-100%. However, the high rates in these two groups were probably because of the small number of studies involved. The number of studies was also small for bipolar depression and the average rates were about 22% (median - 19%), with greater variability across individual studies. The lifetime rates of delusions and hallucinations in patients with BPI disorder far exceeded the rates among those with BPII disorder.

The rates of FRS were high, particularly for the studies of lifetime mania (mean and median- 45%, range up to 59%), current mania (mean - 28%, median - 32%, range up to 48%), and current mixed episodes (mean and median - 32%, range up to 49%). About a fifth of the patients with BD and BPI disorder also reported FRS during psychotic episodes, whereas the average rates in bipolar depression were somewhat lower. None of the studies of patients with BPII disorder reported FRS. However, apart from the current mania group, the number of studies was too small in the other groups to obtain an accurate estimate of the rates.

Mood-congruent psychotic symptoms were far more frequent and were present in about a third to half of the patients. Though some groups such as patients with current BPI disorder, lifetime depression, and lifetime mixed episodes reported very high rates of mood congruence, the number of studies was too small for these rates to be reliable. Mood-incongruent psychotic symptoms were usually reported by about a third of the patients (mean - 33%; median -

37%) apart from two exceptions. Rates were very high (72%-74%) for the lifetime mania and mixed groups, but these were based only on one or two studies. On the other hand, the rates in six studies of current bipolar depression were less than 10%. No studies of BPII disorder reported mood-congruent or incongruent symptoms. Finally, the difficulties of ascertaining mood congruence were reflected by the fact that nine studies had found that about 14% of the patients (range 2%-55%) had both types of symptoms simultaneously.

Table 2 here

Types of delusions, hallucinations, and first-rank symptoms in bipolar disorder

The different types of delusions, hallucinations, and FRS found in BD are shown in Tables 3 and 4. Supplementary Tables 5-7 include the complete details of these studies.

The number of studies from which these rates were derived was generally small, apart from certain exceptions such as those reporting grandiose and persecutory delusions, and auditory, and visual hallucinations. Very few studies had examined the different types of FRS.

Nevertheless, it appeared that both grandiose and referential delusions were equally common in BD, particularly among patients with mania. Persecutory delusions were present in about a third of the patients with BD and were almost equally common in the groups with mania, depression, or mixed episodes. Other common delusions included religious and erotomanic delusions; both were more common in mania and mixed episodes. Somatic

delusions, delusional jealousy, and depressive delusions, particularly delusions of guilt were found in all phases. Auditory hallucinations, especially AVH, were the most frequent types of hallucinations reported in BD and were equally common across all the groups. Visual hallucinations were much less common and found more frequently in mania. Other types of hallucinations were rare including somatic, tactile, olfactory, and gustatory hallucinations. Among the FRS, passivity delusions were the most common, followed by delusional perception, "running commentary" type of hallucinations, "voices conversing", thought echo, thought broadcast, thought insertion, somatic passivity, and thought withdrawal. As expected, the rates of all FRS were more common in mania, BD, and BPI disorders.

Tables 3 and 4 here

Demographic correlates of psychosis in bipolar disorder

Demographic correlates of psychosis in bipolar disorder are included in Table 5. Supplementary Table 8 includes the complete details of these studies. The results showed that there were very few consistent associations of psychotic symptoms with socio-demographic variables in BD. Many studies (n = 27) had not found significant relationships between psychotic BD and any of the demographic characteristics. Moreover, when significant associations were found with demographic parameters in some of the studies, an equal number of studies usually reported contrary results. Finally, the number of studies that had failed to find significant associations of psychosis with individual demographic parameters far outweighed the studies that had found positive associations.

Table 5 here

Clinical correlates of psychosis in bipolar disorder

Clinical correlates of psychosis in bipolar disorder are also shown in Table 5. Supplementary Table 9 includes the complete details of these studies.

(i) The severity of psychosis and severity of illness in psychotic BD: Whether psychotic BD represents a more severe form of the illness has been examined by three groups of studies. The first group examined the severity of psychosis in BD relative to schizophrenia and unipolar depression. The number of studies showing that psychotic symptoms were either less or more severe in BD was exactly equal suggesting that the severity of psychotic symptoms in BD was no different from the other patient groups with psychosis. The second group of studies had focused on the association between psychotic symptoms and the overall severity of BD, or the severity of manic and depressive symptoms. Here, the number of studies showing that the severity of illness or mood symptoms was greater in psychotic BD outnumbered those that did not find a difference. This indicated that the overall severity of the illness and severity of acute episodes was greater in psychotic BD. However, about a third of these studies had found this to be true only for the severity of manic symptoms. Therefore, the association between severe mood symptoms and psychotic BD was largely applicable to patients with current manic episodes. The third group of studies had examined the severity of BD with psychosis in terms of its impact on the course and outcome of the disorder. These are discussed later.

(ii) Other indicators of severity: There was some evidence that psychotic BD was associated with poorer insight and a higher frequency of symptoms of agitation, aggression, and anxiety. Then again, this finding was also derived from the studies of mania, where agitation, violence, lack of insight, and

psychosis often co-occurred. On the other hand, the rates of psychiatric comorbidity did not appear to be greater in those with psychotic BD.

Impact of psychotic symptoms on the course and outcome of bipolar disorder
The impact of psychosis on the different aspects of the course and outcome of BD is summarized in Table 6. Supplementary Table 10 includes the complete details of these studies.

The overall conclusion from these studies was that psychotic BD was not inevitably associated with a more adverse course and poorer outcome of BD. While several studies had found psychosis was associated with a poorer overall outcome, the number of those that had failed to find such an association was almost the same or even more. This trend also appeared to be true for several individual measures of outcome including earlier age of onset, a persistent or chronic course of the illness, lack of remission or recovery, more frequent relapses or recurrences, a greater number of lifetime mood episodes, poor functioning, poor quality of life, and poor functional outcome. Since a large number of studies with reasonable methodological quality had examined these outcome parameters, this lent further support to the notion that psychosis was not always associated with poor outcomes in BD. Moreover, studies that had estimated odds or hazard ratios also showed that psychotic symptoms were not associated with earlier age of onset, poorer functional, or poorer overall outcomes [51, 159, 256, 313, 355]. Though some of the studies based on similar estimations of risk had found adverse outcomes in psychotic BD [103, 104, 137, 157], the positive association of psychosis with poor outcomes in these studies was usually found only in a few outcome measures and not in others [64, 250, 288, 342].

Additionally, negative associations between psychosis and outcome were reported in other domains such as the manic polarity of BD, a seasonal pattern of the illness, the response to lithium treatment, and a poorer outcome with FRS. However, these findings were uncertain because of the small number of studies involved.

Finally, psychosis appeared to be linked to better outcomes in three other areas including a lower proportion of rapid cycling, a shorter duration of illness, and a lowered suicidal risk. The negative association with suicidal behaviour appeared to be particularly strong based on the number of studies and estimations of risk [40, 57, 105, 306].

Nevertheless, psychosis appeared to be more consistently linked with adverse outcomes in some of the other areas. The rate and the duration of hospitalizations were consistently higher among patients with psychotic BD. Some studies had found the risk of hospitalization to be about one and a half times in psychotic BD [209]. Patients with depression were more likely to switch to BD if they had psychotic symptoms. Though this finding was based on only ten studies, some of them had estimated the risk to be between one and a half to two times based on odds ratios [186, 216, 222]. Lastly, the number of studies that found mood-incongruent psychotic symptoms to be associated with a poorer outcome was considerably more than those that had not found such an association.

Table 6 here

DISCUSSION

The current systematic review examined the extent of psychotic symptoms in BD and their impact on the course and outcome of BD based on the 339 studies that were selected. Before focusing on its findings, it is imperative to

understand the strengths and weaknesses of the studies included in this review.

Methodological considerations This review showed that there is no dearth of studies on the subject of psychotic symptoms in BD. Moreover, almost every aspect such as the prevalence of psychotic symptoms, their correlates, and the impact of psychosis on the course and outcome of BD have been systematically assessed by a number of these studies. However, the existing literature has several methodological shortcomings that often make it difficult to reach firm conclusions.

The studies covered a period from 1940 to 2021, during which the definition of BD has undergone many changes. Thus, there may be some difficulty in equating labels such as manic-depressive psychoses and BD. However, there were only minor differences between the definitions in older studies and the current definitions of the disorder. Moreover, leaving out studies conducted before the 1980s would have resulted in a significant loss of data. Psychosis has usually been defined as the presence of delusions and/or hallucinations by most studies. Though this definition fits the current standards and is easily established by using structured interviews [364], a few studies have included formal thought disorder as a part of the definition [142]. This complicates matters since thought disorder is relatively non-specific and more difficult to ascertain. Nevertheless, the broader definition seems to be commonly used [365], while the narrower one has its critics [366]. The method of assessment also had a bearing on the results of the studies. Although the majority of the studies had used structured interviews and validated scales to assess psychotic symptoms, some, especially the older ones had not. However, rather than the assessment method, the inadequate sample size of most of the studies compromised their methodological adequacy. Moreover, almost all

studies included hospital-based patients. The lack of community studies hinders the generalization of these findings to patients with BD in real-world settings. These lacunae in the quality of most of the studies included in the review raise the possibility of a moderate to high risk of bias in the findings of this review. The variability in results could also result from the lack of control for potential confounders such as age [159, 321], gender [357, 374], mood state [8], comorbidity [162], and chronicity of the illness [46]. Although multivariate statistics have been used in many studies to control for these factors, risk estimates are only offered by a few of them, and the estimation of the strength of associations by calculating effect sizes is rare. Finally, there is a lack of studies examining the descriptive and subjective aspects of psychotic symptoms in BD [8].

Principal findings of this review

As a consequence of the methodological variability across the studies, some of the findings of this review were more reliable than the others.

One of the more reliable findings was the very high rates of psychotic symptoms in BD. In keeping with the earlier reviews, more than half of the patients with BD, mania, or mixed episodes developed such symptoms during their lifetimes [2, 3, 5, 14, 89]. Current rates of psychosis were also high and found in a little less than half of these patients. In contrast, earlier reviews have reported that about a third of the patients have psychotic symptoms during their current episodes [6, 367].

Like the earlier reports, psychosis was much more common in mania and mixed episodes than in bipolar depression [3, 5, 8]. Psychosis was about twice as common in BPI compared to BPII disorder. Despite the smaller number of studies of patients with BPII disorder, this has been a consistent finding in the existing literature [3]. This could be because psychosis can be present only

during depressive episodes in BPII disorder according to the current definitions, or because of the lower severity of illness in this subtype [44, 62]. In agreement with the earlier reviews [3-5], a large number of studies found the rates of psychosis to be much higher in bipolar compared to unipolar depression. However, the rates of psychosis were usually lower than those found in schizophrenia [6-8].

The rates of different types of psychotic symptoms were somewhat less reliable, principally because of the smaller number of studies involved. Nevertheless, the trends were similar to the existing reports. Thus, delusions were far more frequent than hallucinations in all phases of BD [2, 3, 5, 8, 10]. The higher rates in mania compared to bipolar depression and BPI compared to BPII disorder were also in keeping with the previous reviews [3, 8-10, 367]. Though based on the smallest number of studies, about a third of the patients reported experiencing FRS, particularly during acute manic episodes. This was almost equal to the rates of FRS reported in the existing literature [2, 3, 8, 10]. Similar to the earlier reports, mood-congruent psychotic symptoms were more common among patients with BD [2, 3, 6, 8, 10]. As found in these reviews, mood-incongruent symptoms were reported in about a third of the patients with BD and the rates were highest for those with mania. However, because of the small number of studies and the difficulties in ascertaining mood congruence, the validity of these findings is questionable. Similarly, the findings regarding the different types of delusions, hallucinations, and FRS were also based on very few studies but conformed to what has been reported earlier [3, 5, 8, 10, 89].

One of the principal objectives of this review was to examine the impact of psychosis on the course, outcome, clinical correlates, and demographic profile of BD. The findings of this aspect of the current review proved to be the most

reliable since they were based on the largest number of studies, which were of moderate to good quality. Moreover, taken together these studies had carried out a comprehensive examination of different facets of BD that could be impacted by the presence of psychosis. The overall conclusion of this section of the review was that psychotic BD is not always associated with a negative impact on the illness. This reflected the continuing debate about the prognostic implications of psychosis in BD, with some reviews concluding that psychosis is associated with a poorer prognosis [9, 11, 12, 89], whereas the majority have found an uncertain impact of psychosis on BD [2, 3, 5, 8, 46]. In line with the other reviews [3, 8, 10], the current one found few consistent associations of psychotic symptoms in BD with socio-demographic variables. Thus, the case for psychosis being associated with an adverse demographic profile [89] was not proven. The findings concerning the clinical correlates were more equivocal. As reported earlier [3, 10, 13], psychotic symptoms were not more severe in BD, particularly when compared to schizophrenia. On the other hand, and in keeping with the existing evidence [2, 3, 12, 89], the severity of the illness in psychotic BD appeared to be consistently greater. However, this finding was largely based on manic symptom-severity, which tends to be inevitably higher than the other phases of BD [2]. Moreover, the genesis of psychotic symptoms is likely to be only partly mediated by clinical severity and partly by other factors such as early-onset, shorter duration of illness, comorbid conditions, and gender [8]. Psychosis was associated with a lack of insight, particularly during severe manic episodes. Then again, because most patients regain insight once mania resolves, the extent of impaired insight was less among patients with psychotic mania compared to those with schizophrenia [61, 161]. Psychosis was also associated with a more frequent occurrence of agitation, anxiety, and hostility, but this association could be a

consequence rather than the cause of psychosis in BD [8]. Finally, comorbid disorders were less common in psychotic BD, which was in agreement with the other reviews [3].

There was greater uncertainty about the impact of psychosis on the other parameters of course and outcome. The number of studies reporting poorer overall outcomes in psychotic BD was no different from those that failed to find such a relationship. Moreover, there was no consistent association between psychotic symptoms and earlier age of onset, lack of remission and recovery, more frequent relapses and recurrences, the persistence of psychosis, poorer functional outcomes, and lithium response. Lastly, psychosis was less likely to be associated with a rapid-cycling course, longer duration of illness, and heightened suicidal behaviour. This emulated the uncertainty in the existing literature regarding the associations of psychosis in BD with an earlier age of onset [2, 89, 370-372], a poorer long-term course [2, 3, 8, 46, 89], impaired functioning [88, 373-375], more frequent suicide attempts [3, 368, 369], more frequent rapid-cycling course [46], predominant manic polarity [376] and lithium response [2, 6, 89, 377]. The lack of impact on functioning was surprising but not unusual. The existing literature suggests that though a significant proportion of the patients with BD have impaired functional and social outcomes, this does not appear to be mediated by the presence of psychotic symptoms [83, 141].

Nevertheless, psychosis was associated with poor outcomes in three domains. Psychosis was associated with a higher risk of switching to BD, which is known to occur in about a fifth of the patients with depression [8]. Psychotic symptoms were also associated with more frequent hospitalizations and longer hospital stays, which has been noted by other reviews [9]. Finally, mood-incongruent symptoms appeared to be associated with poorer overall

outcomes. Most of the earlier reviews have reported both positive and negative associations of mood-congruent symptoms with outcome [2, 3, 6, 46, 250]. However, the most comprehensive review on the subject found that though mood-incongruent symptoms were associated with poor outcomes, the differences between psychotic and non-psychotic BD were small and rarely significant [378]. Moreover, in line with the existing evidence, the current review also found that psychotic BD had a better outcome than schizophrenia [7, 11].

CONCLUSIONS

The current systematic review has shown that there is no paucity of evidence on the subject of psychotic symptoms in BD. However, because of methodological shortcomings of the evidence, there are few consistent and reliable findings. One of them was the high prevalence of psychotic symptoms and the other was the lack of an adverse impact of psychosis on several domains of BD, including its course and outcome. These findings together with the genetic, neurobiological, and neurocognitive evidence suggest that psychotic BD lies on a continuum between non-psychotic forms of the disorder and schizophrenia [379-382]. Mood-incongruent psychotic BD, which is a severe form of BD overlaps with schizophrenia, whereas non-psychotic BD is similar to unipolar disorders [17, 18, 79, 383]. The evidence from this review thus supports the current classification of BD as lying in an intermediate position between unipolar depression and schizophrenia [1]. Finally, from the clinicians' perspective, this review suggests that greater awareness and understanding of this subject is needed so that psychotic BD can be properly diagnosed and adequately treated in routine practice.

ARTICLE HIGHLIGHTS

Research background Psychotic symptoms are very common in bipolar disorder (BD) and have the potential to adversely affect its course, outcome, and treatment. However, despite the considerable amount of research and several reviews on the subject, the impact of psychotic symptoms on the course and outcome of BD remains unclear. Moreover, there are very few systematic reviews on the impact of psychosis in BD.

Research motivation The lack of information about the impact of psychotic symptoms in BD in existing literature prompted the current systematic review. Moreover, it was prompted by the possibility that the presence of such symptoms in BD and their impact on the illness may have significant aetiological, nosological, and clinical implications.

Research objectives The current systematic review was specifically intended to address the gaps in the literature regarding psychotic symptoms in BD. Therefore, it aimed to examine psychotic symptoms in BD and their impact on several domains of BD. This review focused on four groups of studies and four types of psychotic symptoms. The impact of psychotic symptoms was determined by exploring demographic correlates of psychotic symptoms, their clinical correlates, and the influence of psychotic symptoms on different parameters of course and outcome of BD.

Research methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. It undertook an electronic search supplemented by a manual one. Articles were selected in two phases: screening of abstracts and review of full texts. The

methodological quality of the studies and the risk of bias were ascertained by standard tools.

Research results

This systematic review included 339 studies of BD. The results endorsed the high rates of all types of psychotic symptoms found in BD. More than a half to two-thirds of the patients experienced psychosis during their lifetimes. Current psychosis was found in a little less than half of these patients. Delusions were more common than hallucinations. About a third of the patients had first-rank symptoms or mood-incongruent psychotic symptoms. Psychotic symptoms were more frequent in bipolar type I disorder, and in mania or mixed episodes. However, psychosis was associated with an adverse impact only in a few domains of the illness including the severity of BD, lack of insight, more frequent occurrence of agitation, anxiety, and hostility, the rate of and the duration of hospitalizations, switch to BD among patients with depression, and poorer outcomes with mood -incongruent symptoms. No consistent associations were found in other areas, suggesting that psychosis is not always associated with a negative impact on BD. This finding conformed to the current consensus in the literature on psychotic BD.

Research conclusions

Though psychotic symptoms are very common in BD, they are not always associated with an adverse impact on BD and its course and outcome.

Research perspectives

The ongoing debate about the impact of psychosis in BD is yet to be resolved. Studies with more improved methodology are needed to ascertain the true impact of psychotic symptoms in several domains of BD.