Review

Predicting the course and outcome of bipolar disorder: A review

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ABSTRACT

Despite of advances in pharmacological and non-pharmacological treatments, bipolar disorder often entails multiple relapses and impaired psychological functioning. The extent to which modern treatments have influenced the natural course of a mental disorder is uncertain. Prediction of the course and outcome of bipolar disorders continues to be challenging, despite the multiple research efforts worldwide. Due to a lack of laboratory diagnostic tests and biomarkers, psychiatric interview and examination provide the basis for outcome prediction. While considered to have more favorable prognosis than schizophrenia, it is not uncommon for bipolar disorder to include persisting alterations of psychosocial functioning. Although long-term symptomatic remission does not guarantee functional recovery, it may have a favorable impact on long-term overall prognosis. The high degree of treatment resistance in patients with bipolar disorder highlights the need to develop better identification of outcome predictors, prognosis and treatment intervention, designed to reverse or prevent this illness burden. This review summarizes the main factors involved in predicting the course and outcome of bipolar disorder.

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1. Introduction

Prediction of the course and outcome of bipolar disorder (BD) continues to be challenging, despite recent observational studies conducted in North America and Western Europe. Although high diagnostic stability is typical for BD, a recent observational study showed a high prevalence of misdiagnosis and of diagnostic shifts from other psychiatric disorders to BD [59]. BD represents the full spectrum of mood disorders that are chronic and is a major methodological challenge for prediction of the outcome [32] and natural course of the disease [57, 79]. The natural course of BD is characterized by a constant risk of recurrences over a patient’s life span, even 30 to 40 years after onset and up to 70 years of age or more, causing impairment of psychosocial functioning, despite the advances in pharmacological and non-pharmacological treatments [76, 26].

The influence of modern treatment interventions on the natural course of illness is uncertain. While considered to have a more favorable prognosis than schizophrenia, it is not uncommon for BD to include persisting alterations of psychosocial functioning. Although long-term symptomatic remission does not guarantee functional recovery [46, 68, 73], it may have a favorable impact on overall prognosis. Observational long-term studies on patients with BD reported persistent impairment with significant disability, including 19% to 23% of months with moderate impairment and 7% to 9% of months with severe overall impairment [74]. Patients with BD I were unable to carry out work role functions during 30% of assessed months, which is significantly more in comparison to patients with unipolar major depression or BD II (21% and 20%, respectively). This degree of disability is similar to that of schizoaffective disorders [29]. Furthermore, neuropsychological impairment due to BD persists during euthymic states, but is likely to be partially confounded by mild affective symptoms in remitted patients [42].

In view of the higher degree of treatment resistance in patients with BD, there is an alarming need to develop significant prognostic, diagnostic and treatment interventions to prevent the burden of this illness. This review article summarizes the main factors involved in predicting the course and outcome of BD.

1.1. Outcome after first episode

The decade-long McLean-Harvard First Episode Project has systematically followed large numbers of patients from first hospitalization with bipolar or psychotic affective and non affective disorders, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). This study indicates that, despite modern pharmacological treatments, the course and outcome of BD are not satisfactory. Full functional recovery is uncommon and full symptomatic recovery is much slower than syndromal recovery, with earliest morbidity being depressive-dysphoric. Initial depression or mixed-states predicted
relapse into depression and overall morbidity, whereas initial mania without depression predicted relapse into mania, but with an overall better prognosis [43]. Furthermore, data [6] showed that after the first hospitalization for a manic or mixed episode, most patients achieved syndromal recovery after 2 years, but 28% of patients remained symptomatic, and only 43% of patients achieved functional recovery. Moreover, 57% of those patients who achieved syndromic remission switched phases or had new illness episodes during the first 2 years after recovery in the Project. In this study, factors associated with a shorter time to syndromal recovery for 50% of the subjects were female gender, shorter index hospitalization, and lower initial depression ratings. For functional recovery, 43% were older patients with shorter index hospitalizations. Within 2 years of syndromal recovery, 40% of patients experienced a new episode (17% manic, 3% mixed, and 20% depression). Predictors of manic relapse were initial mood-incongruent psychotic features, lower premorbid occupational status, and initial manic presentation. Predictors of depressive relapse were higher occupational status, initial mixed presentation, and the presence of medical or psychiatric comorbidity.

2. Predictors of outcome

2.1. Age at onset

Patients generally experience their first manic episode in their early twenties, although it can be seen at any stage of life, from childhood to old age. Childhood BD usually has a poorer prognosis with long delays to first treatment. Such patients report more episodes, more comorbidities, and rapid cycling and demonstrate severe mania, depression, and fewer days well [36]. Studies reported that, although most bipolar adolescents experience syndromic recovery following their first hospitalization, rates of symptomatic and functional recovery are lower compared to adults [4,68,21].

Data consistently indicated that between 70% and 100% of children and adolescents with BD recover from their index episode, however, up to 80% experience multiple recurrences [11]. BD considerably affects the normal psychosocial development of a child and increases the risk of academic, social, and interpersonal problems (e.g. family, peers, and work), as well as risk of poor health care utilization. Studies suggest that approximately 30% of preadolescents with major depressive disorder (MDD) experience a manic episode and manifest BD within 5 years [25].

In contrast, mania in the elderly appears to be a heterogeneous disorder, where in first-episode mania (very late onset) patients were twice as likely to have an associated comorbid neurological disorder and higher risk of relapse and mortality compared to others with multiple episodes of mania [71].

Population studies tend to find younger ages of onset than clinical trial samples: this is probably due to the age limit and the interventional nature of clinical trials, versus the more real world samples that are enrolled in naturalistic settings [20]. The explanations for these inconsistencies is also probably related to the issue that reported rates of bipolar syndromes are highly variable between studies because of age differences, differences in diagnostic criteria, or restriction of sampling to clinical contacts. The most recent study showed, that experiencing (hypomanic) symptoms is a common adolescent phenomenon that infrequently predicts mental health care use [66]. These findings suggest that the onset of BD can be elucidated by studying the pathway from non-pathological behavioural expression to dysfunction and need for care.

2.2. Pre-illness condition and gender

Both poor functioning and psychosocial adjustment before the onset of the illness predict worse outcome of BD [77,48]. Gender can also be a predictor of outcome, with men and women behaving differently. Men have early onset associated with manic episodes, higher probability of childhood antisocial behavior, higher rates of comorbid alcohol abuse/dependence, cannabis abuse/dependence, and pathological gambling. Women have more depressive episodes, with higher rates of comorbid eating disorders, weight change, and insomnia [30] and higher incidence rates of BD I throughout the adult life [41].

2.3. Symptom severity

Reducing the risk of recurrences, which are common and associated with mood symptoms at initial recovery, can be achieved by targeting residual symptoms in BD. The STEP-BD project (Systematic Treatment Enhancement Program for BD), a multistate observational study [55] conducted in the United States, showed an initial recovery by 58% of patients, with half of them experiencing recurrences after 2 years of follow up and more than twice developing depressive versus manic, hypomanic, or mixed episodes. Factors that significantly affect the depressive recurrence included residual depressive or manic symptoms at recovery and proportion of days the subjects are depressed or anxious in the preceding year.

Recent reports suggested that, apart from the presence of chronic subsyndromal symptoms, the emergence of depressive symptoms also predicts the shorter time to a new episode of BD. It was also observed that presence of subsyndromal depressive symptoms during the first two months after recovery increases the likelihood of depressive relapse [75]. Another study showed that while modest changes in severity of depression are associated with statistically and clinically significant changes in functional impairment and disability in patients with BD, changes in severity of mania or hypomania are not consistently associated with differences in functioning [60]. It is also noteworthy that patients with psychotic features and those with a greater number of previous depressive episodes are more likely to experience subsyndromal depressive symptoms [39,69].

The 12-month Stanley Foundation Bipolar Network outcome study showed that the mean rating for severity of mania/depression was associated with comorbid substance abuse, history of more than 10 prior manic episodes, and poor occupational functioning at study entry [52]. Furthermore, the total number of overall illness episodes was associated with a positive family history of drug abuse, a history of prior rapid cycling, and poor occupational functioning.

The differentiation of mood congruence of psychotic features in mania appears to have prognostic validity. Mood-incongruent psychotic features during the index manic episode predicted a shorter time in remission at 4 years [70]. In naturalistic settings, patients with mania and rapid cycling differ from non rapid cycling in socio-demographic characteristics, treatment prescriptions, and clinical outcome measures with a consistently worse occupational outcome and comorbidities. Rapid cycling represents a longitudinally-severe form of BD, with weak evidence-based diagnostic and therapeutic tools [70]. Higher occupational status, initial mixed presentation, and any comorbidity predict depressive, rather than manic onset [73]. A higher number of hospitalizations and less rapid cycling are more strongly associated with BD I than BD II [18,19], with risk factors including biological rhythm dysregulation, antidepressant or stimulant use, hypothyroidism, and premenstrual and postpartum states [3].

The use of subsyndromal or subthreshold symptoms to broaden the diagnostic criteria for BD is receiving increased attention recently: a topic that is becoming more and more interesting for clinicians [5]. BD continues to be characterized by poor clinical and functional outcomes in many patients. According to recent studies,
subthreshold BD appeared to be at least five times more prevalent than DSM-based syndromal BD [38]. Poor outcomes may be related to subsyndromal symptoms, defined as symptoms that fail to meet the full diagnostic criteria for a mood episode. Several recent studies indicate that subsyndromal symptoms in BD are strongly associated with deficits in both social and occupational functioning. Furthermore, subsyndromal symptoms appear to increase the risk of relapse. Subthreshold BD is highly prevalent and disabling, according to a nationwide survey of more than 9,000 Americans sponsored by the National Institute of Mental Health. Lifetime (and 12-month) prevalence estimates are 1.0% (0.6%) for BP-I, 1.1% (0.8%) for BP-II, and 2.4% (1.4%) for subthreshold BPD. Most respondents with threshold and subthreshold BPD had lifetime comorbidity with other Axis I disorders, particularly anxiety disorders [49]. Further research is needed to assess the prognostic value of subthreshold symptoms in the course of the illness [40].

3. The impact of treatment on the course of illness

3.1. The importance of early intervention

The treatment of BD should strive to alter the course of disease in a positive way. Early intervention and effective treatment are the ultimate goals, but early identification has several barriers which cause approximately 10 years of delay from a patient’s first episode of illness to diagnosis [24,27], jeopardizing the effectiveness of the early treatment intervention [33]. This suggests that the initial lithium therapy within the first 10 years of onset of BD might be more promising than prophylaxis in later life. Similarly, maintenance therapy also appears to be more effective early in the course of BD. A recent report suggests that early-stage patients had significantly lower rates of relapse and recurrence of manic/mixed episodes with such treatments [33]. Furthermore, a history of multiple episodes may be associated with poor response to lithium treatment and that patients with higher numbers of manic episodes exhibit worse outcomes [69,64,15]. These data suggest that preventing recurrent episodes early during the disorder could improve a patient’s long-term prognosis.

In addition, the pharmacological treatment of early-phase BDs lacks specific guidelines for clinicians [17]. The initial prodrome of BD has received very little attention to date and there are no prodrome features that clearly distinguish between patients who eventually develop BD and those who develop other disorders, such as schizophrenia [65].

3.2. Polarity of index episode

Evidence from both the pre-lithium and modern eras suggest that the polarity of the index episode tends to predict the polarity of the subsequent mood episode: a manic index episode tends to predict a manic relapse, whereas a depressive or mixed index episode predicts a depressive relapse [73,14]. Patients with bipolar illness categorized by subtype episodes have significant differences in the time of recovery [31]. Based on a median follow-up of 18 months, the estimated probability of remaining ill for at least one year was 7% for the pure manic patients, compared with 32% for patients that were mixed or cycling, and 22% for the purely depressed patients. It appears that a patient with a first depressive (rather than manic) episode tends to experience a greater burden of depressive symptoms in the later part of life [54]. The polarity of the first mood episode may be a useful tool in distinguishing subsets of bipolar patients at risk for more chronic courses: depressive-onset BD is significantly associated with more lifetime depressive episodes and a greater proportion of time experiencing depression and anxiety in the year prior to assessment.

4. Personality traits

Patient’s personality and temperament are thought to impact both the prognosis and clinical manifestation of BD. Some studies question the current categorical split of mood disorders into BDs and depressive disorders, suggesting that two highly unstable personality features, i.e. the cyclothymic temperament and borderline personality disorder, have more in common with bipolar II disorder than MDD [9]. Studies also suggested [58] that the combination of temperamental factors that are inverse to those of manic syndrome result in mixed episodes. Research findings that are in line with the current familial-genetic models suggest that the DSM-IV’s characterization of BD II should place greater emphasis on temperamentally-based mood and anxious reactivity [1]. Such phenotypic characterization may assist in genotyping; however, its predictive value on actual illness outcome still requires more research [2].

5. Psychiatric comorbidity

Psychiatric comorbidity is often associated with earlier onset of bipolar symptoms, more severe course, poorer treatment compliance, and worse outcomes related to suicide and other complications. Patients with BD frequently experience comorbidities, including substance-use disorders, with deleterious effect on the course and outcome of disease [67,72]. Clinicians must evaluate and monitor the presence and the development of psychiatric comorbidity and medical conditions to ensure prompt, appropriate intervention and to avoid iatrogenic complications.

5.1. Substance abuse

Comorbid alcoholism in patients with BD leads to poorer psychosocial adjustment and slower recovery [62,7]. Patients with alcohol-induced disorders prior to the onset of BD are usually older and more likely to recover faster compared to those whose alcohol problems commence after BD is diagnosed and tend to experience more time with affective episodes and symptoms. Bipolar patients who are lifetime smokers are more likely to have a young age onset of mood disorder, greater severity of symptoms, poorer functioning, history of suicide attempts, and a lifetime history of comorbid anxiety and substance-use disorders. Smoking may also be associated independently with suicidal behavior in BD patients [53]. The effects of the onset sequence of bipolar- and cannabis-use disorders are less pronounced than the effects observed in co-occurring alcohol and BDs [63], though cannabis-use is associated with more time in affective episodes and with rapid cycling. Most cannabis-use disorders remit immediately after hospitalization, followed by rapid rates of recurrence.

BD patients with comorbid substance-use disorders of any kind may present clinical features that could compromise adherence and response to pharmacological treatment. BD patients with comorbid substance-use disorder are significantly more compromised in social functioning and less likely to be diagnosed with BD I and to present a severe manic symptomatology [46].

5.2. Attention deficit/hyperactivity disorder

Comorbid attention deficit/hyperactivity disorder (ADHD) and anxiety disorders, including those present during relative euthymia, predict a poorer course of BD [47,35]. Similarly, comorbid panic disorder is associated with a higher likelihood of rapid cycling [19]. A recent study showed that comorbid anxiety impacts health-related quality of life in patients with BD I, but not in patients with BD II [34].
5.3. Life events

BD patients have severe stressful life events which are associated with slower recovery and higher relapse rates. Stress and age have been linked to changes in mood symptoms among bipolar adolescents [11,25]. There is no significant interaction between stress and number of episodes in the prediction of bipolar recurrence; however, the interaction of early severity and stressful life events significantly predicts recurrence in a manner consistent with the sensitization hypothesis [22]. Few studies have examined that BD patients who are more distressed by their relatives’ criticisms have more severe depressive and manic symptoms and proportionately fewer days well [50]. History of childhood abuse acts as a disease course modifier in patients with BD as well [12]. Other than associations between high emotionality and unipolar depression, studies examining the relationship between temperament, recent and remote life events, and psychopathology among the offspring of parents with BD found that there is an association between psychopathology and the number of recent negative life events, but no association between psychopathology and the number of early losses [23]. Childhood adversity may be a risk factor for vulnerability to early-onset illness and an array of stressors may be relevant not only to the onset, recurrence, and progression of affective episodes, but also to the highly prevalent substance-abuse comorbidities as well [56].

5.4. Neurocognition

Despite the gap between clinical and functional recovery, verbal memory appears to best predict psychosocial functioning in bipolar patients, with low-functioning patients being more impaired than highly-functioning patients in verbal recall and executive functions [45,37]. Recent analyses have revealed modest impairment in executive functioning, memory, and attention in both hypomanic and depressed bipolar patients, along with additional fine motor skills impairment [44]. Bipolar depressed and hypomanic patients differ with respect to the nature of their memory impairments. Depressed patients are more impaired compared with euthymic patients on tests of verbal recall and fine motor skills. Psychosocial functioning is impaired across all three patient groups. These cognitive difficulties may help explain the patient’s impairment of daily functioning (that occurs even during remission), which is in line with the finding that full symptomatic recovery (remission) fails to guarantee functional recovery [73,6,33].

Evidence suggests that neurocognition declines steadily over the early course of schizophrenia, but is more stable in BD. A recent study found that during a 5-year period, schizophrenic subjects showed stability over time in attentional measures, but greater variability in other domains [13]. Impaired insight and other neurocognitive dysfunctions are correlated among symptomatic as well as remitted bipolar patients [78]. Cognitive impairment seems to be related to a worse clinical course and poorer functional outcome. Recent findings suggest that patients with BD lose hippocampal, fusiform, and cerebellar gray matter at an accelerated rate compared with healthy control subjects. This tissue loss can be associated with deterioration in cognitive function and illness course [51].

5.5. Suicidal risk

It has been established that 25% to 50% of patients with BD attempt suicide at least once in their lifetime [28]. The polarity of patients’ first reported mood episode suggests a depression-prone subtype with a greater probability of suicide attempt [16]. Generally, patients with mood disorders have a higher risk of death by suicide (15% to 30%) and BD II patients are at greater risk than BD I patients [30]. Comorbid anxiety disorders may also play a role in this characteristic of BD by elevating the risk for suicidal ideation and attempts [61]. The rates of mixed depression among suicide attempters is much higher as compared to nonsuicidal bipolar II and unipolar depressive outpatients, suggesting that suicide attempters are primarily mixed depressive patients with predominantly BD II [8].

6. Potential paradigm of outcome prediction: staging models

Berk et al. offered insight into the progressive nature of many disorders by suggesting a staging model to predict outcome in BD (Stage 0–5) [10]. BD begins with an at-risk, asymptomatic period after which patients begin to exhibit mild or non-specific symptoms and may progress to manifest the range of prodromal patterns. The first threshold episode is then followed by the first relapse and, subsequently, by a pattern of periods of euthymia and recurrences. Some patients may have syndromal or symptomatic recovery, others may have an unremitting or treatment-refractory course. It is possible that all these stages require specific therapeutic interventions and that the impact of comorbidity, specific treatments, comorbid personality disorder, adherence, and response to therapy could differ in each stage. Berk’s staging model, which emphasizes a longitudinal approach, rather than a merely cross-sectional view, needs to be further justified.

7. Conclusions

Despite the considerable research efforts in this area, the psychiatric interview and examination focusing on the longitudinal course specifiers will still be the main source of prognostic information to guide physicians in their assessment of BD in the upcoming years. Better and reliable course predictors for individual patients are required to provide tailored therapies, which are the desirable future goals of an individual treatment plan. Although research on the benefits of psychopharmacological and psycho-educational therapies in BD has progressed significantly in the last decades, there are still uncertainties concerning how to identify the best therapeutic options for a given patient and how to most accurately predict the outcomes. In fact, there is no real evidence on which patient will respond to which drug, i.e. predictors of differential drug responsiveness warrants further research. Gaps in our knowledge about therapy for BD could be addressed more effectively if the diagnosis of the condition occurred earlier in the course of the illness; this warrants the provision of effective psycho-education to treating physicians as well as caregivers.

In our review, we were able to include some selection of the literature only, therefore our view is limited: the literature is huge and somewhat inconsistent in their conclusions related to the importance of these factors predicting outcomes. The substantial amount of sometimes-inconclusive findings does not let us discuss all the variations in the related papers because of the space limitation of this overview. More research is needed to clarify for example the differences found in population-based studies versus clinical trials, whether these differences are due to the different methodology and/or the diverse populations studied.

In addition to the pharmacogenomic evaluation of subject data from long-term observational studies, more dimensional descriptions of the disorder are needed to maximize the homogeneity of its subtypes. The predictive value and use of mood-congruent versus mood-incongruent psychotic symptoms, mixed episodes,
cognitive symptoms, and predominant polarities are limited by the current specifiers of BD. DSM-V needs to consider a change in the categorical descriptors to more reliable dimensional markers, stimulating and refining research for predictors of outcome.

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