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Course and outcome of bipolar disorder – focusing on depressive aspects

Tamas Treuer[1] and Mauricio Tohen[2]

[1] *Area Medical Center Vienna, Eli Lilly & Company, Budapest, Hungary*
[2] *Lilly Research Laboratories, Indianapolis, and McLean Hospital, Harvard Medical School, Belmont, USA*

Abstract

The prognosis of an illness is perhaps relatively more valuable in psychiatry than in other therapeutic areas, because the lack of a laboratory-based diagnostic test and poor biological markers in mental disorders limit outcome predictions based mostly on the information from the psychiatric interview and examination. This is particularly true in bipolar disorder. In this chapter the authors summarize the main factors predicting course and outcome in bipolar disorder with a focus on depressive symptoms. The natural course, the impact of first episode, the impact of depressive phase, cycle length, onset, age, gender, type of illness, personality traits and temperament, co-morbidity, family history, life events, and outcome features will be reviewed. Conceptual models and their prognostic value will be discussed as well.

Introduction

The prognosis of an illness is perhaps relatively more valuable in psychiatry than in other therapeutic areas, particularly because the lack of a laboratory-based diagnostic test and poor biological markers in mental disorders limit outcome predictions based mostly on the information gathered during the psychiatric interview and examination. Furthermore, clinical features are not always reliably available, and their impact is not always clear in assessing the outcome in the case of an individual patient. The assessment is further complicated by the fact that bipolar disorder in general represents a dimensional condition within a full spectrum of mood disorders [1].

Although there is agreement among researchers that bipolar spectrum disorders are severe, chronic, and lifelong conditions, and that breakthrough depression usually presents higher risks for long-term treatment than mania, there are several methodological issues in the study of the natural course of bipolar disorder [2]. Despite a considerable amount of research, the course and outcome of bipolar disorder still remain highly unpredictable. Likewise, it is difficult to determine the effect of treatment on the natural course of bipolar disorder that, despite treatment, still involves multiple relapses and impaired psychosocial functioning [3].

While identifying and treating the illness early in its time course may be associated with a better prognosis, there are several barriers to early identification; the delay from the first episode of illness to a diagnosis of bipolar disorder is approximately 10 years [4]. This delay poses a threat for the effectiveness of early treatment intervention, especially because data suggest that beginning lithium therapy within the first 10 years of illness may provide better outcomes than beginning prophylaxis later in life for patients with bipolar disorder [5]. Furthermore, a history of multiple previous episodes may be associated with poor response to lithium [6, 7], although these findings are limited by the lack of a comparator and the inclusion of subjects who had previously failed to respond to lithium. Similarly, long-term divalproex [8], non-pharmacological therapies [9], and maintenance therapy with olanzapine [10] have been found to be less effective in preventing relapses in patients with a high number of previous episodes.

The very high degree of co-morbidity and treatment resistance in outpatients with bipolar disorder highlights the need to develop new treatment approaches, much earlier illness recognition, diagnosis, and intervention in an attempt to reverse or prevent this illness burden [11]. Although full symptomatic remission does not guarantee functional recovery [12–14], it may have a favorable impact on long-term prognosis.

In this chapter we will summarize the main factors predicting course and outcome in bipolar disorder with a focus on depressive symptoms. The natural course, the impact of the first episode, the impact of the depressive phase, cycle length, age of onset, age, gender, type of illness, personality traits and temperament, co-morbidity, family history, life events, and outcome features will be reviewed. Conceptual models such as staging and outcome dimensions and their prognostic value will also be discussed.

Natural course

Researchers agree that bipolar spectrum disorders are severe chronic conditions, and should be considered lifelong disabilities [11], regardless of the impact of modern treatment on the natural course of the illness. It is uncertain how modern treatment interventions can significantly influence the natural course of the illness. High diagnostic instability is considered a feature of bipolar disorder, and a recent naturalistic study found a high prevalence of misdiagnosis and diagnostic shift from other psychiatric disorders to bipolar disorder [15]. More than half of severe mood disorders become bipolar disorder, and the risk of depression developing into bipolar disorder is lifelong [15, 16].

The decade-long McLean-Harvard First Episode Project has systematically followed large numbers of patients with DSM-IV bipolar or psychotic disorders from their first hospitalization. The project's findings indicate that the course of Bipolar I disorder is much less favorable than had been formerly believed, despite modern clinical treatment with mood-stabilizing and other

pharmchologic agents. Full functional recovery from initial episodes was uncommon, and full symptomatic recovery was much slower than early syndromal recovery; most early morbidity was depressive-dysphoric, as reported in mid-course, and initial depression or mixed-states predicted more later depressive episodes and overall morbidity, whereas initial mania or psychosis predicted later mania and a better prognosis [17].

Naturalistic and long-term studies showed that patients with bipolar disorder develop persistent impairment: patients experienced some degree of disability during the majority of long-term follow-up including 19–23% of the time with moderate and 7–9% of the time with severe overall impairment [18]. One study found that Bipolar I patients were completely unable to carry out work role functions during 30% of assessed months, which was significantly more than for unipolar major depression or Bipolar II patients (21% and 20%, respectively). Neuropsychological impairment persists during euthymic states, but it is confounded partly by mild affective symptoms in remitted patients. The clinical representations of these persistent alterations are related to the degree of disability [19].

The recurrence risk of bipolar disorders is about twice that of unipolar depression. Furthermore, recovery is more frequent among unipolar than among bipolar patients, although 5-year remission rates were found to be independent of the number of episodes [16]. There appears to be a constant risk of recurrence over the life-span up to the age of 70 or more, even 30 to 40 years after onset [20]. The long-term course usually causes significant handicaps and problems in the lives of patients, and in many cases leads to disability [21].

Illness recurrence and the course of syndromal and functional recovery

Most of the evidence from both the pre-lithium and modern eras suggests that the index episode tends to predict the polarity of the subsequent major mood episode: a manic index episode tends to predict a manic relapse, whereas a depressive index episode predicts a depressive relapse [22]; indexed mixed episodes have been found to predict relapse into a depressive episode [14]. The presence of at least two manic/hypomanic symptoms in the index episode is associated with a higher rate of family history of Bipolar I disorder, a higher score for suicidal thoughts during the episode, a longer duration of the episode, and a higher affective morbidity during the observation period [23].

Within 4 years of first lifetime hospitalization for mania, prospective data show that most subjects achieved syndromal recovery by 2 years, but 28% remained symptomatic, only 43% achieved functional recovery, and 57% switched phases or had new illness episodes after achieving recovery [24]. In this study, factors associated with a shorter time to syndromal recovery for 50% of the subjects were female sex, shorter index hospitalization, and lower initial depression ratings. The 43% who achieved functional recovery were more often older and had shorter index hospitalizations. Within 2 years of syn-

dromal recovery, 40% experienced a new episode of mania (20%) or depression (20%), and 19% switched phases without recovery. Predictors of manic recurrence were initial mood-incongruent psychotic features, lower premorbid occupational status, and initial manic presentation. Predictors of depression onset were higher occupational status, initial mixed presentation, and any co-morbidity [24].

Targeting residual symptoms in maintenance treatment may represent an opportunity to reduce risk of recurrence of bipolar disorder. Another 2-year follow-up study of the clinical features associated with the risk of recurrence in patients with bipolar disorder receiving treatment found that 58% of patients subsequently achieved recovery [25]. During up to 2 years of follow-up, half of these individuals experienced recurrences, with more than twice as many developing depressive episodes *versus* manic, hypomanic, or mixed episodes. Residual depressive or manic symptoms at recovery and proportion of days depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence. Residual manic symptoms at recovery and proportion of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence [25]. Another recent report [26] suggests that it is not just chronic subsyndromal symptoms that predict shorter time to a new episode, but rather their emergence, particularly the emergence of depressive symptoms.

Although most bipolar adolescents experience syndromic recovery following their first hospitalization, rates of symptomatic and functional recovery are much lower [12, 13, 27]. Few studies have examined the clinical, neuropsychological, and pharmacological factors involved in the functional outcome of bipolar disorder. The variable that appears to best predict psychosocial functioning in bipolar patients is verbal memory; low-functioning patients are cognitively more impaired than highly functioning patients on verbal recall and executive functions [28]. Few studies have examined whether co-morbid personality disorders and other clinical factors can predict functional morbidity in bipolar disorder. Residual depression predicts poorer residential and social/leisure outcomes independent of personality disorders or maladaptive traits [29].

The mortality of patients with bipolar disorder is considerably higher than that of the general population. At least 25–50% of patients with bipolar disorder attempt suicide at least once in their lives [30]. Polarity of patients' first reported mood episode suggests that depression-prone subtypes have a greater probability of suicidal acts [31]. Patients with mood disorders in general have a higher risk of death by suicide (15–30%) than healthy people, however Bipolar II patients may be more likely to attempt suicide than Bipolar I patients. Co-morbid anxiety disorders may also elevate risk for suicidal ideation and attempts [32]. The rates of mixed depression among bipolar and non-bipolar depressive suicide attempters is much higher than previously reported among non-suicidal Bipolar II and unipolar depressive outpatients, suggesting that suicide attempters come mainly from mixed depressives who

have predominantly Bipolar II disorder [33]. Recent findings show that while modest changes in severity of depression are associated with statistically and clinically significant changes in functional impairment and disability in patients with bipolar disorder, changes in severity of mania or hypomania are not consistently associated with differences in functioning [34].

Dimensions of outcome and staging models

Berk and colleagues have suggested a staging model to predict outcome (Stage 0–Stage 5) [35]. Staging models are widely used in clinical medicine, and offer an insight into the progressive nature of many disorders. According to Berk, bipolar disorder begins with an at-risk, asymptomatic period, then patients begin to exhibit mild or non-specific symptoms that usually progress to manifest the range of prodromal patterns that have been described in the literature. The first threshold episode may then be followed by a first relapse, and subsequently followed by a pattern of periods of euthymia and recurrences. Some patients may have syndromal or symptomatic recovery, while others may have an unremitting or treatment refractory course. It is possible that all these stages require specific therapeutic interventions, and the impact of comorbidity, specific treatment, personality, adherence, and response to therapy could differ in each stage. Additional research is needed to clarify the usefulness of Berk's staging model to complement existing and proposed classifications of bipolar disorder, with an emphasis on a longitudinal dimension instead of a merely cross-sectional view.

The impact of treatment on the course of illness

The delay from the first episode of illness to a diagnosis of bipolar disorder is approximately 10 years, a circumstance that is at odds with the notion that early treatment intervention may contribute to a better prognosis. Studies have shown that bipolar disorder outcome worsens as the number of manic episodes increases [6], suggesting that prevention of recurrent episodes early during the disorder could improve long-term prognosis.

The initial prodrome of bipolar disorder has received very little attention to date and there are no prodromal features that clearly distinguish between patients who go on to develop bipolar disorder and those who develop schizophrenia [36]. Several authors point out that pharmacological treatment of the early phase of bipolar disorders lacks specific guidelines [37]. Knowledge is limited on how to identify prodromal bipolar from unipolar depression, but even mania is frequently misdiagnosed. This is key because the outcome of mania is not as good as was formerly believed [38].

Although the impact of different treatment options for bipolar disorder is discussed elsewhere in this book, it is worth noting that few effective treat-

ments exist for acute bipolar depression. Furthermore, the effectiveness and safety of specific treatments such as standard antidepressant agents for depressive episodes associated with bipolar disorder have not been well studied. Because episodes of depression are the most frequent cause of disability among patients with bipolar disorder, it is important to determine whether adjunctive antidepressant therapy reduces symptoms of bipolar depression without increasing the risk of mania and therefore changing the course and outcome of the disorder. A recent double-blind controlled trial showed that the use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch [39]. It is also important to determine the benefits of the continued use of a typical antipsychotic agent following remission from an acute manic episode. Studies show that there are no short-term benefits with the continued use of a typical antipsychotic after achieving remission from an episode of acute mania. In fact, its continued use is associated with detrimental effects including relapse into depression [40].

Finally, a recent report suggested that early-stage (but not intermediate-or later-stage) patients had a significantly lower rate of relapse/recurrence of manic/mixed episodes with some treatments but not with others [10]. Subsyndromal symptoms are common during maintenance treatment and appear to be associated with relapse into an episode of the same polarity [26, 41]. Co-morbid anxiety symptoms in patients with bipolar depression have a negative impact on treatment outcome, so treatment interventions should focus on reducing both depressive and anxiety symptoms in these patients [42].

Predictive factors affecting prognosis

Age at onset and gender

The average age of onset of a first manic episode is 21 years, but onset may occur at any age from childhood to old age. Childhood-onset bipolar disorder usually has a poorer prognosis, and it is associated with long delays to first treatment, averaging more than 16 years. Patients with childhood or adolescent onset retrospectively report more episodes, more co-morbidities, and rapid cycling; prospectively, they demonstrate more severe mania, depression, and fewer days well [43].

Data have consistently shown that 70–100% of children and adolescents with bipolar disorder will eventually recover from their index episode, however, despite ongoing treatment, up to 80% will experience recurrences after recovery [44]. Bipolar disorder has a considerable effect on the normal psychosocial development of the child and increases the risk for academic, social, and interpersonal (family, peers, work) problems, as well as for health care utilization. Some studies suggest that approximately 30% of preadolescents with

major depressive disorder experience a manic episode and manifest bipolar disorder within 5 years [45].

Mania in the elderly appears to be a heterogeneous disorder. In elderly patients with first-episode mania who were followed for three to 10 years, men had a higher risk of mortality, and compared to patients with multiple episodes of mania, elderly patients with first-episode mania were twice as likely to have a co-morbid neurological disorder [46].

Previous findings suggest that men have a significantly earlier onset of first-episode mania and bipolar disorder associated with childhood antisocial behavior; women have more depressive episodes than manic episodes and higher incidence rates of Bipolar II disorder throughout adult life, except for early life, and a greater likelihood of rapid cycling [47]. More men than women report mania at the onset of Bipolar I disorder, and men also have higher rates of co-morbid alcohol abuse/dependence, cannabis abuse/dependence, pathological gambling, and conduct disorder [48]. Women report higher rates of co-morbid eating disorders, weight change, appetite change, and middle insomnia during depressive episodes [48]. However, no gender differences appear to exist between male and female subjects in time to remission from the index episode, number of recurrences, and time spent with any clinical or subclinical mood symptom over a 48-week period, at least when similar treatment strategies are adopted [49].

Type of onset, type of disorder

The length of untreated individual illness episodes in bipolar disorder varies from several weeks to several months, and depends on the type of episode. There are significant differences in time to recovery in patients with bipolar disorder by episode subtype [47, 50]. Based on a median follow-up of 18 months, the life-table estimate of the probability of remaining ill for at least 1 year was 7% for the pure manic patients compared with 32% in patients who entered the study with episodes that were mixed or cycling. Purely depressed patients had a 22% probability of remaining ill, approximating rates found in patients without bipolar disorder who have episodes of depression. However the duration of individual episodes also depends on response to treatment, and 15–30% of patients with mood disorders suffer from persisting alterations of personality or social interaction, or from persisting symptoms. Rapid-cycling and mixed states are associated with a poorer prognosis and non-response to anti-manic agents. Risk factors for rapid cycling include biologic rhythm dysregulation, antidepressant or stimulant use, hypothyroidism, and premenstrual and postpartum states [51].

Patients with bipolar disorder have an average of four episodes during the first 10 years of their illness. In general, poorer functioning and poorer psychosocial adjustment before the onset of illness predict worse outcome [52, 53]. After that, the average length of time between episodes is between 1 and

2 years. In both Bipolar I and II disorder, 60–70% of manic episodes occur immediately before or after a major depressive episode, and the interval between episodes tends to decrease as the individual ages. Differentiation of mood congruence of psychotic features in mania evidently has prognostic validity. Mood-incongruent psychotic features during the index manic episode predicted a shorter time in remission at 4 years [54]. Higher occupational status, initial mixed presentation, and any co-morbidity predicts depressive rather than manic onset [14]. Higher number of hospitalizations and less rapid cycling is associated with Bipolar I disorder as compared to Bipolar II [55, 56].

Personality traits and temperament

Personality and temperament are thought to impact prognosis and the clinical manifestation of bipolar disorder. Studies have suggested that mixed episodes may result from a mixture of inverse temperamental factors to a manic syndrome [57]. Some studies question the current categorical split of mood disorders into bipolar 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 major depressive disorder [58]. Several research findings that are in line with current familial-genetic models of this disorder suggest that the DSM-IV characterization of Bipolar disorder II must include a greater emphasis on temperamentally based mood and anxious reactivity [59]. Such phenotypic characterization may assist in genotyping; however its predictive value on outcome still requires more research [60].

Family history and genetics

The application of genomics to clinical practice is limited at present, but is expected to grow rapidly. Despite some recent successes, identifying genes for bipolar disorder through classic human genetic studies is not consistent; the main issue is the lack of replication of the findings in this field [61]. There are many possible reasons for this relatively slow discovery. Bipolar disorder is a complex polygenic disorder, with variable penetrance and phenotypic heterogeneity, and it overlaps and is interdependent with other neuropsychiatric disorders. In addition, the effects of environmental factors (epigenetic modifications, effects of stress, infections, drugs, medications) on the expression of the phenotype are not fully understood nor factored into human genetic linkage studies [62]. There is increasing evidence that genome-wide association studies represent a powerful approach to the identification of genes involved in common human diseases [63]. The first genome-wide association study of bipolar disorder showed that several genes, each of modest effect, reproducibly influence disease risk [64].

Bipolar II depression, subsyndromal depression, and mixed depression

Mixed depression is probably a key component of the continuum concept of mood disorders, and it might have a predictive role in the course of bipolar disorder. Recent findings suggest that the prevalence of mixed depression is high in patients with bipolar disorders. Mixed depression is defined by the combination of depression (major depressive episode) and non-euphoric, usually subsyndromal, manic or hypomanic symptoms [65]. The reemerging concept of mixed depression also influences how we see the boundaries between bipolar and depressive disorders.

Bipolar II disorder and mixed depression are relatively understudied, despite a prevalence of about 5% in the community and about 50% in depressed outpatients [65]. Prospective studies have shown that the longitudinal weekly symptomatic course of Bipolar I disorder is chronic, that the symptomatic structure is primarily depressive rather than manic, and that subsyndromal and minor affective symptoms predominate, although symptom severity levels fluctuate [66]. Depressive episodes and symptoms, which dominate the course of Bipolar I and II disorder, appear to be more disabling than corresponding levels of manic or hypomanic symptoms. Table 1 summarizes the predictive value of depressive symptoms on the course of bipolar disorder. Subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment; and subsyndromal hypomanic symptoms appear to enhance functioning in Bipolar II disorder [67]. Sub-syndromal symptoms in bipolar disorder impair functioning and diminish quality of life. Findings suggest that the presence of subsyndromal depressive symptoms during the first 2 months significantly increases the likelihood of depressive relapse [26]. Patients with psychotic features and those with a greater number of previous depressive episodes were more likely to experience subsyndromal depressive symptoms.

As noted previously, because a substantial number of patients with bipolar disorder present with an index depressive episode, it is likely that many are misdiagnosed with unipolar major depression. Whether or not antidepressants worsen the course of bipolar disorder is still being debated, because misdiagnosed patients are often treated with antidepressants, which, if used improperly, are known to induce mania and provoke rapid cycling [68]. Furthermore, it appears that a first depressive rather than manic episode in bipolar disorder might lead to a subsequent course with a greater burden of depressive symptoms [69]. Depressive-onset bipolar disorder is significantly associated with more lifetime depressive episodes and a greater proportion of time with depression and anxiety in the year prior to assessment. However, the quantity and severity of weeks in symptomatic affective states are possibly greater predictors of affective burden in Bipolar I patients than the quantity and direction of affective switches [70]. Analysis of assessments in clinical trials revealed that over 80% of the treatment effect is attributable to the indirect effects of improvements in the depressive factors of the Montgomery-Asberg

Table 1. Predictive value of depressive symptoms in the course of bipolar disorder*

Onset and index episode
• Index mixed episodes have been found to predict relapse into a depressive episode
• It is likely that many patients presenting with an index depressive episode are misdiagnosed with unipolar major depression
• One third of preadolescents with major depressive disorder experience a manic episode and manifest bipolar disorder within 5 years
• Lower initial depression ratings are associated with shorter time to syndromal recovery
• A depressive onset is predicted by higher occupational status, initial mixed presentation, and any co-morbidity
• Polarity of patients' first reported mood episode suggests a depression-prone subtype with a greater probability of past suicide attempt
• Depressive-onset bipolar disorder is significantly associated with more lifetime depressive episodes and a greater proportion of time with depression and anxiety
Course, number and length of episodes
• The symptomatic structure of bipolar II disorder is primarily depressive rather than manic
• Twice as many patients develop depressive episodes as manic, hypomanic, or mixed episodes
• Residual depressive or manic symptoms at recovery and proportion of days depressed are significantly associated with shorter time to depressive recurrence
• The longest duration of episodes was found for mixed episodes, while depressive episodes have an intermediate duration and manic episodes are the shortest
• 60–70% of manic episodes occur immediately before or after a major depressive episode, and manic episodes often precede or follow the major depressive episodes
• Shorter time to a depressive recurrence can be predicted if residual depressive or manic symptoms are still present at recovery
• Rapid cycling can be related to a higher number of prior depressive episodes
• Patients with psychotic features and those with a greater number of previous depressive episodes were more likely to experience subsyndromal depressive symptoms
• 80% of the treatment effect is attributable to the indirect effects of improvements in the depressive symptoms
Risk for long term-prognosis
• Breakthrough depression represents higher risks for long-term treatment than mania
• Every new episode of depression brings a new risk for mania
• The risk of depression developing into bipolar disorder remains constant lifelong
• Subsyndromal depressive symptoms during the first 2 months after recovery significantly increases the likelihood of depressive relapse
Functional Recovery – Outcome
• Depressed patients are more impaired than euthymic or hypomanic patients on tests of verbal recall and fine motor skills
• Residual depression predicts poorer residential and social/leisure outcomes independent of personality disorders or maladaptive traits
• Suicide attempters come mainly from mixed depressives with predominantly Bipolar II base
• Subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment

* All the statements in this table are referenced in the text

Depression Rating Scale like sadness, negative thoughts, detachment, and neurovegetative symptoms, and changes in factor scores are highly correlated with changes in clinical improvement [71].

Co-morbidity

Bipolar disorder has frequent co-morbidities that worsen prognosis, especially in association with substance use disorders [72, 73]. The relative age at onset of alcohol use and bipolar disorders is associated with differences in the course of both conditions. A first hospitalization for mania is associated with a period of recovery from co-morbid alcohol abuse [74, 75]. Those patients with alcohol-use problems prior to bipolar disorder are usually older, more likely to recover, and more likely to recover quickly than those whose alcohol problems occur after their diagnosis of bipolar disorder. In contrast, those who have bipolar disorder first spend more time with affective episodes and symptoms of an alcohol-use disorder during follow-up. Co-morbid alcoholism is also usually related to poorer psychosocial adjustment [55].

Slower recovery has been associated with co-morbid drug abuse [76, 77]. Attention deficit/hyperactivity disorder and anxiety disorders, including those present during relative euthymia, also predict a poorer bipolar course [78, 79]. Co-morbid panic disorder is associated with a higher likelihood of rapid cycling [56]. One recent study showed that anxiety co-morbidity impacts health-related quality of life in patients with Bipolar disorder I but not in Bipolar disorder II [80].

Little is known about the treatment of psychiatric co-morbidities in bipolar disorder, because their treatment is largely empirically based rather than based on controlled data [81]. Many studies have examined the prevalence and predictive validity of axis II personality disorders among unipolar depressed patients, but few have examined these issues among bipolar patients [82]. Findings suggest that clinicians should be more vigilant for co-morbid personality and bipolar disorder, and less reluctant to diagnose it [82, 83]. When structured assessment of personality disorder is performed during a clinical remission, less than one in three bipolar patients meets full syndromal criteria for an axis II disorder [84]. Borderline personality disorder and bipolar disorder can often co-occur, but their relationship is not consistent or specific. Existing data fail to support the conclusion that borderline personality disorder and bipolar disorders exist on a spectrum, but allows for the possibility of partially overlapping etiologies [85].

Bipolar patients with lifetime smoking are more likely to have earlier age at onset of mood disorder, greater severity of symptoms, poorer functioning, history of a suicide attempt, and a lifetime history of co-morbid anxiety and substance use disorders. Smoking may also be independently associated with suicidal behavior in bipolar disorder [86]. The effects of the sequence of onset of bipolar and cannabis use disorders are less pronounced than observed in co-

occurring alcohol and bipolar disorders [87]. 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.

Individuals with bipolar disorder are differentially affected by several stress-sensitive medical disorders such as circulatory disorders, obesity, and diabetes mellitus. Individuals with respiratory disorders, infectious diseases, epilepsy, multiple sclerosis, migraine, and circulatory disorders may also have a higher prevalence of bipolar disorder [88]. The increasing medical burden in bipolar disorder is not simply a result of psychiatric symptoms and the attendant dysfunction [89]. Psychiatric co-morbidity is often associated with earlier onset of bipolar symptoms, more severe course, poorer treatment compliance, and worse outcomes related to suicide and other complications. It is still uncertain whether the medical co-morbidities are subsequent to the bipolar diagnosis or subsequent to its treatment [90]. To ensure prompt, appropriate intervention while avoiding iatrogenic complications, the clinician must evaluate and monitor patients with bipolar disorder for the presence and the development of co-morbid psychiatric and medical conditions.

Life events

Stressful life events can unfavorably alter the course of the illness, and negatively influence the adherence to maintenance treatment. They have been associated with slower recovery and higher relapse rates. Stress is linked to changes in mood symptoms among bipolar adolescents, although correlations between life events and symptoms vary with age [91]. There is no significant interaction between stress and episode number in the prediction of bipolar recurrence, and the interaction of early adversity severity and stressful life events significantly predicts recurrence in a manner consistent with the sensitization hypothesis [92].

Few studies have examined the prognostic value of family factors in the course of bipolar disorder. Patients who were more distressed by their relatives' criticisms had more severe depressive and manic symptoms and proportionately fewer days well [93]. Besides associations between high emotionality and unipolar depression, studies that examine the relationship between temperament, recent, and remote life events, and psychopathology among the offspring of parents with bipolar disorder 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 [94]. In this population, any effect of undesirable life events would appear to be mediated through the association with emotionality. 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 the highly prevalent substance abuse co-morbidities as well [95].

Neurocognition

Recent analyses have revealed modest impairment in executive functioning, memory, and attention in both hypomanic and depressed bipolar patients, with additional fine motor skills impairment in the latter [96]. Bipolar depressed and hypomanic patients differ with respect to the nature of their memory impairment. Depressed patients are more impaired compared to euthymic patients on tests of verbal recall and fine motor skills. Psychosocial functioning is impaired across all three patient groups, but only in depressed and hypomanic patients does this correlate significantly with neuropsychological performance. These cognitive difficulties, especially related to verbal memory, may help explain the impairment regarding daily functioning, even during remission [97], and these are in line with the findings that full symptomatic recovery (remission) does not guarantee functional recovery [6, 14, 24].

While considerable evidence suggests that neurocognition declines steadily over the early course of schizophrenia, but is more stable in bipolar disorder, very little known about the longitudinal trait stability of neurocognitive performance in bipolar disorder. One recent study found that patients with bipolar disorder showed stability over time in attentional measures but greater variability in other domains over a 5-year period [98]. Impaired insight and other neurocognitive dysfunctions are correlated among symptomatic as well as remitted bipolar patients [99]. Cognitive impairment seems to be related to a worse clinical course and poor functional outcome, however further studies are needed to clarify whether a severe course of illness is associated with more pronounced cognitive disorders and whether psychotic symptoms during the acute phase of the illness can predict cognitive deficits in patients with bipolar disorder later in the illness. Recent findings suggest that patients with bipolar disorder 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 [100].

Future trends and research

Despite considerable research efforts in this area, the psychiatric interview and an examination focusing on the longitudinal course specifiers remain the main source of prognostic information to guide physicians in their assessment of bipolar disorder. Although tailored therapy is the favorable future goal of an individual treatment plan, more research is needed to establish better and more reliable course predictors for individual patients. Besides pharmacogenomic evaluation of subject data from long-term naturalistic studies, more dimensional descriptions of the disorder are warranted to maximize subtype homogeneity. The predictive value and use of mood-congruent *versus* mood-incongruent psychotic symptoms, mixed episodes, cognitive symptoms, and predominant polarities is limited by current specifiers of bipolar disorder [101].

DSM-V needs to consider a change in the categorical descriptors to more reliable dimensional ones, thus stimulating and refining research in the field further [102]. Depressive symptoms, which dominate the longitudinal symptomatic course of bipolar disorder, should receive more attention in the clinical assessment of patients, and the predictive role and impact of these depressive aspects on treatment decisions should be clarified further in upcoming research.

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