Chapter 3
Course and Outcome of Bipolar Disorder: Focus on Depressive Aspects

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Abstract The presence of depressive symptoms dominates the longitudinal course of bipolar disorder (BD) and predicts functional impairment. Despite great progress in understanding the biological basis of BD, the course and outcome of the illness can only be predicted using clinical variables. This chapter summarizes the main factors that predict course and outcome in BD with a focus on depressive symptoms. The natural course of the illness, the impact of the first episode, the impact of the depressive phase, cycle length, onset, age, gender, type of illness, personality traits, temperament, comorbidity, family history, life events, and outcome features will be reviewed. Conceptual models such as disease staging and their prognostic value will also be discussed.

Keywords Bipolar disorder • Course • Outcome • Predictors • Mixed depression • Clinical diagnosis

3.1 Introduction

Despite great progress in understanding the biological basis of bipolar disorder (BD), the course and outcome of the illness can still only be predicted using clinical variables. However, clinical features are not always reliable or available, and their impact cannot be applied directly to predict the outcome of an individual patient. The assessment is further complicated by the fact that BD represents a dimensional condition within a full spectrum of mood disorders and is often accompanied by psychiatric comorbidity (Kessler et al. 2006).

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Several methodological issues affect the study of the natural course of BD (Wittchen et al. 2003). Despite a considerable amount of research, the course and outcome of BD still remain highly unpredictable. Likewise, it is difficult to determine the effect of treatment on the natural course of an illness that, despite best evidence-based treatment, still involves multiple relapses and impaired psychosocial functioning (Goldberg et al. 1995). There is, however, agreement among researchers that BD is a severe, chronic, and disabling lifelong condition and that breakthrough depression usually presents higher risk for long-term functional impairment than mania. While identifying and treating the illness early in its time course may improve the chance of a better prognosis, there are several barriers to early intervention. These include the well-known delay of approximately 10 years from the first episode of illness to a diagnosis of BD (Hirschfeld et al. 2003). This is particularly true for the many patients who present first with depressive episodes and much later with mania or hypomania, making the BD diagnosis impossible until later in the illness. Looking at the other clinical variables in patients who present with depression—such as melancholic or psychotic features, family history, and age of onset—may help identify BD earlier so that appropriate treatment can be begun. This delay in diagnosis poses a threat for the effectiveness of early treatment interventions, 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 BD (Franchini et al. 1999). Furthermore, a history of multiple previous episodes may be associated with poor response to lithium (Tohen et al. 1990a; Swann et al. 1999), 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 (Calabrese et al. 2005), non-pharmacological therapies (Scott et al. 2007), and maintenance therapy with olanzapine (Ketter et al. 2006) have been found to be less effective in preventing relapses in patients with a high number of previous episodes.

The very high degree of comorbidity and treatment resistance in outpatients with BD 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 (Post et al. 2003). Although full symptomatic remission does not guarantee functional recovery (Tohen et al. 1990b, 2000, 2003), it may have a favorable impact on long-term prognosis.

This chapter will summarize the main factors that predict course and outcome in BD with a focus on depressive symptoms. The natural course of the illness, the impact of the first episode, the impact of the depressive phase, cycle length, age of onset, age, gender, type of illness, personality traits, temperament, comorbidity, 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.

3.2 Natural Course

Researchers agree that bipolar spectrum disorders are severe chronic conditions that should be considered lifelong disabilities (Post et al. 2003). The impact of modern treatment on the natural course of the illness is uncertain. In addition, high diagnostic instability is considered a feature of BD. A recent naturalistic study found a high prevalence of misdiagnosis and diagnostic shift from other psychiatric disorders to BD (Salvatore et al. 2007). More than half of severe mood disorders become BD, and the risk of depression developing into BD is lifelong (Salvatore et al. 2007; Angst et al. 2005). Naturalistic and long-term studies showed that patients with BD develop persistent functional impairment; that is, patients experienced some degree of disability during most of their long-term follow-up including 19–23 % of the time with moderate impairment and 7–9 % of the time with severe overall impairment (Baca-Garcia et al. 2007; Judd et al. 2008). One study found that bipolar I (BD-I) patients were completely unable to carry out work role functions during 30 % of the assessed months, which was significantly higher than rates in individuals with major depressive disorder (MDD) or bipolar II (BD-II) (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 (Marneros et al. 1991).

The recurrence risk of BD is about twice that of MDD. Furthermore, recovery is more frequent among MDD than BD patients, although five-year remission rates were found to be independent of the number of episodes (Angst et al. 2005). There appears to be a constant risk of recurrence over the life-span up to the age of 70 or more, even 30–40 years after onset (Angst et al. 2003). This long-term course usually causes significant handicaps and problems in the lives of patients and, in many cases, leads to disability (Nolen et al. 2004).

3.3 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 (Calabrese et al. 2004); indexed mixed episodes have been found to predict relapse into a depressive episode (Tohen et al. 2003). The presence of at least two manic/hypomanic symptoms in the index episode is associated with increased family history of BD-I, a higher score for suicidal thoughts during the episode, a longer duration of the episode, and a higher affective morbidity during the observation period (Maj et al. 2006).

The McLean-Harvard First-Episode Project has systematically followed large numbers of patients with BD and other psychotic disorders from their first hospitalization. The project's findings indicate that the course of BD-I is much less favorable than had formerly been believed, despite modern clinical treatment with mood-stabilizing and other pharmacological 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 midcourse, and initial depression or mixed states predicted an increased number of depressive episodes and overall morbidity, whereas initial mania or psychosis predicted later mania and a better prognosis (Baca-Garcia et al. 2007).

Within four years of first lifetime hospitalization for mania, prospective data show that most subjects achieved syndromal recovery by two years, but 28 % remained symptomatic, only 43 % achieved functional recovery, and 57 % switched phases or had new illness episodes after achieving recovery (Tohen et al. 2003). 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 two years of syndromal 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 comorbidity (Tohen et al. 2003).

Targeting residual symptoms in maintenance treatment may represent an opportunity to reduce the risk of recurrence of BD. Another two-year follow-up study of the clinical features associated with risk of recurrence in patients with BD receiving treatment found that 58 % of patients subsequently achieved recovery (Perlis et al. 2006). For up to two 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 spent depressed or anxious in the preceding year were significantly associated with shorter time to depressive recurrence. Residual manic symptoms at recovery and the proportion of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence (Perlis et al. 2006). Another recent report (Perlis et al. 2006) suggested 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 adolescents with BD experience syndromic recovery following their first hospitalization, the rates of symptomatic and functional recovery are much lower (Tohen et al. 1990b, 2000, 2006). Few studies have examined the clinical, neuropsychological, and pharmacological factors involved in the functional outcome of BD. The variable that appears to best predict psychosocial functioning in BD patients is verbal memory; low-functioning patients are cognitively more impaired than high-functioning patients on verbal recall and executive

functions (Martinez-Aran et al. 2007). Few studies have examined whether comorbid personality disorders and other clinical factors can predict functional morbidity in BD. However, residual depression predicts poorer residential and social/leisure outcomes independent of personality disorders or maladaptive traits (Loftus and Jaeger 2006).

The mortality of patients with BD is considerably higher than that of the general population. At least 25–50 % of patients with BD attempt suicide at least once in their lives (Jamison 2000). The polarity of a patient's first reported mood episode suggests that depression-prone subtypes have a greater probability of suicidal acts (Chaudhury et al. 2007). Patients with mood disorders in general have a higher risk of death by suicide (15–30 %) than healthy people; however BD-II patients may be more likely to attempt suicide than BD-I patients. Comorbid anxiety disorders may also elevate the risk for suicidal ideation and attempts (Simon et al. 2007a). The rates of mixed depression among BD and non-BD depressive suicide attempters are much higher than previously reported among non-suicidal BD-II and MDD outpatients, suggesting that suicide attempters come mainly from mixed depressives who predominantly have BD-II (Balazs et al. 2006). Recent findings show that while modest changes in the severity of depression are associated with statistically and clinically significant changes in functional impairment and disability in patients with BD, changes in the severity of mania or hypomania are not consistently associated with differences in functioning (Simon et al. 2007b).

3.4 Prognostic Staging Models

During the last 10 years, prognostic staging models for BD have attracted growing attention by raising the possibility of defining stage-specific strategies for treatment (Kapczinski et al. 2014).

The proposed models use findings from clinical studies of treatment and functioning to stage the illness and integrate the potential role of neurocognitive, neuroimaging, and peripheral biomarkers. Most studies to date indicate that the progression to late stages of the illness predicts worse overall prognosis and poorer response to standard treatment. Berk and colleagues suggested a staging model to predict outcome (stages 0–5) (Berk et al. 2007), suggesting that BD begins with an at-risk, asymptomatic period. Patients then begin to exhibit mild or nonspecific symptoms and 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, 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. In general, a greater number of episodes imply a progression to a later stage with poorer treatment response and prognosis. The

persistence of neurocognitive impairment is associated with poorer psychosocial functioning at any stage. Peripheral biomarkers of inflammation are more likely present at the end stage of BD, consistent with the hypothesis of a neuroprogression of the illness (Kauer-Sant'Anna et al. 2009). However, significant medical and substance abuse comorbidities must be considered as potential confounders. Some neuroimaging findings also suggest some kind of disease progression, but this needs confirmation.

Additional research is needed to clarify the usefulness of the staging model to complement existing classifications of BD, with an emphasis on a longitudinal dimension instead of a merely cross-sectional view. Also, in the near future, improved staging models may include biological markers in addition to clinical variables.

3.5 The Impact of Treatment on the Course of Illness

The 10-year delay from the first episode of illness to a diagnosis of BD is an important impediment to early treatment intervention and possibly a better prognosis. Studies have shown that BD outcome worsens as the number of manic episodes increases (Tohen et al. 1990b), suggesting that prevention of recurrent episodes early during the disorder could improve long-term prognosis.

The initial prodrome of BD has received very little attention to date, and there are no prodromal features that clearly distinguish between patients who go on to develop BD and those who develop schizophrenia (Thompson et al. 2003). Several authors point out that pharmacological treatment of the early phase of BD lacks specific guidelines (Conus et al. 2006). Knowledge is limited as to how to distinguish prodromal BD from MDD, but even mania is frequently misdiagnosed. This is key because the outcome of mania is not as good as was formerly believed (Conus and McGorry 2002).

Although the impact of different treatment options for BD is discussed elsewhere in this book, it is worth noting that few effective treatments exist for acute bipolar depression and prevention of recurrent episodes. Furthermore, the effectiveness and safety of specific treatments such as standard antidepressant agents for depressive episodes associated with BD have not been well studied. Because episodes of depression are the most frequent cause of disability among patients with BD, 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 to the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch (Sachs et al. 2007). It is also important to determine the benefits of the continued use of typical antipsychotic agents following remission from an acute manic episode. Studies show that there are no short-term benefits

associated with continued use of a typical antipsychotic after achieving remission from an episode of acute mania. In fact, its continued use may be associated with detrimental effects, including relapse into depression in some cases (Zarate and Tohen 2004). On the other hand, despite the recent FDA approval of two atypical antipsychotics for the treatment of bipolar depression (quetiapine and lurasidone) as monotherapy and adjunctive treatment to mood stabilizers, the long-term effect on illness prognosis is unknown (Loebel et al. 2014). Finally, a recent report suggested that early-stage (but not intermediate- or later-stage) patients had a significantly lower rates of relapse/recurrence of manic/mixed episodes with some treatments but not with others (Ketter et al. 2006). Subsyndromal symptoms are common during maintenance treatment and appear to be associated with relapse into an episode of the same polarity (Tohen et al. 2006; Frye et al. 2006). Comorbid 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 (Tohen et al. 2007).

3.6 Predictive Factors Affecting Prognosis

3.6.1 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 BD usually has a poorer prognosis and is associated with long delays to first treatment, averaging more than 16 years. Patients with childhood or adolescent onset retrospectively report more episodes, more comorbidities, and rapid cycling; prospectively, they demonstrate more severe mania, depression, and fewer days well (Leverich et al. 2007).

Data have consistently shown that 70–100 % of children and adolescents with BD will eventually recover from their index episode; however, despite ongoing treatment, up to 80 % will experience recurrences after recovery (Birmaher and Axelson 2006). BD 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 healthcare utilization. Some studies suggest that approximately 30 % of preadolescents with MDD experience a manic episode and manifest BD within five years (Geller et al. 1994).

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. Compared to elderly patients with early onset and multiple episodes of mania, elderly patients with first-episode mania were twice as likely to have a comorbid neurological disorder (Tohen et al. 1994).

Previous findings suggest that men have a significantly earlier onset of first-episode mania and BD associated with childhood antisocial behavior; women have more depressive episodes than manic episodes and higher incidence rates of BD-II

throughout adult life, except for early life, and a greater likelihood of rapid cycling (Marneros 2006). More men than women report mania at the onset of BD-I, and men also have higher rates of comorbid alcohol abuse/dependence, cannabis abuse/dependence, pathological gambling, and conduct disorder (Kawa et al. 2005). Women report higher rates of comorbid eating disorders, weight change, appetite change, and middle insomnia during depressive episodes (Kawa et al. 2005). 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 (Benedetti et al. 2007).

3.6.2 Type of Onset and Type of Disorder

The length of untreated individual illness episodes in BD 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 BD by episode subtype (Sachs et al. 2007; Keller et al. 1986). Based on a median follow-up of 18 months, the life-table estimate of the probability of remaining ill for at least one year was 7 % for pure manic patients compared with 32 % for 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 BD 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 nonresponse to antimanic agents. Risk factors for rapid cycling include biological rhythm dysregulation, antidepressant or stimulant use, hypothyroidism, and premenstrual and postpartum states (American Psychiatric Association 2002). Patients with BD have an average of four episodes during the first 10 years of their illness (Tsai et al. 2001; Meeks 1999). After that, the average length of time between episodes is between one and two years. In both BD-I and BD-II, 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 shorter time in remission at four years (Tohen et al. 1992). Higher occupational status, initial mixed presentation, and any comorbidity predicted depressive rather than manic onset (Tohen et al. 2003). Increased number of hospitalizations and less rapid cycling were associated with BD-I as compared to BD-II (Coryell et al. 1989, 1992).

3.6.3 Personality Traits and Temperament

Personality and temperament are thought to impact prognosis and the clinical manifestation of BD. Studies have suggested that mixed episodes may result from a mixture of inverse temperamental factors to a manic syndrome (Rottig et al. 2007). 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 BD-II than MDD (Benazzi 2006). Several research findings that are in line with current familial-genetic models of this disorder suggest that the characterization of BD-II must include a greater emphasis on temperamentally based mood and anxious reactivity (Akiskal et al. 2006a). Such phenotypic characterization may assist in genotyping; however its predictive value on outcome still requires more research (Akiskal et al. 2006b).

3.6.4 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 BD through classic human genetic studies is not consistent; the main issue is the lack of replication of the findings in this field (Kato 2007). There are many possible reasons for this relatively slow discovery. BD 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 (Le-Niculescu et al. 2007). There is increasing evidence that genome-wide association studies represent a powerful approach to the identification of genes involved in common human diseases (Wellcome Trust Case Control Consortium 2007). The first genome-wide association study of BD showed that several genes, each of modest effect, reproducibly influence disease risk (Baum et al. 2008).

3.7 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 BD. Recent findings suggest that the prevalence of mixed depression is high in patients with BD. Mixed depression is defined by the combination of depression (a major depressive episode)

and non-euphoric, usually subsyndromal, manic, or hypomanic symptoms (Benazzi 2007). The reemerging concept of mixed depression also influences how we see the boundaries between bipolar and depressive disorders. A major addition in the DSM-5 is the introduction of mixed features in patients with MDD, defined as the presence of at least two criteria of the opposite pole (American Psychiatric Association 2013).

BD-II and mixed depression are relatively understudied, despite a prevalence of about 5 % in the community and about 50 % in depressed outpatients (Benazzi 2007). Prospective studies have shown that the longitudinal weekly symptomatic course of BD-I 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 (Judd et al. 2002).

Depressive episodes and symptoms, which dominate the course of BD-I and BD-II, appear to be more disabling than corresponding levels of manic or hypomanic symptoms. Table 3.1 summarizes the predictive value of depressive symptoms on the course of BD. Subsyndromal depressive symptoms, but not subsyndromal manic or hypomanic symptoms, are associated with significant impairment, and subsyndromal hypomanic symptoms appear to enhance functioning in BD-II (Benazzi 2007). Subsyndromal symptoms in BD impair functioning and diminish quality of life. Findings suggest that the presence of subsyndromal depressive symptoms during the first two months significantly increases the likelihood of depressive relapse (Tohen et al. 2006). 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 BD present with an index depressive episode, it is likely that many are misdiagnosed with MDD. Whether or not antidepressants worsen the course of BD 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 (Goldberg 2003). Furthermore, it appears that a first depressive rather than manic episode in BD might lead to a subsequent course with a greater burden of depressive symptoms (Perlis et al. 2005). Depressive-onset BD 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 BD-I patients than the quantity and direction of affective switches (Mysels et al. 2007). Analysis of assessments in clinical trials revealed that over 80 % of the treatment effect was attributable to the indirect effects of improvements in the depressive factors of the Montgomery-Asberg Depression Rating Scale (MADRS) like sadness, negative thoughts, detachment, and neurovegetative symptoms, and changes in factor scores were highly correlated with changes in clinical improvement (Williamson et al. 2006).

Table 3.1 Predictive value of depressive symptoms in the course of bipolar disorder[a]

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 major depressive disorder
• One third of preadolescents with major depressive disorder experience a manic episode and manifest bipolar disorder within five 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 comorbidity
• 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 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 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 lifelong
• Subsyndromal depressive symptoms during the first two months after recovery significantly increase 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

[a]All the statements in this table are referenced in the text

3.8 Comorbidity

BD has frequent comorbidities that worsen prognosis, especially in association with substance-use disorders (Tohen 1999; Tohen et al. 1998). The relative age at onset of alcohol use and BD is associated with differences in the course of both conditions. A first hospitalization for mania is associated with a period of recovery from comorbid alcohol abuse (Strakowski et al. 1992, 2005). Those patients with alcohol-use problems prior to BD are usually older, more likely to recover, and more likely to recover quickly than those whose alcohol problems occur after their diagnosis of BD. In contrast, those who have BD first spend more time with affective episodes and symptoms of an alcohol-use disorder during follow-up. Comorbid alcoholism is also usually related to poorer psychosocial adjustment (Coryell et al. 1989). Slower recovery has been associated with comorbid drug abuse (Strakowski et al. 1998; Baethge et al. 2005). Attention deficit/hyperactivity disorder and anxiety disorders, including those present during relative euthymia, also predict a poorer course of BD (Otto et al. 2006). Comorbid panic disorder is associated with a higher likelihood of rapid cycling (Coryell et al. 1992). One study showed that anxiety comorbidity impacts health-related quality of life in patients with BD-I but not BD-II (Albert et al. 2008).

Little is known about the treatment of psychiatric comorbidities in BD because their treatment is largely empirically based rather than based on controlled data (Singh and Zarate 2006). Many studies have examined the prevalence and predictive validity of personality disorders among MDD patients, but few have examined these issues among BD patients (George et al. 2003). Findings suggest that clinicians should be more vigilant for comorbid personality disorders and BD and less reluctant to diagnose them (George et al. 2003; Barbato and Hafner 1998). However, when structured assessments of personality disorders are performed during clinical remission of BD, fewer than one in three BD patients meet full syndromal criteria for a personality disorder (Paris et al. 2007). For instance, borderline personality disorder and BD can often co-occur, but their relationship is not consistent or specific. Existing data fail to support the conclusion that borderline personality disorder and BD exist on a spectrum, but allow for the possibility of partially overlapping etiologies and syndromatic presentation (Stromberg et al. 1998).

BD patients with lifetime smoking are more likely to have an earlier age of onset of mood disorder, greater severity of symptoms, poorer functioning, history of a suicide attempt, and a lifetime history of comorbid anxiety and substance-use disorders. Smoking may also be independently associated with suicidal behavior in BD (Ostacher et al. 2006). The effects of the sequence of onset of BD and cannabis-use disorders are less pronounced than observed in co-occurring alcohol-use disorders and BD (Strakowski et al. 2007). Cannabis use is associated with more time spent in affective episodes and with rapid cycling. Most cannabis-use disorders remit immediately after hospitalization, followed by rapid rates of recurrence. Individuals with BD are disproportionately 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 BD (McIntyre et al. 2007). The increased medical burden in BD is not simply a result of psychiatric symptoms and their corresponding dysfunction (Kupfer 2005).

Medical comorbidity is often associated with earlier onset of BD symptoms, more severe course, poorer treatment compliance, and worse outcomes related to suicide and other complications. It is still uncertain whether the medical comorbidities are a consequence of BD, another manifestation of the condition, or adverse effects of its pharmacological treatment (Krishnan 2005). To ensure prompt, appropriate intervention while avoiding iatrogenic complications, the clinician must evaluate and monitor patients with BD for the presence and the development of comorbid psychiatric and medical conditions.

3.9 Life Events

Stressful life events can unfavorably alter the course of the illness and negatively influence adherence to maintenance treatment. They have been associated with slower recovery and higher relapse rates. Stress is linked to changes in mood symptoms among BD adolescents, although correlations between life events and symptoms vary with age (Kim et al. 2007). There is no significant interaction between stress and episode number when predicting BD recurrence, and the interaction of early adversity severity and stressful life events significantly predicts recurrence in a manner consistent with the sensitization hypothesis (Dienes et al. 2006).

Few studies have examined the prognostic value of family factors on the course of BD. Patients who were more distressed by their relatives' criticisms had more severe depressive and manic symptoms and proportionately fewer days well (Miklowitz et al. 2005). Besides associations between high emotionality and MDD, studies that examined the relationship between temperament, recent and remote life events, and psychopathology among the offspring of parents with BD found an association between psychopathology and the number of recent negative life events, but no association between psychopathology and the number of early losses (Duffy et al. 2007). 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 comorbidities as well (Post and Leverich 2006).

3.10 Neurocognition

Recent analyses have revealed modest impairment in executive functioning, memory, and attention in both hypomanic and depressed BD patients, with additional fine motor skills impairment in the latter (Malhi et al. 2007). BD 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 (Martinez-Aran et al. 2004), and these are in line with findings that full symptomatic recovery (remission) does not guarantee functional recovery (Tohen et al. 1990b, 2003). While considerable evidence suggests that neurocognition declines steadily over the early course of schizophrenia but is more stable in BD, very little is known about the longitudinal trait stability of neurocognitive performance in BD. One study found that patients with BD showed stability over time in attentional measures but greater variability in other domains over a five-year period (Burdick et al. 2006). Impaired insight and other neurocognitive dysfunctions correlate among symptomatic as well as remitted BD patients (Varga et al. 2006). 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 BD later in the illness. 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 (Moorhead et al. 2007).

3.11 Future Trends and Needs

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 BD. Although tailored therapies are the preferred 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 are limited by current specifiers of BD (Vieta 2006).

Future diagnostic classification systems need to reconsider relying solely on categorical descriptors and include dimensional measures of the different phases of BD, thus further stimulating and refining research in the field (Kupfer et al. 2007). New studies using the RDoC (research domain criteria) in addition to categorical diagnostic constructs may prove useful in providing biological markers to aid disease staging and better treatment matching to improve outcomes.

Depressive symptoms dominate the longitudinal course of BD and predict functional impairment. Therefore they deserve more attention in the clinical assessment of patients, on treatment decisions, and in future studies. Finally, we hope that in the not too distant future, biomarkers such as brain imaging will become a tool in the selection of treatment and the prediction of outcome in patients suffering from this devastating condition.

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