The Longitudinal Course of Bipolar Disorder

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Course of illness is central to our focus on bipolar disorder due to the lifelong nature of this illness in the majority of patients. In this overview, we highlight areas of consensus and debate on factors that impact course of illness. Findings on age at onset, psychiatric comorbidity, frequency of episodes, cycle pattern, rapid cycling, mixed symptoms, and precipitants of episodes including use of substances and antidepressants and lithium discontinuation are discussed. The diversity and range of presentation and even course of illness become quickly apparent in this review. Highlighting these factors rather than seeking a unifying theory should be a productive way to refine our ability to identify additive factors contributing to course of illness for patients with bipolar disorder.

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There is increasing understanding of and information available on bipolar disorder. We are gradually gaining improved insight and detail on the pathophysiology of this major mental illness. Debate continues regarding factors that may influence the course and severity of bipolar illness, as well as the long-term outcome of bipolar disorder. This debate includes the recent focus on the impact of specific features of the illness, such as rapid cycling and the presence of mixed symptoms, on long-term course. As well, there are extensive studies and discussions in terms of the impact of long-term treatment on the course of illness for patients with bipolar disorder.

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In this article, we will review information on course of illness. Features such as rapid cycling, mixed states, and substance abuse have been implicated in treatment response as well as overall course of illness. Features of the illness that may be pertinent to longitudinal outcome include age at onset, impact of psychiatric comorbidity, frequency of episodes, cycle pattern and features, precipitants of episodes, and substance abuse.

Due to the extensive literature in this area, we will focus on recent studies, without attempting a comprehensive review. The literature contains a substantial number of papers that are based on small samples. These works are important for their value in generating hypotheses and providing a foundation for larger trials. However, in this review, we will focus principally on work from larger population-based samples in order to clarify major findings in this area.

A computerized literature search using the MEDLINE and Psychiatric Information databases identified pertinent articles in the English language. Additional references were identified from published studies and textbooks. In addition, work currently in press that was known to the authors was included, as well as personal communications of results.

FINDINGS

Age at Onset

The majority of patients with bipolar disorder will experience significant symptoms before the age of 25 years.[1] However, there are some patients who develop new onset of illness in much later decades. Onset of symptoms of bipolar illness after the age of 60 years is likely due to secondary medical causes including major medical or neurologic illnesses.[2]

A family history of affective illness has been associated with an earlier onset of illness and the possibility of a genetic anticipation phenomenon,[3–7] and there is evidence of a correlation between age at onset in bipolar siblings.[8] A cohort effect is seen, since age at onset tends to decrease in successive generations of bipolar family members, and historically the prevalence of bipolar disorder is increasing in youth.[9] Extensive debate continues as to the presentation and prevalence of childhood bipolar disorder, as well as presenting symptoms for children who then go on to develop a full-blown course of the illness. This literature will not be addressed in this article, which is concerned primarily with adult-onset bipolar illness.

Early age at onset (younger than 17 years) has been associated with more severe course of illness, family history of bipolar disorder, and multiple episodes (≥ 20) of hypomania/mania and depression even when corrected for age at onset.[10] This more severe course of illness is hypothesized by some investigators to be related to the number and severity of depressive episodes.[11] Data relating to age at onset and the development of rapid cycling remain ambiguous. While some reports find an association between early age at onset and eventual rapid cycling,[10,12] there is also evidence that a later age at onset contributes to shorter cycle lengths.[9] Early age at onset of a depressive episode has also been linked to increased likelihood of developing mania.[13]

Evidence regarding the connection between age at onset and the presence of mixed states is inconsistent. This is exemplified by patients with mixed states who have been reported to have younger, similar, or later age at onset of illness compared to those without mixed symptoms.[14–18] Evidence regarding the duration of illness associated with mixed states is similarly ambiguous.[14–16]

Psychiatric Comorbidity

The long-term outcome of bipolar disorder is varied across the spectrum of patients who suffer from the illness. One of the striking features that may contribute to a more difficult course of illness is that of psychiatric comorbidity.

Many patients in large naturalistic samples, including the Stanley Foundation Bipolar Network, report a high percentage of comorbidity (S. L. McElroy, M.D., written communication, March 2000, and references 10, 19, 20). In a study conducted by the Stanley Foundation Bipolar Network, it was concluded that, in a population of 288 patients, bipolar disorder was twice as likely to be accompanied by another lifetime Axis I psychiatric disorder (66%) than to exist by itself (33%) (S. L. McElroy, M.D., written communication, March 2000). The 2 most common comorbid conditions were an anxiety disorder and substance use: panic disorder and social phobia were the most prevalent anxiety disorders, and alcohol and marijuana were the most commonly abused substances.

Symptoms of anxiety and panic disorder followed by hypomania seem to complicate the course of illness. In addition, panic attacks during mania, as well as bipolar disorder manifesting as episodic obsessive-compulsive disorder, were reported.[19] Those individuals with both an anxiety disorder and bipolar disorder are likely to experience a more severe course than patients without a comorbid anxiety disorder.

A clinical study assessing Axis I comorbidity in bipolar patients examined substance abuse in 134 hospitalized bipolar I patients and found that 33% met criteria for an alcohol use disorder and 34% met criteria for a drug use disorder.[21] A study recently conducted by Goldberg et al.[22] found that a history of substance abuse further complicates the course of illness and has significant treatment implications, such as lower rates of remission and poor response to lithium in those with as opposed to without a history of substance abuse. In addition, substance use was associated with poor treatment compliance.[23]

Frequency of Episodes

There is general agreement that the duration between the first, second, and third episodes is often much longer than the duration between later full episodes of bipolar illness. In particular, even observations dating from Kraepelin's work support that the time between the first, second, and third episodes may be quite extended.[24] However, an increased frequency of episodes or more continuous symptoms have been reported in patients with earlier age at onset of illness and significant family history of illness.[10] Treatment variables may impact duration between episodes since early episodes may be inadequately treated—one factor that, some have speculated, could allow a more virulent form of the illness to develop.[25]

Beyond the first few episodes, the evidence supports an increased frequency of episodes followed by a relative stabilization. It is also becoming increasingly recognized that a small percentage of patients with a substantial number of episodes may experience greater difficulty stabilizing to a euthymic state.[26] Given the significant alteration of neurophysiologic functioning for both mania and depression, one could speculate that with multiple episodes, the brain has a decreasing capacity to maintain a euthymic state.

One proposed model of a progressive increased frequency of episodes is that of a sensitization or kindling mechanism.[27] However, while this pattern of increasing frequencies appears to have applicability for certain patients, it is not apparent that the majority of patients are likely to experience similar increased frequency or more continuous cycling.[28] Kraepelin in 1921 described a small percentage of patients prior to the current medication era that developed this pattern, but did not describe it for the majority.[24] Other studies have reported through retrospective life charting that some patients begin cycling at yearly frequency from their first episodes onward.[29] Additionally,

in our current era of utilization of multiple medications, including antidepressants, that may impact course of illness, it is difficult to evaluate variations in cycle frequency in a clear fashion.

Cycle Pattern

The number of cycle patterns has been well described in other publications.[9,29–33] It is apparent that some patients may have a predictable stereotypical pattern moving from mania to depression or from depression to mania with each episode. On the other hand, some patients may have an unpredictable and variable expression of the illness. Pattern of episodes has implications for course of illness, as improved treatment responsivity has been demonstrated in patients with a mania-to-depression pattern.[34]

There has been increasing appreciation for patients with bipolar II disorder concerning the pattern of moving from depression to hypomania and generally experiencing more depressive symptoms. Consistent with the potential implications of the more difficult-to-treat depression-to-hypomania pattern are the data supporting increased density of symptoms and continued disability for patients with bipolar II disorder, though fewer hospitalizations occur.[35] Persistent depressive symptoms over a 2-year follow-up period predicted poor long-term prognosis in a study of 113 bipolar patients followed for 15 years.[36]

There are conflicting data regarding the seasonal patterns to mood episodes in patients with bipolar disorder. Twenty-eight percent of patients enrolled in the Stanley Foundation Bipolar Network Naturalistic Follow-up Study report seasonal variation in their mood states, with winter being associated with depression and spring or summer with mania or hypomania,[10] suggesting a seasonal component to the illness. In a smaller study, the National Institute of Mental Health (NIMH) found that 93% of patients diagnosed with a seasonal affective disorder were found to suffer from a bipolar disorder.[37] However, multiple studies assessing this relationship have resulted in either insignificant or conflicting reports of a relationship between season and mood state.

One factor not always considered is that another variable contributing to seasonality in mood disorders is a reaction to the anniversary of a past traumatic event rather than a reaction to the climate or actual season. A study conducted at the University of Patras Medical School in Greece[38] showed that anniversary reactions may constitute a subgroup of seasonal mood disorders manifesting in both depressive and manic episodes.

Impact of Other Course Features

An additional course-of-ilness feature is rapid cycling, which is defined by DSM-IV as 4 distinct episodes a year either separated by 2 months of wellness or a switch in polarity. It is clear that rapid cycling is more common in women than in men.[39,40] In one study, the proportion of rapid cycling was 72% among women versus 28% among men.[41] The presence of rapid cycling has implications for course of illness since these patients demonstrate differential response to standard pharmocotherapies.[12,42–47] The literature regarding the impact of antidepressant use on rapid cycling will be discussed later in this review.

An important piece of work out of the Depression Collaborative Studies supports that rapid cycling may be a transient course feature versus necessarily a long-term course pattern.[48,49] Other researchers endorse that a more severe form of rapid cycling, which includes continuous cycling between subthreshold mania and depression or hypomania and depression, can occur in some severely ill patients.[50,51] Due to the chronicity of illness in patients who exhibit this pattern, it is difficult to determine whether this is a manifestation of natural course of illness or due to the effect of treatment variables, such as long-term use of psychotropic medication, including antidepressants. Work from the Stanley Foundation Bipolar Network suggests that ultradian cycling is associated with a worsening course of illness.[10] More research on the development and characteristics of individuals who exhibit ultradian or ultra-fast rapid cycling will need to be completed to help us further understand this manifestation of bipolar illness.

Similarly, evidence regarding the impact of mixed features on course of illness is quite conflicting. While some research supports the observation that patients with mixed mania take longer to recover from an acute episode and tend to demonstrate poorer outcomes than patients with pure mania,[18,52–55] other studies have documented similar outcomes for those with mixed and manic episodes.[21,30] The presence of mixed states has also been significantly associated with increased likelihood of comorbid substance abuse disorder[56] and with increased suicidal ideation and attempts when compared with pure mania.[18,57,58] Further research on the implications of mixed features for course of illness and outcome in bipolar illness needs to be conducted to clarify these important issues.

The literature is limited on the impact of psychotic features on course of illness. There is some evidence that patients with psychotic symptoms more often have a family history that includes psychotic mood disorders,[59] and the presence of psychotic symptoms is associated with poor functioning and a more chronic course of illness.[60–66] Some reports suggest that the presence of psychosis during mania is associated with a differential response to lithium treatment. However, these findings are both positive[67] and equivocal.[68] Whether or not psychotic symptoms are mood congruent or mood incongruent may mediate treatment outcome and course.

Precipitants of Episode

There is increasing recognition that, as with most major medical and mental illnesses, the vulnerability to developing new episodes is affected by the stress in individuals'

lives. Individuals who experience severe negative life events are significantly delayed in achieving recovery versus their peers, and there is evidence that stressful life events can influence medication compliance, further worsening prognosis.[69] While it is not possible to eliminate stress from any of our lives, given major life events that are a natural part of life, the communication of stress management and other related skills is important. Patients must also learn to recognize early prodromal symptoms and to take appropriate measures. This particular area is currently under more formal investigation.[70,71]

Both variations in sleep-wake cycles and circadian rhythm disturbances have been implicated in the precipitation of manic or hypomanic episodes. For those patients with bipolar disorder, it is clear that the duration and quality of sleep is important to monitor. It seems many bipolar patients have difficulty maintaining a stable sleep-wake cycle, but instead have a tendency for both bedtime and wake time to be shifted later in the day. This could be partially attributed to lifestyle, in that severely ill patients are unlikely to work and tend to keep weekend-like hours.[72] Side effects due to psychotropic medications also may contribute to this instability, as in the instance of lithium, which appears to delay the timing of both melatonin secretion and activity in rodents.[73,74]

Changes in sleep-wake schedule, such as those that occur during time zone changes or that are due to sleep deprivation, can cause or exacerbate a manic, mixed, or hypomanic episode.[72,75] Recently, a disturbance in social rhythms was implicated in the pathophysiology of rapid cycling as well.[76] In an experimental setting, a few patients who exhibited rapid cycling were successfully treated with extended bed rest in darkened rooms, minimizing the prolonged exposure to light and extended periods of wakefulness common in our culture.[77] Another therapeutic technique[78] hypothesizes that stabilizing the sleep-wake cycle can aid to prevent relapse in patients with bipolar disorder.

An individual's lifestyle can significantly affect course of illness. Lifetime prevalence of substance and alcohol abuse are more common in bipolar disorder than any other Axis I psychiatric illness, at greater than 60% of the population.[56,79] Individuals with earlier onset of bipolar I disorder are more likely to have a history of or current alcohol or substance abuse problems than those with later onset.[80–85] The controversy continues over whether substance use precipitates affective symptoms in patients who may not otherwise have developed an affective illness. Most data support the possibility that substance use is seen both before and after the onset of bipolar symptoms, and that members of each group and their families should be studied more closely to further explore this relationship.[56,86–88] There is evidence that past and/or current substance abuse worsens the course of illness and is predictive of poor treatment response.[22,89–91] Furthermore, substance use is inversely correlated with medication and treatment compliance, which also has the potential to worsen course of illness.[21,23,92]

The cessation or minimization of use of additional substances or alcohol is important to reduce any contribution to the development of new episodes or possibly a more severe course of illness. This, in part, is due to the failure of remission of affective disturbances associated with continued substance abuse, which appears to be a direct effect of substance abuse.

Aside from the use of substances, there continues to be very active debate as to the long-term impact of antidepressants. The concern derives from literature demonstrating increased switch into mania[93–97] and possibly cycle acceleration in patients treated with antidepressants.[98–104] It is difficult to sort the extent of switch into mania that is due to the natural course of illness and the extent that is attributable to use of antidepressants.[105] In a study of 51 patients diagnosed with either bipolar I or II disorder,[106] retrospective chart review revealed that 82% switched from depression to mania during antidepressant treatment. Thirty-five percent of these switches were attributed to the antidepressant. Additionally, 46% of those with antidepressant-induced mania also experienced cycle acceleration. However, more recent evidence suggests that continuation of antidepressant therapy does not relate to increased risk of mania, and that discontinuation of antidepressants following remission may increase the risk of depression relapse for bipolar patients.[107] While it is clear that antidepressant agents may serve as mood-destabilizing agents in patients with a history of mania,[108] the long-term impact of using these agents in patients is not yet known. Further research may inform the risk-benefit decision of utilizing these agents for those patients who suffer from chronic and severe depressive episodes.

New classes of medication are coming into use, in particular, the atypical antipsychotics and the third-generation anticonvulsants. The atypical antipsychotics appear to maximize stabilization in some patients. In particular, we have the most information on clozapine, which has been in use for over 30 years in Europe, and open but controlled studies support a long-term mood stabilization impact of this medication.[109,110] Additionally, anecdotal and accumulating data on treatment response support that other atypical antipsychotics may also have significant impact on the likelihood of developing new episodes.[111]

Some studies evaluating the efficacy of lithium in naturalistic settings have supported that many patients with initial good response do not have a sustained response, whether due to noncompliance or loss of efficacy of the drug.[112–117] Other reports support long-term responsivity to lithium, suggesting that many patients with either less severe illness or fewer complicating factors may have a sustained response.[118,119] An additional benefit of lithium appears to be the decrease in likelihood of suicide and self-harm behavior.[120–123]

There has been interesting debate in the literature on the impact of discontinuation of successful treatment. The majority of work has focused on the impact of discontinuation of lithium.[119,124,125] There is general agreement that abrupt discontinuation of lithium leads to a high probability of onset of a new episode in formerly stabilized patients, whereas a more gradual decrease in lithium appears to minimize this risk. Gradual discontinuation in bipolar II patients appears to have a sustained impact. In patients with bipolar I disorder, 5 years after lithium discontinuation, whether it has been gradually or abruptly discontinued, there is a high likelihood of a new episode in over 90% of these patients. There is less consensus on whether prior discontinuation of lithium reduces its subsequent treatment effectiveness.[126–129]

CONCLUSIONS

Importantly, as with a number of aspects of bipolar disorder, it may be limiting to search for a unifying theory to bind our understanding of course features. Rather, it may be more beneficial to develop an awareness that a number of cumulative factors, many of which may be difficult to identify at this time, will contribute to and define the course of illness. Some patients may have minimal episodes in their life, either because of overall treatment compliance, infrequent or nonexistent substance use, or a family history of a less severe form of the illness. Other patients, however, may experience an extremely chronic course, which may be due to genetic vulnerability, extensive use of substances, and medical and/or neurologic events.

This brief overview of some of the newer and developing views on course of illness for patients with bipolar disorder highlights areas of consensus and debate. We are gradually refining our abilities to diagnose and evaluate patients, and because of the number of large studies underway, e.g., the STEP-Bipolar program, Stanley Foundation Bipolar Network, and several European studies, we can expect future progress. While early age at onset and psychiatric comorbidity have received increasing appreciation as contributing factors of a more severe course, the interplay of treatment, cycle pattern, frequency of episodes, and features of illness is now an increasing focus of research.

As the range of treatments has expanded over the last 10 years, there has also developed an increased uncertainty of not only the critical role of medications but also the numerous other factors that play into the development of new episodes and the impact of these factors on the overall course of illness. Areas of active research are many, and we can expect significant progress in our understanding and approach to this illness over the next 10 years.

An important advance is the increased inclusion of psychosocial therapies in the treatment of bipolar disorder. Many outcome studies find continued impairment in the social and occupational functioning of bipolar patients despite reduction in clinical symptomatology.[10,65,130,131] Recent data emphasize the importance of combining pharmacologic and psychosocial approaches to maximize patient response.[132–134]

In sum, we are gradually adding to our understanding of the course of illness as described and studied by such researchers as Kraepelin and Angst. The number of studies examining overall course of illness and specifically studies examining both medication and nonmedication strategies can be expected to substantially improve our overall understanding of this significant illness. This understanding will guide us in developing focused interventions to minimize the possibility of a more severe course of illness for many patients.

Drug name: clozapine (Clozaril and others).

Disclosure of off-label use: The authors of this article have determined that, to the best of their knowledge, clozapine is not approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

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