Early intervention in bipolar disorders: opportunities and pitfalls

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ABSTRACT

- The early phases of bipolar disorders are difficult to diagnose and have specific treatment issues. The initial polarity of the illness is more commonly depressive, yet in counterpoint, mania is required for diagnosis; consequently, there is often a substantial delay in the initiation of appropriate therapy.
- There is good evidence that lithium in particular is most effective early in the illness course, and that its efficacy declines after multiple episodes. The notion of neuroprotection reflects this, and furthermore suggests that appropriate therapy may prevent the neurostructural and neurocognitive changes seen in the disorder. Inappropriate therapy may worsen the course of the illness.
- Patients with a first episode have specific psychosocial needs, and adherence to medication is relatively poor. There is a need for early identification, and to develop treatments and services applicable to the specific needs of this population.

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The notion of early intervention in psychiatric disorders has been led by the work in schizophrenia, highlighted in this Supplement by McGorry et al, *page S8*. Early intervention in bipolar disorders has not received comparable attention, despite a need for early intervention treatment strategies. Such complacency cannot continue, particularly as recent Australian data indicate that bipolar disorder is one of the most common psychiatric conditions, with an estimated lifetime prevalence of 1.2%[1] and a 12-month prevalence of 0.5%.[2] Furthermore, it is perhaps the most lethal of all psychiatric disorders, predominantly because of the substantial suicide risk, with estimates showing that, in people with bipolar disorder in the 25–34-year age group, suicide risk is between 18% and 19%.[3] The onset of bipolar disorder characteristically occurs during adolescence,[4] yet there is a substantial delay to diagnosis and the initiation of treatment concordant with treatment guidelines for bipolar disorder, particularly in young people.[5] Because of these issues, individuals with bipolar disorder may have increased rates of unemployment, relationship breakdown and poorer overall functioning,[2] outcomes that, with appropriate therapy, have more likelihood of improvement than in other comparable illnesses.[6]

The key issues in the field are the complexities in making an early and appropriate diagnosis, and the benefits accruing from early intervention with evidence-based therapy, such that treatment response may be better early in the course of the illness, with some suggestion that appropriate therapy may be neuroprotective (ie, may prevent the process of neuronal loss).[7] In counterpoint, there are clear risks associated with inappropriate therapy. The most evident of these is the use of antidepressant monotherapy, which may be associated with manic switching and increasing cycle frequency.[8] In early onset illness, there may be a consequent delay in age-specific development, with several psychosocial impacts indicating the need for specific psychosocial interventions. These are the issues that we will highlight in this article.

Issues in the diagnosis of bipolar disorder

During adolescence and early adulthood, mania is often atypical, mixed or dysphoric. This, together with the other obstacles to diagnosis outlined in Box 1, makes the recognition of mania more complex than it appears. This is crucial, as it is the identification of mania or hypomania that marks a mood disorder as being bipolar. Currently, many patients experience a significant delay between the onset of their first symptoms and their diagnosis with bipolar disorder. One study indicated that only 53% of patients were correctly diagnosed with bipolar disorder in the first year, while in the remaining patients it took an average of 7.5 years until a correct diagnosis was made.[9] This time lag is more likely to represent the delay in manic or hypomanic episodes after initial depressive phases than to indicate misdiagnosis per se. This delay in manic symptoms creates a diagnostic and treatment dilemma — it is not possible using current diagnostic nomenclature (such as the *Diagnostic and statistical manual of mental disorders* 4th edition, text revision [DSM-IV-TR]) to diagnose the illness earlier in its course.

Evidence increasingly indicates that earlier identification may allow for appropriate pharmacological and psychosocial treatments to be commenced sooner, potentially reducing the collateral damage often associated with prolonged duration of untreated illness. There is also evidence, particularly for lithium, that pharmacological treatments are more efficacious early in the illness course.[10]

Identification of the initial prodrome to bipolar disorders is helpful. Bipolar disorder often has an insidious onset in late childhood, adolescence or early adulthood, with relatively minor oscillations in mood that are mainly depressive in nature.[11] Earlier onset is also correlated with increased risk of psychotic features, higher comorbidity and poorer clinical course.[12] Other studies have shown a range of symptoms and behaviours pre-dating illness onset, including depressed and irritable mood, anger dyscontrol, anxiety, and periods of fluctuating sleep and energy.[13] However, these symptoms are of low specificity, and further research on the definition of the prodromal phase of bipolar disorders is needed before we can identify patients going through this phase of illness.

The index episode in bipolar disorder is typically depression,[14] and the bulk of the associated morbidity is also related to the depressive phase of the disorder. The ratio of depressive to manic features in bipolar I disorder is 3 : 1, whereas in bipolar II disorder the ratio of depression to hypomania is 47 : 1.[15] This creates a scenario in which young people with developing bipolar disorder present with depression, and are at risk of being misdiagnosed as unipolar. Antidepressants are capable of inducing mixed states, rapid cycling, and induction of mania in susceptible individuals. Antidepressant-induced manias are also more likely to be dysphoric than euphoric,[16] and mania in young people is indeed more likely to be dysphoric.[17] This increases the risk that dysphoria and irritability will continue to be seen as part of the depression. At the most severe end, evidence also indicates that suicide is a disproportionate risk in mixed states.[18]

There is evidence that depressive episodes in bipolar disorder are phenomenologically distinct from unipolar depression; this "signature" of bipolar depression is shown in Box 2.[19] Clinical attention

1 Obstacles to diagnosis of bipolar disorder — recognition of mania is essential for diagnosis

- Patients often deny or misattribute symptoms of mania
- Mild symptoms of mania can be pleasant, with better functioning, and are not necessarily distressing
- Mania is rarely treated unless there is a history of severe mania
- Mixed states are often confused with agitated depression
- Disruptive symptoms and irritability can be interpreted as an abnormal personality
- In children, mania is frequently misdiagnosed as attention deficit hyperactivity disorder
- Any psychotic symptoms can be seen as diagnostic of schizophrenia not mania
- Substance use is more common in younger patients and substance-induced mania is more often mixed and dysphoric rather than euphoric
- Comorbid conditions (eg, anxiety, alcoholism) can cloud presentation ◆

towards these unique bipolar depressive features may improve the recognition of bipolar disorder, particularly after the release of new rating instruments for clinicians.[20] Currently, screening instruments for hypomania, including the Mood Disorder Questionnaire, are already available in routine clinical care to detect potential bipolarity in young people presenting with depression.[21]

Treatment implications of early intervention

There is often a substantial delay between the onset of bipolar disorder and the introduction of mood stabilising medication, with one study reporting a delay of 9.3 years.[22] This lag may be due to delay before a first manic or hypomanic episode, or to complicated presentations such as those with mixed episodes or comorbidities.

There are many potential consequences of delayed introduction of mood stabilisers. Lithium may be less effective if not started early,[23] but this finding is not universal.[24] Delayed treatment initiation is linked with an adverse impact on many clinical variables, including poorer social adjustment, more hospitalisations, increased risk of suicide, increased rates of comorbidities (particularly, substance abuse), forensic complications resulting from committing felonies while unwell, and impairment in age-specific developmental tasks.[25-27] Post's neurosensitisation model suggests that multiple episodes lead to permanent alterations in neuronal activity, which may be transduced at the level of gene expression. This may be the neurobiological basis of a greater liability to relapse and the potentially poorer response to medication in patients with multiple episodes.[28]

Neuroprotection

Even within the early phases of the illness, there is growing evidence to suggest the presence of disease-related neuroanatomical and neurochemical abnormalities in key brain regions that regulate cognition and mood.[29,30] These changes may be progressive and related to both illness course and treatment outcome.

Importantly, recent evidence indicates some medications may provide neuroprotection from this neuroanatomical change. In particular, lithium has been shown in a number of studies to have neuroprotective properties.[31,32] Imaging data suggest that adolescents with bipolar disorder who are taking mood stabilisers may be protected from the volume loss[33] otherwise described in the disorder. Preclinical studies suggest that atypical antipsychotic drugs may have pharmacological properties that could produce neurotrophic or neuroprotective effects. Recent clinical data indicate that these atypical agents prevent structural changes in first-episode psychosis and, specifically, in bipolar disorder, and one trial shows grey matter volume increases after 4 weeks of lithium administration.[34] Thus, the role of established mood stabilisers as neuroprotective agents is being increasingly established. This accumulation of evidence is increasingly supporting neuroprotection as a key therapeutic target in early intervention.

Psychosocial implications of early intervention

Optimal management of the early phase of bipolar disorders involves more than medication. In a cohort of 87 patients with first-episode bipolar mania, we have shown that, despite generally high rates of syndromal recovery, 41% failed to reach symptomatic remission after 12 months, and only 39% of individuals returned to their premorbid level of functioning.[35] Residual features include anxiety, in particular social phobia, and consequent restriction of social function. A high proportion of patients misused illicit substances, and medication adherence was a particular problem.

Based on these unmet treatment needs, developments in psychological therapies in bipolar disorder have a number of basic aims, including: alleviating symptoms; improving psychosocial functioning; assisting the patient to understand and accept the illness; and preventing or reducing the incidence of relapse and recurrence of episodes.

The major psychosocial therapy techniques used in bipolar disorder that have demonstrated some efficacy are interpersonal and social-rhythm therapy,[36] cognitive behaviour therapy,[37] psychoeducation[38] and family-focused therapies.[39] One of the more interesting recent studies has further demonstrated that, while there is no overall improvement using cognitive behaviour therapy in bipolar disorder, those who have experienced fewer than 10 episodes of the illness show significant improvements with cognitive behaviour therapy.[37] This indicates that the ability to respond to adjunctive psychological treatment decreases as the disorder becomes more chronic, again highlighting the importance of early intervention.

All the therapies listed have a core base in addressing the contribution of medication non-compliance, disrupted social and biological rhythms, stressful life events, and dysfunctional coping

2 The signature of bipolar depression

- Hypersomnia or increased daytime napping
- Other "atypical" depressive symptoms such as "leaden paralysis" and hyperphagia
- Psychotic features and/or pathological guilt
- Psychomotor slowing; "flatness"
- Abrupt onset or offset of episodes; postpartum onset
- Prodrome of cyclothymia or hyperthymia (trait labile or mildly elevated mood)
- Seasonal pattern of symptoms
- Lability of mood, irritability or subthreshold manic symptoms
- Family history of bipolar disorder ◆

3 First-episode bipolar disorder

Challenges

- Poor insight in young patients having a first episode of bipolar disorder (which improves after multiple episodes) leads not infrequently to problems with medication adherence
- Higher comorbidity with alcohol and other substance use, suicidal behaviour and psychotic symptoms
- Interference of illness with age-specific educational, social, and psychosexual development
- More rapid relapse with medication discontinuation
- Greater symptom severity with early-onset illness
- Impact of illness on the family

Advantages of early intervention

- The resilience and optimism of youth
- Medication may be most effective in the first episode
- Potential for neuroprotection if treated early with mood stabilisers
- Psychoeducational and psychosocial interventions more efficacious if given early in the illness course
- Prevention of secondary sequelae (affecting family relationships, psychosexual development, and vocational development) ◆

styles. However, in young adults, there should be further clinical consideration of factors such as therapeutic engagement, educational and vocational counselling, and discussion of progress through age-appropriate developmental tasks[34] to encourage their development into adulthood.

Based on these possible biological and psychological outcomes, we propose that the adoption of a staging model for bipolar disorder would assist in the development of treatments that could be tailored to illness stage, as the specific needs of patients with a first episode vary greatly from those of treatment refractory patients. There are specific obstacles to illness acceptance and, consequently, treatment adherence, in the early phase of disorders. In this regard, specific psychosocial interventions are needed. The evidence that some mood stabilisers, particularly lithium, are most effective early in the illness course reinforces this notion. This is reflected by the growing acceptance of the importance of neuroprotection as a therapeutic target. There is a need to develop treatments and services applicable to the specific needs of this population (Box 3). These interventions merit research to validate their utility. The increased focus on bipolar disorder, and in particular on early intervention,[40] raises hope that outcomes in this serious disorder are amenable to comprehensive intervention.

Competing interests

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