See article by Gignac et al

What Happens Now? The Importance of Naturalistic Course After First Mania

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Bipolar disorder presents a substantial burden to patients and their loved ones because of its recurrent nature, persistent symptoms, and associated comorbid conditions.[1] The first episode occurs most frequently before the age of 25 years and is among the top 10 causes of disability-adjusted life years among youth worldwide.[2,3] With a population estimate of 74 million youth in the United States (www.childstats.gov), about 3%[4] or 2.2 million will meet criteria for bipolar disorder, in sharp contrast to about 15,800 cases of childhood cancer (www.cancer.gov; a ratio of about 140:1). If the diagnosis is expanded to those who have a bipolar spectrum, the numbers of those affected double.

Studying Natural Course

Because of the public health importance of bipolar disorder and its recurrent and chronic nature, it is imperative to understand the natural course of the disorder to better inform patients and families about what to expect. Additionally, pharmacologic treatments for bipolar disorder carry unpleasant and difficult-to-tolerate side effects that are particularly challenging for youth (and anyone else) to take for a long time; clear information about natural course is essential so that patients and their families can decide about the benefits and risks of discontinuing or refraining from long-term treatment. To obtain this information, we need to follow patients from their first episode to construct an inception cohort. The study by Gignac and colleagues[5] does this by integrating findings from the literature to provide a prognostic model essential to help patients and clinicians alike to understand the benefits and risks of treatment. To determine the naturalistic course of an inception bipolar cohort, it would be optimal to follow untreated patients, an option neither ethical nor practical. The next option is to identify patients at the time of their first mood episode (depressive or manic) or their first hospitalization—and then follow them for as long as possible. Several obstacles can make interpretation of these longitudinal data difficult: patients who are more disabled will refuse to participate or drop out of the study more frequently than those less disabled (volunteer bias); those with more comorbid conditions, especially substance abuse disorders or anxiety, have a similar volunteer bias; treatments may be given (and taken) consistent (or not) with state-of-the-art guidelines (treatment effect bias); our imperfect treatments cause substantial adverse effects that can accumulate over time with frequent shifts of treatment to lessen this burden; and antidepressants, the class with the least data supporting its use[6] but most frequently prescribed, can worsen the course by causing mixed states, rapid cycling, or treatment-emergent affective switch to mania or hypomania. Additionally, with increasing evidence about the importance of psychotherapy,[7,8] especially for those with comorbid anxiety,[9] the inclusion of those patients who receive psychotherapy in longitudinal studies would clarify the effectiveness of this important intervention. Thus, it would be optimal to follow a cohort with guideline-concordant treatment (including psychotherapy) so that we know the outcomes under the best treatment conditions. For many complex logistical reasons, such a study is unlikely to happen. We will need to make do with what is available.

In the meta-analysis by Gignac and colleagues, they used an index manic episode or hospitalization for mania as the seminal event. Over 80% of the cohort had psychotic mania. Studies included were published as early as 1990 and as late as 2009, with dropout rates between 11% and 38%. Treatment patterns have shifted since then, away from lithium and more toward second and third generation antipsychotics along with a rise in the use of lamotrigine (and, as mentioned before, with continued use of antidepressants despite studies that question their use[6]). Injectable antipsychotics are now available, with some evidence of better outcomes[10] but with limited use. Nevertheless, let's examine the clinical implications of the results of this important meta-analysis.

Clinical Significance

Overall, over 80% reached syndromal recovery within 6 months, leaving a substantial minority who did not. Outcomes were not improved when expanded to a 12-month follow-up—ie, those who recovered mostly did so within the first 6 months. So the good news is that most will recover, but the bad news is that many will not—and perhaps those who do not recover should be the subject of intense investigation to find treatments that work. Raising the bar, the authors found that symptomatic recovery occurred in over 60% of patients at 1 year. Here again, however, understanding outcomes of the remaining 40% is critical to our efforts to find efficacious treatments. Finally, manic, mixed, or depressive recurrence occurred at rates of 25.7% at 6 months, 41.0% at 1 year,

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and 59.7% by 4 years. When we do the math, if 60% have symptomatic recovery at 1 year and 41% have a recurrence at 1 year (meaning that 59% remain free of recurrence), then the proportion who remain well and are free of recurrence after their first manic episode or hospitalization is about 59% of 60% or about 35%. In other words, 65% will not be well after a year. These data are consistent with the 12-month observational outcome data from STEP-BD[11] and the 6-month data from the comparative effectiveness study LiTMUS[12] that compared moderate tolerable doses of lithium with optimal personalized treatment (OPT) versus OPT without lithium. In those studies, about 25% fully recovered and stayed well for 6 to 12 months; these results include those with guideline-concordant treatment (but not with psychotherapy) as all participants were treated by experts in managing bipolar disorder. The observation that most improvement occurred within the first 6 months also supports the design of LiTMUS as well as the design of Bipolar CHOICE[13]—a study that compared lithium and quetiapine as the base of treatment.

What are the implications of the findings from this meta-analysis? First, we need better treatments. Second, we need to better use the treatments we have. This is especially true for psychotherapy, given the empirical support for various psychosocial treatment modalities[14] such as family-focused treatment, family psychoeducation,[15–18] cognitive-behavioral therapy,[19,20] interpersonal and social rhythm therapy,[21,22] and group psychoeducation[22] in improving medication adherence, preventing mood episode recurrences, reducing residual mood symptoms, and improving psychosocial functioning. Third, we need better interventions to address comorbid problems that patients with bipolar disorder often face, among them cognitive deficits,[24,25] anxiety disorders, and emotion regulation difficulties.[26] Fourth, we need better data about the effects of targeting inflammation and oxidative stress, including smoking cessation.

Our challenge is to find interventions that improve the course of the disorder—whether these include rational polypharmacy, psychotherapy, or lifestyle changes, we clearly need to serve our patients better.

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