Bipolar Phenomenology: Have We Learned All We Can Learn?

What are the chances that a patient who presents with unipolar depression will eventually convert to bipolar disorder? What clues, if any, are evident in a patient's presenting symptoms? In this issue of the *Journal*, Fiedorowicz and colleagues (1) study the conversion rate of major depression to bipolar disorder and examine whether the presence of subthreshold hypomanic symptoms, either alone or in relation to other established risk factors, help predict which patients might convert from unipolar depression to bipolar disorder over the course of time.

Accurate diagnosis of bipolar disorder remains an all-too-common clinical challenge, even when using standardized diagnostic tools and measures. Survey studies of members of the National Depressive and Manic Depressive Association, now called the Depression and Bipolar Support Alliance, have found that more than two-thirds of its members had previously had their bipolar disorder misdiagnosed, most frequently as major depression, followed by anxiety disorders, schizophrenia, and substance use disorders (2). Delays in diagnosis are common, with patients frequently reporting 10 years between onset of affective symptoms and formal diagnosis of bipolar disorder. Moreover, lengthy delays in starting mood-stabilizing treatments can be costly and have been linked to higher rates of suicidal behavior, poorer social adjustment, and higher hospitalization rates (3).

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Thus, more accurately predicting which patients with depression are likely to convert to bipolar disorder would have the potential to substantially reduce patient suffering and mortality. The Fiedorowicz et al. study, an extension of work published 15 years ago as part of the National Institute of Mental Health's Collaborative Depression Study (4), is notable for prospectively following a large number of patients (N=550) for a mean of 17.5 years. The authors found that in this time span, nearly one in five patients originally diagnosed with major depression eventually converted to bipolar I disorder (7.5%) or bipolar II disorder (12.2%), nearly twice the rate observed in their earlier study. Consistent with previously established risk factors, those patients who converted were more likely to be younger, have a lower age at illness onset, and have a greater severity of illness (i.e., with psychosis).

The presence of subthreshold hypomanic symptoms proved more equivocal as a predictor of conversion. Despite baseline screening for five manic symptoms at any severity level (elevated or expansive mood, unusual energy, less need for sleep, increases in goal-directed activity, and grandiosity), the majority of patients who ultimately converted to bipolar disorder did not have any symptoms of hypomania at baseline. While the presence of subthreshold hypomanic symptoms was associated with the subsequent onset of mania or hypomania, and while each symptom contributed additive risk for eventual conversion, even three or more baseline manic symptoms yielded a sensitivity of 16% for detecting patients who developed bipolar disorder. The positive predictive value using three or more symptoms as a cutoff was only 42%, below what many would consider clinically helpful as a screening measure.

Could treatment have affected the observed conversion rate? While the study was prospective, it did not control for treatment, and patients undoubtedly received a wide range of medications, including antidepressants. While those with a history of

subthreshold hypomanic symptoms were not differentially prescribed antidepressants, the role of antidepressants in possibly altering the outcome of bipolar illness remains unclear and controversial. Acute placebo-controlled trials of antidepressants in bipolar disorder have shown neither higher response rates nor higher switch rates than placebo (5), although some longer-term studies have suggested a greater risk of cycle acceleration (6) or mixed depressive states (7). The conversion rate in the Fiedorowicz et al. study is generally in keeping with conversion rates reported in other prospective cohort studies, though lower than rates observed in some child and adolescent populations (8).

Refined examinations of bipolar phenomenology appear to be reaching their limit of clinical utility. Despite a plethora of phenomenological studies, the predictive power of symptomatology appears frustratingly inadequate in discriminating, in a more definitive manner, between unipolar and bipolar diatheses. Whether focused on the qualitative distinctions between unipolar and bipolar depressive symptoms or looking for the presence of subthreshold hypomanic symptoms as in the present study, no symptoms, symptom clusters, or individual patient factors have enabled us to accurately identify which patients are most likely to convert. Instead, bipolar disorder continues to reveal itself as increasingly heterogeneous: beyond our current DSM-IV classifications of manias, depressions, and mixed states, clinicians and researchers observe mixed depressions, mixed hypomanias, cyclic irritability, spectrum illnesses, and highly recurrent major depressions. Other definitions of bipolar phenomenology also appear increasingly arbitrary, as rapid cycling appears more as a continuum of cycling rather than as a discrete cut point of four episodes or more per year (9). And, while there is hope that biomarkers may one day aid in more accurate diagnosis or prognosis, we have yet to find neurobiological markers pathognomonic of the disease.

Given current limitations in diagnosis and prognosis, perhaps our focus should turn to *prevention* of mood disorders. Current preventive studies are being explored in children and adolescents who are at risk of developing mood disorders by virtue of having prodromal forms of major affective illnesses or strong genetic loading. Garber and colleagues (10) recently reported results from a large randomized trial showing benefits of cognitive-behavioral therapy as a preventive strategy for adolescents who are at elevated risk of developing depression. Studies examining prevention of bipolar disorder in high-risk youths are currently under way using a modified form of family-focused therapy. Miklowitz and Chang (11) have hypothesized that reducing stress, conflict, and affective arousal may promote symptom stabilization, enhance functioning, and perhaps forestall the development of the illness. Early studies using pharmacological interventions in children at risk for bipolar disorder have shown positive results in open (12, 13) but not controlled trials (14). Whether psychosocial or pharmacological strategies can ultimately delay, minimize, or even prevent full expression of mood disorders is as yet unclear, but they offer promise in lowering the long-term morbidity and mortality associated with these difficult disorders.

Such strategies might also be adapted for adults who appear to be at risk for conversion yet whose symptoms are not yet severe enough to warrant a change in diagnosis. Current therapies, such as cognitive-behavioral therapy, family-focused therapy, and interpersonal social rhythm therapy have all been shown to promote treatment adherence, reduce symptom severity, and prolong time to relapse in patients with full-threshold bipolar disorder. Adapting core features of these treatments, such as educating patients on the signs and symptoms of mood dysregulation, the importance of managing stress, the protective effects of daytime routine, and well-regulated sleep-wake cycles, may help patients better manage their symptoms and recognize early warning signs of affective change. Such strategies may alter the trajectory of affective illnesses or minimize their severity, despite our current inability to definitively diagnose the core disorder.

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