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Is There Validity to the Bipolar Prodrome?

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Bipolar disorder is a debilitating chronic psychiatric disorder with high likelihood of progression to multiple morbidities and early mortality.[1] It is deserving of rigorous research efforts to understand the mechanisms and risk factors for developing the disorder in order to prevent its onset and progression.[2] There are a number of studies that have now identified key clinical risk factors for developing bipolar disorder, including, most consistently, a family history of bipolar disorder.[3,4] Nevertheless, there are few tools available to help clinicians identify which individuals are most at risk for developing bipolar disorder based on early affective signs and symptoms.

In this issue of the *Journal of Clinical Psychiatry,* Faedda et al[5] present the findings from a systematic review aimed at addressing this important area. In 26 published reports meeting selection criteria, researchers found that mood lability, major depression, subsyndromal mood symptoms (eg, hypomanic symptoms with or without major depression, cyclothymia, and bipolar disorder not otherwise specified), major depression with psychotic features, and other psychotic disorders were identified as consistent precursors to bipolar disorder. Bipolar disorder was also predicted by pediatric onset of depression and persistence or co-occurrence of hypomanic or depressive symptoms. Importantly, prospectively identified precursors of bipolar disorder appeared years prior to syndromal onset, often with significant early morbidity and disability. Methods across reports varied widely in terms of design, duration of follow-up, and ages and populations investigated. Nevertheless, it is clear from this review that early clinical identification may be feasible in bipolar disorder.

Prospective findings have been consistent with findings from family-risk studies, which have found that family members of bipolar disorder probands also have high rates of mood and other psychiatric disorders.[6] However, longitudinal follow-up of offspring of parents with bipolar disorder, for example, show variable rates of conversion to full mood syndromes, ranging from 8.5% to 40%,[7] influenced by a variety of factors that have modest predictive power.

To assist with the assessment of precursor symptoms to bipolar disorder, researchers have developed the Bipolar Prodrome Symptom Interview and Scale (BPSS), which is a semistructured interview that can be administered prospectively (BPSS-P)[8] and retrospectively (BPSS-R)[9] to individuals and families affected by bipolar disorder. The BPSS-R has demonstrated that youth with bipolar I disorder commonly have a long, predominantly slow-onset mania prodrome that includes subthreshold manic and depressive symptoms. There are inherent selection and recall biases in retrospective study designs. On the other hand, prospective studies are time intensive and commonly yield low base rates of bipolar conversion, even among help-seeking adolescents and young adults.[10] Importantly, findings from prospective and retrospective studies have been consistent, reassuring us of some degree of specificity of the bipolar prodrome. Notwithstanding, the BPSS has yet to be used across multiple settings, and its predictive validity requires further investigation.

Early mood and anxiety symptoms are important predictors of progression in a number of disorders[11] and can result in either homotypic (similar diagnostic) or heterotypic (different diagnostic) outcomes.[12] Some have argued that the overall low specificity of prodromal symptoms and signs in bipolar disorder makes it challenging to predict the initial development of bipolar disorder based solely on early phenomenology.[13] Researchers are turning to other ways of conceptualizing this early phenomenology, basing their assessment either on potentially more reliable core symptoms[14,15] or on constructs, such as those provided by the Research Domain Criteria (RDoC).[16] The predictive validity of these alternative ways of conceptualizing early phenomenology remains to be tested.

Others have argued that prodromal assessments based on phenotypic information, family history, or both have led to insufficient predictive validity. This may be due to the heterogeneous clinical presentation and complex etiopathogenesis of bipolar disorder, suggesting that it is unlikely that a single factor (or an exclusive approach) will predict the development of bipolar disorder. Consequently, some researchers have turned their attention to identifying biological markers associated with clinical symptoms of impending mania to increase chances for early detection and prevention of bipolar disorder. For example, neuroimaging has been used to identify biological targets such as aberrant brain structure and function supporting emotion processing, emotion regulation, and reward processing in individuals with and at familial risk for developing bipolar disorder.[17] This work is aimed both to bridge a clinical assessment of mood symptoms with biologically mediated brain abnormalities and to advance our understanding of the

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pathophysiology of bipolar disorder development. However, what remains unexplained is whether neurobiological factors that precede bipolar disorder represent early risk markers or compensatory mechanisms that may help prevent the onset of bipolar disorder. Moreover, as in the case of symptoms, we have not been able to distinguish the neural circuit abnormalities in bipolar disorder from other brain-based disorders. In addition, we lack a biological perspective on the mechanisms that confer risk for or resilience from bipolar disorder and have no reliable prognostic markers for which individuals will go on to develop lifelong illness and which will not.

On final analysis, it is clear that we need to integrate multiple sources of evidence in order to feel confident about the predictive validity of a bipolar prodrome. This may require sample sizes on the order of Big Data and a bioinformatics approach that integrates complex data from symptom, family, and biological assessments across the bipolar neurodevelopmental trajectory.[18] This will certainly mitigate the problem of insufficient sampling to facilitate more accurate characterization and staging of bipolar disorder.[19] Research efforts should be aimed to refine our phenotypic and neurobiological understanding of the bipolar prodrome.[20] The potential impact of determining how early abnormalities relate to the onset and course of bipolar disorder is high, as it can elucidate ideal times for intervention to preempt onset and prevent the consequences of recurrent illness.

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