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Review

Clinical risk factors for bipolar disorders: A systematic review of prospective studies

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ABSTRACT

Background: Early phases and suspected precursor states of bipolar disorder are not well characterized. We evaluate the prevalence, duration, clinical features and predictive value of non-affective psychopathology as clinical risk factors for bipolar disorder in prospective studies.
Methods: We screened PubMed, CINAHL, PsycINFO, Embase, SCOPUS, and ISI-Web of Science databases from inception up to January 31, 2014, following PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and searched: bipolar disorder AND [antecedent* OR predict* OR prodrom* OR prospect* OR risk*] AND [diagnosis OR development]. We included only English language reports on prospective, longitudinal studies with two structured clinical assessments (intake and follow-up); no DSM intake diagnosis of bipolar-I or -II; diagnostic outcome was bipolar-I or -II. Details of study design, risk factors, and predictive value were tabulated.
Results: We found 16 published reports meeting selection criteria, with varying study design. Despite heterogeneity in methods, findings across studies were consistent. Clinical risk factors of bipolar disorder were early-onset panic attacks and disorder, separation anxiety and generalized anxiety disorders, conduct symptoms and disorder, ADHD, impulsivity and criminal behavior.
Limitations: Since risk factors identified in some prospective studies are predictive of other conditions besides bipolar disorder, these preliminary findings require replication, and their sensitivity, specificity and predictive value need to be assessed.
Conclusions: Clinical risk factors for bipolar disorder typically arise years prior to syndromal onset, include anxiety and behavioral disorders with unclear sensitivity and specificity. Prospectively identified clinical risk factors for bipolar disorder are consistent with retrospective and family-risk studies. Combining clinical risk factors with precursors and family-risk may improve early identification and timely and appropriate treatment of bipolar disorder.

Contents

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1. Introduction

Bipolar disorder has an estimated lifetime prevalence of 2.1% (both types I and II) (Merikangas et al., 2011) among US adults, and 1.8% in children and adolescents, both in the US and internationally (Van Meter et al., 2011). It is associated with very high costs (Dilsaver, 2011), high rates of morbidity and mortality, especially among cases with early onset, along with significant disruption of cognitive, behavioral, educational, vocational and interpersonal functioning (Murray and Lopez, 1996; Leverich et al., 2007; Post et al., 2010).

As evidence grows that illness-duration, especially duration of untreated illness, might worsen outcome (Leverich et al., 2007; Post et al., 2010), increased attention has been directed towards early recognition of bipolar disorder as a public health priority (Merikangas et al., 2011; Leverich et al., 2007; Post et al., 2010; Faedda et al., 1995). Also, in retrospective studies, younger age-at-onset is correlated with greater delay of diagnosis and treatment onset, underscoring the importance of timely diagnosis of bipolar disorder in children and adolescents (Leverich et al., 2007).

One of the most important goals of early diagnosis and treatment is preventing the development of comorbid conditions and disability. Untreated bipolar disorder in juveniles increases the risk of addictive, anxiety and other psychiatric disorders, further complicating diagnosis and treatment, reducing treatment-adherence, and increasing costs (Leverich et al., 2007; Post et al., 2010).

Prevalence, clinical features, duration and predictive value of early symptoms and potential predictors of bipolar disorder are not well characterized (Fig. 1). Most efforts to characterize prodromal features used retrospective assessments or prospective follow-up/outcomes in offspring of adults diagnosed with bipolar disorder (Duffy, 2010). The early phases of pre-syndromal bipolar disorder in children and adolescents have been identified in retrospective reports; they are typically described as chronic or intermittent instability or dysregulation of mood, activity and sleep patterns, with rigidity, inflexibility, emotional and behavioral difficulties (Leverich et al., 2007; Post et al., 2010; Faedda et al., 1995; Axelson et al., 2011).

Using the syndromal threshold to define illness onset does not permit identification of a population at risk. Even relying on attenuated syndromes (notably, DSM cyclothymic and bipolar disorder not otherwise specified) includes some cases that progress to bipolar-I and -II, with cases whose diagnosis remains stable but follow a chronic, disabling course. Therefore, the value of attenuated syndromes in preventative efforts remains limited. Finally, isolated symptoms, while identifying a population at risk, lack predictive value and might be a relatively late manifestation in the unfolding of the illness.

The prodromal features of bipolar disorder are also of great clinical interest also due to the resemblance of manic symptoms to the externalizing symptoms seen in childhood disruptive behavior disorders, and of anxiety and depressive symptoms of internalizing disorders. An alternative approach has used general measures of psychopathology (e.g. Child Behavior Checklist [CBCL]), family history of mood disorders or other diagnoses to identify populations at risk, again with limited predictive value (Duffy, 2010; Papachristou et al., 2013).

The relationship between bipolar disorder and early anxiety, disruptive behavior or substance use symptoms or disorders is difficult to clarify, and is often attributed to comorbidity. However, in the early course of bipolar disorder, it might be impossible to determine when these are truly independent co-occurring conditions or clinical manifestations of pre-syndromal bipolar disorder.

Given the limitations of alternative methods, only prospective observation of populations at risk can adequately assess the predictive value of proposed risk factors.

To address the need for better prediction and earlier recognition of this potentially debilitating chronic illness, in 2011 the International Society for Bipolar Disorder convened a “Task-force on Prodromes of Bipolar Disorder” to review scientific evidence, summarize findings on early psychopathology preceding syndromal bipolar disorder, and make research recommendations. Within that process we have reviewed the research literature on prodromal features of bipolar disorder, both affective features (Faedda et al., 2013) and non-affective symptoms. In the present review, we focused on prospective studies of non-affective psychopathology or clinical risk factors (Fig. 1) that may help characterize the pre-syndromal or prodromal phase of bipolar disorder.

Research questions were: 1) is there evidence of a prodromal phase of bipolar disorder in prospective studies? 2) Are there specific premorbid clinical risk factors (non-affective signs and symptoms) that predict bipolar disorder? 3) What are the nature, timing, and duration of these factors? 4) How sensitive and specific are these clinical risk factors in predicting later diagnosable bipolar disorder? 5) Do prodromal phases differ by subtype (bipolar-I vs. bipolar-II)?