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Research report

Childhood-compared to adolescent-onset bipolar disorder has more statistically significant clinical correlates

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ABSTRACT

Background: The strengths and limitations of considering childhood-and adolescent-onset bipolar disorder (BD) separately versus together remain to be established. We assessed this issue.
Methods: BD patients referred to the Stanford Bipolar Disorder Clinic during 2000–2011 were assessed with the Systematic Treatment Enhancement Program for BD Affective Disorders Evaluation. Patients with childhood- and adolescent-onset were compared to those with adult-onset for 7 unfavorable bipolar illness characteristics with replicated associations with early-onset patients.
Results: Among 502 BD outpatients, those with childhood- (< 13 years, $N=110$) and adolescent- (13–18 years, $N=218$) onset had significantly higher rates for 4/7 unfavorable illness characteristics, including lifetime comorbid anxiety disorder, at least ten lifetime mood episodes, lifetime alcohol use disorder, and prior suicide attempt, than those with adult-onset (> 18 years, $N=174$). Childhood- but not adolescent-onset BD patients also had significantly higher rates of first-degree relative with mood disorder, lifetime substance use disorder, and rapid cycling in the prior year. Patients with pooled childhood/adolescent – compared to adult-onset had significantly higher rates for 5/7 of these unfavorable illness characteristics, while patients with childhood- compared to adolescent-onset had significantly higher rates for 4/7 of these unfavorable illness characteristics.
Limitations: Caucasian, insured, suburban, low substance abuse, American specialty clinic-referred sample limits generalizability. Onset age is based on retrospective recall.
Conclusions: Childhood- compared to adolescent-onset BD was more robustly related to unfavorable bipolar illness characteristics, so pooling these groups attenuated such relationships. Further study is warranted to determine the extent to which adolescent-onset BD represents an intermediate phenotype between childhood- and adult-onset BD.

1. Introduction

Bipolar disorder (BD) is a common condition characterized by recurrent episodes of mood elevation and depression that inflict considerable human and economic costs (Dilsaver, 2011). The substantial phenomenological and biological heterogeneity of bipolar disorder makes diagnosis and treatment challenging. Over the past several decades, there have been important advances in the nosology of psychiatric disorders in general, and in bipolar disorder in particular (American Psychiatric Association, DSM-5 Task Force, 2013). There has also been increasing appreciation of the need for better understanding of neurobiology and the development of biomarkers (Teixeira et al., 2013). Further, researchers have sought to identify specific characteristics, such as temperament, that may mediate the putative influence of genotype on phenotypic outcome in early-onset affective disorders (Akiskal, 1995). However, symptom-based classifications of patients into more homogeneous subgroups, such as unipolar versus bipolar mood disorders, as well as bipolar I versus bipolar II disorders, have not yielded robust relationships with biological markers (Escamilla and Zavala, 2008). In contrast, onset age has been identified as a clinical marker that may define more homogenous, neurobiologically distinctive subgroups (Benazzi, 2009; Etain et al., 2012). For example, childhood-onset bipolar disorder has been associated with an increased rate of having a first-degree relative with a mood disorder in most (9/13) recent studies (Baldessarini et al., 2012; Bellivier et al., 2001, 2003; Benazzi, 2009; Hamshere et al., 2009; Leverich et al., 2007; Lin et al., 2006; Ortiz et al., 2011; Rende et al., 2007), but not in a minority (4/13) of such studies (Carter et al., 2003; Ernst and Goldberg, 2004; Javaid et al., 2011; Tozzi et al., 2011).

Juvenile onset of bipolar disorder has been associated with both diagnostic challenges and delays to appropriate treatment

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(Leverich et al., 2007). Researchers have struggled to delineate a clear clinical picture of childhood onset bipolar disorder, particularly owing to the complex contributions of temperament and age-dependent affective presentations, as well as the extensive potentially confounding influences of substance use, anxiety, and personality disorder comorbidities (Akiskal, 1998). Given the dramatic social consequences of delayed treatment in bipolar disorder, researchers have sought particularly to identify which genetic factors, environmental influences, and subtle psychopathological features may predispose individuals to the development of full-blown affective episodes (Akiskal, 1995; Akiskal et al., 1985). As such, recent studies have commonly focused upon relationships between early age at onset and multiple unfavorable illness characteristics (Jacobs et al., 2014). Significant associations were found between early-onset bipolar disorder and lifetime history of suicide attempt in twelve (Azorin et al., 2013; Bellivier et al., 2001; Carter et al., 2003; Coryell et al., 2013; Etain et al., 2012; Hamshere et al., 2009; Lin et al., 2006; Moor et al., 2012; Ortiz et al., 2011; Perlis et al., 2009; Rende et al., 2007; Tozzi et al., 2011) of fifteen (Ernst and Goldberg, 2004; Javaid et al., 2011; Manchia et al., 2008) studies, worse mood outcome in seven (Azorin et al., 2013; Baldessarini et al., 2012; Benazzi, 2009; Coryell et al., 2013; Leverich et al., 2007; Ortiz et al., 2011; Perlis et al., 2009) of seven studies, substance use disorders in ten (Azorin et al., 2013; Carter et al., 2003; Coryell et al., 2013; Ernst and Goldberg, 2004; Etain et al., 2012; Javaid et al., 2011; Leverich et al., 2007; Lin et al., 2006; Perlis et al., 2009; Rende et al., 2007) of twelve (Moor et al., 2012; Ortiz et al., 2011) studies, prior year rapid cycling in seven (Carter et al., 2003; Ernst and Goldberg, 2004; Hamshere et al., 2009; Leverich et al., 2007; Lin et al., 2006; Ortiz et al., 2011; Perlis et al., 2009) of nine (Coryell et al., 2013; Etain et al., 2012) studies, anxiety disorder in five (Azorin et al., 2013; Leverich et al., 2007; Moor et al., 2012; Ortiz et al., 2011; Perlis et al., 2009) of eight (Carter et al., 2003; Coryell et al., 2013; Etain et al., 2012) studies, and alcohol use disorder in two (Azorin et al., 2013; Lin et al., 2006) of eight (Carter et al., 2003; Coryell et al., 2013; Etain et al., 2012; Javaid et al., 2011; Leverich et al., 2007; Moor et al., 2012) studies.

In contrast to the consistency of studies finding early-onset bipolar disorder associated with higher rates of unfavorable illness characteristics, there has been substantial variation in definitions (e.g. first mood episode (Benazzi, 2009; Ernst and Goldberg, 2004; Leverich et al., 2007)) versus first reliable diagnosis (Javaid et al., 2011; Manchia et al., 2008) of early-onset. Further variability has existed in selection of boundaries between onset age subgroups. However, fifteen (Azorin et al., 2013; Baldessarini et al., 2012; Bellivier et al., 2001, 2003; Benazzi, 2009; Coryell et al., 2013; Etain et al., 2012; Hamshere et al., 2009; Lin et al., 2006; Manchia et al., 2008; Moor et al., 2012; Ortiz et al., 2011; Perlis et al., 2009; Rende et al., 2007; Tozzi et al., 2011) of nineteen (Carter et al., 2003; Ernst and Goldberg, 2004; Javaid et al., 2011; Leverich et al., 2007) studies published since 2000 with at least one finding that was replicated by a different group used three onset age groups. Most studies have used an aggregated childhood/adolescent/$\pm$early adulthood-onset definition of early-onset, with a majority of such studies using upper age bounds for early-onset ranging between 21 and 23 years (Azorin et al., 2013; Bellivier et al., 2001, 2003; Benazzi, 2009; Carter et al., 2003; Coryell et al., 2013; Ernst and Goldberg, 2004; Etain et al., 2012; Hamshere et al., 2009; Javaid et al., 2011; Lin et al., 2006; Manchia et al., 2008; Ortiz et al., 2011; Tozzi et al., 2011). In contrast, a minority of studies, mostly based in the United States, have defined separate childhood- and adolescent-onset groups, setting upper bounds for childhood-onset groups at the commencement of puberty (12–13 years of age) (Baldessarini et al., 2012; Leverich et al., 2007; Moor et al., 2012; Perlis et al., 2009; Rende et al., 2007). To date, findings of studies using aggregated childhood/adolescent/$\pm$early adulthood- compared to separate childhood- and adolescent-onset groups have largely overlapped, but no study has directly compared childhood- and adolescent-onset groups considered separately versus in aggregate.

Some investigators used developmental stages to define onset age groups, yielding separate very early- (i.e. childhood, age <13 years) and early-onset (i.e. adolescent, age 13–18 years) groups to compare to adult-onset (age >18 years) groups (Baldessarini et al., 2012; Leverich et al., 2007; Moor et al., 2012; Perlis et al., 2009; Rende et al., 2007). However, other investigators used larger single early-onset (i.e. pooled childhood/adolescent, age ≤ 18 years or ≤ 21 years) groups to compare to adult-onset (age >18 years or >21 years) groups (Coryell et al., 2013; Etain et al., 2012). Other investigators still used admixture analyses, which yielded even larger early-onset (e.g. pooled childhood/adolescent/young adult, e.g. age ≤ 23 years) groups to compare to groups of patients with yet later onset (Azorin et al., 2013; Bellivier et al., 2001, 2003; Benazzi, 2009; Carter et al., 2003; Ernst and Goldberg, 2004; Hamshere et al., 2009; Javaid et al., 2011; Lin et al., 2006; Manchia et al., 2008; Ortiz et al., 2011; Tozzi et al., 2011).

We assessed naturalistic, observational data to test the hypothesis that using childhood-onset rather than adolescent-onset or pooled childhood/adolescent-onset to define early-onset would yield more robust associations with unfavorable illness characteristics.

2. Methods

We performed a PubMed search using the keywords “bipolar disorder” AND “onset age,” “age at onset,” “childhood onset,” OR “early onset.” Studies published after 2000 reporting at least one positive association between early-onset and an unfavorable illness characteristic that was also found by at least one other study published after 2000 were included. Studies using age at first hospitalization as the definition for onset were excluded. Primary unfavorable illness characteristic measures were such characteristics related to early-onset bipolar disorder in at least two published studies.

We studied outpatients with bipolar I disorder or bipolar II disorder, referred by community practitioners (primarily psychiatrists) to the Stanford University Bipolar Disorder Clinic between 2000 and 2011. Patients were assessed with the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation, (Sachs et al., 2002, 2003) which included the Structured Clinical Interview for DSM (First, 1997) mood disorders module and the Clinical Global Impression for Bipolar Disorder-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The Stanford University Administrative Panel on Human Subjects approved the STEP-BD protocol and the similar subsequent Stanford-specific Assessment, Monitoring, and Centralized Database protocol, which were both in accordance with the Helsinki Declaration of 1975. All subjects provided both verbal and written informed consent prior to participation.

Assessment of onset age was based on patient retrospective recall of the first occurrence of a syndromal hypomanic, manic, mixed, or major depressive episode. Patients were categorized based on bipolar disorder onset age by developmental level as having childhood- (age <13 years), adolescent- (age 13–18 years), and adult- (age >18 years) onset.

For each subject, selected clinical comorbidities and other unfavorable illness characteristics were recorded. Prior severity of bipolar disorder was assessed based on self-report of having had at least 10 prior lifetime mood episodes. Current severity of bipolar disorder was assessed using CGI-BP-OS, along with current mood state. Rapid cycling in the prior year was defined as having four or more mood episodes within the prior 12 months. Family history of mood disorder was defined by patient report of having a first degree relative with a professionally diagnosed mood disorder.