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Gender by onset age interaction may characterize distinct phenotypic subgroups in bipolar patients

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ABSTRACT

Objective: Although bipolar disorder (BD) is a common recurrent condition with highly heterogeneous illness course, data are limited regarding clinical implications of interactions between gender and onset age. We assessed relationships between onset age and demographic/illness characteristics among BD patients stratified by gender.

Methods: Demographic and unfavorable illness characteristics, descriptive traits, and clinical correlates were compared in 502 patients from Stanford University BD Clinic patients enrolled in the Systematic Treatment Enhancement Program for BD between 2000 and 2011, stratified by gender, across pre-, peri-, and post-pubertal (<12, 13–16, and >17 years, respectively) onset-age subgroups.

Results: Among 502 BD patients, 58.2% were female, of whom 21.9% had pre-pubertal, 30.7% peri-pubertal, and 47.4% post-pubertal onset. Between genders, although demographics, descriptive characteristics, and most clinical correlates were statistically similar, there were distinctive onset-age related patterns of unfavorable illness characteristics. Among females, rates of 6/8 primary unfavorable illness characteristics were significantly higher in pre-pubertal and peri-pubertal compared to post-pubertal onset patients. However, among males, rates of only 3/8 unfavorable illness characteristics were significantly higher in only pre-pubertal versus post-pubertal onset patients, and none between peri-pubertal versus post-pubertal onset patients.

Limitations: Caucasian, insured, suburban, American specialty clinic-referred sample limits generalizability, onset age based on retrospective recall.

Discussion: We describe different phenotypic presentations across age at illness onset groups according to gender. Among females and males, peri-pubertal and post-pubertal onset age groups were more different and more similar, respectively. Further investigation is warranted to assess implications of gender-by-onset-age interactions to more accurately delineate distinctive BD phenotypes.

1. Background

Bipolar disorder (BD) is a severe, recurrent condition affecting a substantial percentage of individuals worldwide (Merikangas et al., 2011). Despite its considerable prevalence, uncertainty remains as to the details of how BD differs between genders (Diflorio and Jones, 2010). However, unlike the significant excess of women with unipolar mood disorders (Blehar et al., 1998), studies have found no difference in overall (considering Type I and Type II in aggregate) prevalence of BD between male and female patients (Burt and Rasgon, 2004; Kawa et al., 2005).

Nevertheless, a similar overall prevalence of BD by gender does not preclude there being important clinical distinctions between male and female bipolar patients. Indeed, differential patterns of clinical characteristics have been consistently noted between male and female BD patients. Specifically, the course of the disorder itself appears to differ, with women exhibiting longer (Barrett et al., 2008) and more frequent (Diflorio and Jones, 2010; Saunders et al., 2014) depressive episodes, as well as more mixed mania and hypomania (Suppes et al., 2005), antidepressant induced mania (Burt and Rasgon, 2004), rapid cycling (Arnold, 2003), predominant episode depressive polarity (Nivoli et al., 2011), higher rates of lifetime comorbid eating (McElroy et al., 2011), anxiety disorders (Arnold, 2003), sleep disturbances (Kawa et al., 2005),

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migraines (Saunders et al., 2014), and thyroid disease (Marangell, 2008). Investigators have found gender differences in the presentation of neuropsychological disturbances, including executive function (Barrett et al., 2008) and simple working memory during both periods of affective dysregulation and euthymia (Suwalska and Lojko, 2014). In contrast, data are equivocal regarding gender differences across bipolar subtypes (Diflorio and Jones, 2010).

Further, men with BD tend toward presentation of predominantly manic polarity (Barrett et al., 2008), and higher rates of lifetime alcohol (Nivoli et al., 2011) and substance (Arnold, 2003; Hendrick et al., 2000) use disorders and behavioral and legal problems (Baldassano et al., 2005; Kawa et al., 2005). There may also be social implications of gender differences; one group found less cumulative severity and number of episodes in ever-married versus never-married women but not men, suggesting that among BD patients, men may be less sensitive to the positive effects of social support than women (Lieberman et al., 2010).

Age at onset, however, has had conflicting gender-related findings (Kennedy et al., 2005), with studies both supporting (Arnold, 2003; Kennedy et al., 2005) and rejecting (Hendrick et al., 2000) gender-related onset age differences. Onset age has been proposed as a means of dividing heterogeneous BD presentations into clinical subgroups with more homogenous clinical features, suggesting that further study into a gender by onset age interaction is warranted (Holtzman et al., 2015; Strober, 1992). Specifically, early onset BD has been shown to predict more unfavorable illness characteristics, including worse illness course (Geoffroy et al., 2013; Leboyer et al., 2005; Leverich et al., 2007). There has been significant discussion of the inadequate exploration of the implications of the female gender on treatment and the clinical course in bipolar disorder (Burt and Rasgon, 2004). As such, we investigated the putative gender by onset age interaction in order to identify more valid and robust markers for distinct clinical phenotypes in BD, and to explore more profoundly the differential illness presentation of women, particularly in a subset of bipolar patients suggested to have a worse illness course.

2. Methods

Subjects were referred by community practitioners (primarily psychiatrists) to the Stanford University Bipolar Disorder Clinic between 2000 and 2011. Further description of recruitment methods, inclusion/exclusion criteria (Perlis et al., 2004), and categorical unfavorable illness characteristic selection are described elsewhere (Holtzman et al., 2015). Outpatients with bipolar I disorder or bipolar II disorder were assessed using the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) Affective Disorders Evaluation (Sachs et al., 2002, 2003). These assessments included the Structured Clinical Interview for the fourth edition of the Diagnostic and Statistical Manual of mental disorders (DSM-IV) (First, 1997) mood disorders module and the Clinical Global Impression for Bipolar Disorder-Overall Severity (CGI-BP-OS) score (Spearing et al., 1997). The STEP-BD and subsequent Stanford-specific Assessment, Monitoring, and Centralized Database protocols were both approved by the Stanford University Administrative Panel on Human Subjects. Prior to participation in the study, all subjects provided both verbal and written informed consent.

Determination of onset age relied upon patient retrospective recall of the first occurrence of a syndromal hypomanic, manic, mixed, or major depressive episode according to DSM-IV. Patients were assigned one of three mutually exclusive categories based on BD onset age: pre-pubertal- (age $\leq$12 years), peri-pubertal- (age 13–16 years), and post-pubertal- (age $\geq$17 years) onset. Definitions based upon presumptive pubertal stage were thought to demonstrate validity in the gender-stratified context (Development, 2013). All patients were evaluated for the presence of the following 8 unfavorable illness characteristics which fall into 4 categories: presence of comorbid psychiatric illness (anxiety disorder, alcohol use disorder, substance use disorder, eating disorder); family history (history of anxiety disorder, first degree relative with a mood disorder); course of illness (greater than 9 lifetime mood episodes, rapid cycling in the prior year); history of alcohol use disorder; history of substance use disorder; and severity of illness (history of suicide attempt, rapid cycling in the prior year, and history of an eating disorder). These unfavorable illness characteristics were chosen on the basis of a previous literature review of studies that found a positive association between unfavorable illness characteristics and early onset bipolar disorder, described in more detail elsewhere.

Other descriptive characteristics (onset age, illness duration, CGI-BP-OS [a measure of illness severity]) and clinical correlates (history of psychosis, history of psychiatric hospitalization, number of psychotropic medications, no psychotropic medications, antidepressant use, and complex pharmacotherapy (Goldberg et al., 2009) were assessed to further characterize the previously delineated subgroups. Retrospective recall of experiencing at least 10 prior lifetime mood episodes was used as a measure of past illness course severity. Family history was defined as having a first-degree relative with a history of reliably diagnosed mood disorder, and prior year rapid cycling as having four or more mood episodes within the prior 12 months.

Statistical analyses were performed using R software Version 3.0.1 (R Foundation, Vienna, Austria) on an Apple MacBook Air computer (Apple Corporation, Cupertino, CA) and included unpaired t-test comparisons for continuous variables and Chi-Square test comparisons for categorical variables. Analyses primarily included the assessment of relationships between developmental stage and unfavorable illness characteristics that were determined in a prior publication, both with combined genders and, as our primary analysis, stratified by gender (Holtzman et al., 2015), as well as other descriptive characteristics and clinical correlates. The significance of differences in demographic, descriptive characteristics, clinical correlates, and unfavorable illness characteristics were also measured across genders with aggregated developmental stages. Logistic regression analyses were used to assess roles of demographic parameters with significant relationships with onset age that could mediate observed relationships between onset age and illness characteristics. A two-tailed significance level was used with $p < 0.05$, not adjusted for multiple comparisons. We additionally used admixture analysis to depict the distribution of onset subgroups, using a tri-modal, early-intermediate-late model for the genders in aggregate and separately (Goodwin et al., 2007).

Finally, a finite mixture model with normal components (admixture analysis) and maximum likelihood estimation was used to fit theoretical age at onset distributions to the male and female specific strata, as described elsewhere (Bellivier et al., 2001; Manchia et al., 2008). For the admixture analysis, in both the female and male specific strata, we imposed the constraint that the resulting theoretical model must divide the observed distribution of onset age into three normal distributions, in accordance with the previously described onset age distribution within our sample (Holtzman et al., 2015).

3. Results

Data were collected for a total of 502 BD patients, of whom 51.8% had bipolar II disorder, 58.3% were female, and 80.0% Caucasian, with a mean onset age of 17.9 ($\pm$8.4) years. Dividing patients into