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Does age at onset have clinical significance in older adults with bipolar disorder?

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Abstract

Objective—While age at onset may be useful in explaining some of the heterogeneity of bipolar disorder (BD) in large, mixed age groups, investigations to date have found few meaningful clinical differences between early *versus* late age at onset in older adults with BD.

Methods—Data were collected from sixty-one subjects aged 60 years and older, mean (SD) age 67.6 (7.0), with BD I (75%) and II (25%). Subjects were grouped by early (<40 years; *n*=43) *versus* late (≥40 years; *n*=18) age at onset. Early *versus* late onset groups were compared on psychiatric comorbidity, medical burden, and percentage of days well during study participation.

Results—Except for family history of major psychiatric illnesses, there were no differences between the groups on demographic or clinical variables. Patients with early and late onset experienced similar percentages of days well; however, those with early onset had slightly more percentage of days depressed than those with late onset (22% *versus* 13%)

Conclusion—Distinguishing older adults with BD by early or late age at onset has limited clinical usefulness.

Keywords

bipolar disorder; age at onset; elderly

Introduction

Although a number of investigators have suggested that age at illness onset may be useful in explaining the heterogeneity of bipolar disorder (BD) pathogenesis, phenotype, or treatment response in large, mixed age groups (Leboyer *et al.*, 2005), investigations to date have found few meaningful *clinical* differences between early *versus* late age at onset in older-adults with BD (Broadhead and Jacoby, 1990; Wylie *et al.*, 1999; Depp *et al.*, 2004). Except for

reduced overall psychopathology in those with late-onset, Depp and colleagues (Depp *et al.*, 2004) identified no significant differences on demographic variables, family history, number of medical diagnoses, or presence of psychosis or substance use disorders in 87 community-dwelling patients with BD 40 years and older. Further, two studies examined the effects of age at onset in treatment outcomes of elderly inpatients with BD (Broadhead and Jacoby, 1990; Wylie *et al.*, 1999). Broadhead and Jacoby (Broadhead and Jacoby, 1990) found that early and late onset patients were clinically indistinguishable, except that the early onset patients experienced more severe illnesses than those with late onset and that late onset had a more fragile recovery. In contrast, Wylie and colleagues (Wylie *et al.*, 1999) found that patients with late-onset BD were more likely to have psychotic features (73.3% *versus* 43.8%), yet they experienced faster symptom improvement than the early onset group. Since studies of late-life BD have mainly focused on hospitalized inpatients (Depp and Jeste, 2004), samples biased to the more severe illness presentation may be blurring meaningful distinctions between early and late onset BD in *elderly outpatients*.

As well noted, the variable definition of age at onset for BD has been problematic for geriatric psychiatry. Every decade from the 20s to the 60s has been used as the dividing line for early *versus* late onset (Wylie *et al.*, 1999; Leboyer *et al.*, 2005; Goodwin and Jamison, 2007). Through admixture analysis of ages of onset, Bellivier and colleagues (Bellivier *et al.*, 2001) identified three distinct sub-groups of early, intermediate, and late-onset, peaking at 17, 27, and 46 years. These results were replicated in an independent sample of 368 BD I patients, in which identical mean ages at onset were identified (Bellivier *et al.*, 2003). A separate group identified three ages at onset, peaking at 18.1, 24.3, and 41 years in a sample of Sardinians with BD I (Manchia *et al.*, 2008). Hence, there is support for distinguishing sub-groups of patients with BD based on early *versus* late age at onset. However, it is unclear whether onset age is useful in distinguishing sub-groups of patients in clinical samples of older adults.

Our goal in this analysis was to extend previous analyses of onset age in BD to a well-characterized group of elderly outpatients. To do so, we examined various factors, including demographics, psychopathology, and treatment response to determine whether classifying older adults with BD by age at onset revealed any meaningful differences between the two groups. Our study was exploratory, primarily examining the effects of age at onset in BD on medical comorbidity, treatment response, and study outcome.

Methods

Subjects

As elsewhere reported (Fagiolini *et al.*, 2009), the Bipolar Disorder Center for Pennsylvanians (BDCCP) Study was a multi-center randomized controlled study involving subjects with BD. This study was designed to test the efficacy of an Enhanced Clinical Intervention (ECI), a psycho-educational intervention. All subjects received a standardized, well-accepted drug regimen and were randomized to receive ECI or usual supportive care. Inclusion criteria were: age 12 years or older with a DSM-IV diagnosis of BD I, BD II, BD not otherwise specified (NOS), or schizoaffective disorder bipolar subtype. Exclusion criteria were: IQ $\leq$ 70, current substance or alcohol dependence, organic mental disorder, and unstable or severe medical illness or other medical contraindication to treatment with mood stabilizers, antidepressants, or antipsychotic medications, including pregnancy or breast-feeding. The present analysis includes 61 subjects, ages 60 years and older, with BD I ($n=43$) and II ($n=18$) confirmed through a research diagnostic interview using the Structured Clinical Interview for DSM-IV (SCID) (First *et al.*, 2002). They were recruited from academic and community based practices between November 2003 and July 2005. Special efforts were made to recruit African-Americans.

All subjects provided written informed-consent, approved by the Institutional Review Board at the University of Pittsburgh, in accordance with the Helsinki Declaration of 1975. Seventy-seven subjects were screened for study participation. Six subjects did not participate because of (1) dementia ($n=2$), (2) inconvenience of study procedures ($n=2$), or (3) being too physically ill to participate ($n=1$), and (4) death ($n=1$). Ten subjects had missing data that could not be retrieved regarding medical illness burden ($n=8$) and age at onset ($n=2$). One subject entered the study, but did not receive treatment, so there was no information on outcome. Subjects were not required to have acute psychiatric illness to enter the study; most subjects entered the protocol euthymic or with mild depressive symptoms. Roughly 80% of the subjects were referred by mental health providers for research participation.

Measures

At baseline, a complete assessment of mood state, comorbid psychiatric disorders, treatment, social and role function, and care utilization was conducted (Fagiolini *et al.*, 2009). Related to this report, we measured (baseline) medical illness burden using the Cumulative Illness Rating Scale, modified for geriatric patients (CIRS-G) (Miller *et al.*, 1992). At study entry and over longitudinal follow-up, we assessed mood symptoms with the clinical global improvement (CGI) scale, as operationalized for BD (Spearing *et al.*, 1997). Euthymic subjects were seen at least every other month while participating in treatment. Symptomatic subjects were seen as often as weekly based on the clinical judgment of the study psychiatrist. Age at onset was defined as age of first mood episode (depressive, manic, hypo-manic, or mixed). Lifetime duration of illness was defined as age at onset subtracted from current age.

Statistical analyses

Corresponding with prior reports (Wylie *et al.*, 1999; Depp *et al.*, 2004), we divided early *versus* late age at onset at 40 years. This decision was supported by examining the entire group of BDCP subjects with information on age at onset, including adolescent and middle-aged participants ($n=308$), which showed two peaks of onset, one in late teens/early 20s and another in early 40s (Data available upon request). Early *versus* late age of onset subjects were compared with χ^2 -test for categorical measures, group *t*-tests for continuous measures, and Spearman correlations for associations. Linear regression and smoothing splines were used to characterize medical burden according to age, duration of illness, and age of onset. 'Days well' was defined with cut-off score of ≤ 2 or less CGI scale. Number of days well was calculated by adding up the number of days between consecutive CGI scores of 1 or 2. In the case of subjects, switching states between consecutive visits, with one score being higher than 2, then half of the days were added to each state. Days depressed was defined with cut-off score of ≥ 3 on the CGI depression scale and < 2 or less CGI mania scale. Days manic was defined with cut-off score of > 3 on CGI mania and depression scales. All available CGI scores for each subject were used for this report, up until time of study termination. Percentages of days well, depressed, and manic were calculated by number of days in that state divided by number of days in study. No imputation was performed for missing data.

Results

Demographic and clinical characteristics of the subjects are presented in Table 1. The distribution of age of onset of the sample is presented in Figure 1. The mean (SD) age of the full sample was 67.6 (7.0) years. Onset of first mood episode and family history of psychiatric illness differed significantly between the groups. There were no differences in overall medical burden, number of organ systems affected, or burden within a specific organ

system between early or late onset. In a regression model, neither age of onset nor lifetime duration of BD was found to be related to percentage of days well ($F=0.03$, $df=258$, $p=0.96$).

While patients with early and late onset experienced similar percentage of days well, those with early onset experienced more days depressed (22%; $SD=20$) than those with late onset (13%; $SD=25$) ($\chi^2=5.25$, $df=1$, $p=0.022$). There was a trend to greater study completion in those with later onset (89% *versus* 65%; $\chi^2=3.57$, $df=1$, $p=0.059$); however, numbers of hospitalizations for psychiatric or general medical reasons during longitudinal follow-up were not statistically different between the two groups. Reasons for premature termination in the early onset group were: refusal/inconvenience of study procedures (8), relocation (3), medical problems (2), increased level of care (2), and change in diagnosis (1). Reasons for premature termination in the late onset group were: non-response to treatment (1) and relocation (1).

We repeated the analyses of medical burden and percentage of days well using cutoffs for early *versus* late onset at ages 20 and 30. We found no significant differences between early *versus* late onset using the younger ages of onset for medical burden or percentage of days well.

Discussion

Despite the compelling arguments of using age at onset to identify more homogeneous groups of individuals with BD, we found few meaningful clinical differences distinguishing older adults with BD classified based on age at onset. While older adults with BD experienced roughly the same percentage of 'days well' regardless of early *versus* late onset, those with early onset experienced slightly more depressed days than those with late onset. Our results confirm, in a clinical outpatient sample of elderly adults with BD, the findings of previous reports (Broadhead and Jacoby, 1990; Wylie *et al.*, 1999; Depp *et al.*, 2004). Those reports and ours suggest that busy clinicians with limited time and resources will not find age at onset generally helpful in the clinical management of their patients with BD.

Our finding of different rates of family history of major psychiatric disorder in those with early *versus* late onset BD is congruent with a similar finding in particular with major depressive disorder (Nierenberg *et al.*, 2007). Nierenberg and colleagues identified positive family history of mood disorders associated with younger age of onset probands with major depressive disorder and twice as frequent among women compared with men, but not associated with a distinct and homogenous phenotype. Further, they did not find any substantial differences between those with and without a reported family history of mood disorders in terms of severity of depression, specific depressive symptoms or subtypes, comorbid conditions, functioning, or course (recurrences). Similar to their report, even though a few variables achieved statistical significance, these differences were not of clinical significance.

Limitations to our findings need to be considered. First, this is a mostly 'negative' study with a small sample size. We acknowledge that there may be subtle clinical differences in subgroups of patients with BD based on age at onset that may become apparent in much larger samples. Second, the accuracy of age at onset may have been influenced by the reliability or availability of patients, family, or medical records. Third, the finding in our research subjects may not generalize to patients seen outside of an academic medical center. As we indicate in our methods, we attempted to recruit subjects with BD broadly representative of the greater Pittsburgh metropolitan area. Given the low percentage of Latinos in Western Pennsylvania, we were not able to recruit significant numbers of Latinos. Special efforts were made to recruit African American subjects; however, the 7%

representation of African Americans is lower than the 13.2% African American population in Allegheny County (<http://quickfacts.census.gov/qfd/states/42/42003.html>). The under-representation of African-Americans might well be explained by differences in access to and seeking of care, or diagnostic biases toward psychotic disorder (Depp and Jeste, 2004). Whether there is differential mortality in African American (or Latino) elders with BD is an intriguing question that has not been examined to our knowledge.

Recent reports have identified clinical differences in early *versus* later age at onset in middle aged adults with BD. Perlis and colleagues (Perlis *et al.*, 2009) found that compared with patients with onset of mood symptoms after age 18 years ($n=1187$), those with onset before age 13 ($n=1068$) experienced earlier recurrence of mood episodes after initial remission, fewer days euthymic, and greater impairment in function and quality of life over two-year follow-up. Penttilä and colleagues (Penttilä *et al.*, 2009) found differences in MRI measures of cortical folding among those with onset before the age of 25 years ($n=22$) *versus* those with onset between age 25 and 45 years ($n=14$) ('intermediate onset'). Those with intermediate onset had significantly reduced sulcal index in the right dorsolateral prefrontal cortex in comparison to both early-onset BD patients and healthy subjects, and lower global sulcal indices in both hemispheres in comparison to healthy subjects. These clinical differences based on age at onset detected in middle-aged adults with BD, not evident in our older sample, may be partly explained by differential mortality ('survivor effects').

'Survivor effects' may render an older group of patients with BD more homogeneous than younger and middle-age groups. More severely ill patients with BD likely have died before achieving old age because of suicide or medical comorbidity. While it may be the case that the more virulent cases of BD arise in early age, those with early onset who achieve old age represent more resilient members of the cohort. Additionally, more virulent late-onset cases may be associated with accelerated rates of mortality. Hence, older adults with BD likely represent more resilient individuals, regardless of age at onset.

Age of onset may prove more fruitful to examine young and middle-aged adults with BD rather than older adults. Based on the collection of 'negative' reports in older adults, it is difficult to argue for additional studies in old age. Age of onset may be more significant in late-life depression because it distinguishes etiologically different pathways to depression (Alexopoulos, 2003), while BD represents a more genetically/biologically-based illness that is more narrowly determined (Schloesser *et al.*, 2008). Over the past decade, the age of onset distinction has lost currency among investigators in the field of geriatric psychiatry in favor of a more pathologically based understanding (Alexopoulos, 2006).

Noting the limitations above, we believe that our report is an important addition to the literature in late-life BD. Our study possesses a number of methodological strengths, including the use of a relatively large sample, a cohort of patients all over the age of 60 years, and two-year longitudinal follow-up of treatment response. Based on our findings and those of prior reports, we argue that in contrast to other clinical variables associated with late-life mood disorders, such as comorbid anxiety and severity of depression (Whyte *et al.*, 2004; Gildengers *et al.*, 2006; Andreescu *et al.*, 2008), distinguishing older adults with BD by late or early age at onset appears to have limited clinical utility.

Key points

- In elderly adults with bipolar disorder, distinguishing between early and late onset does not identify clinically significantly different subgroups in terms of medical comorbidity, treatment response, or study outcome.

- Older adults with bipolar disorder experienced roughly the same percentage of “days well” regardless of early versus late onset.
- Those with early onset bipolar disorder experienced slightly more depressed days than those with late onset.

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Figure 1.
Distribution of ages at onset in subjects with BD.

Table 1

Demographic and clinical characteristics of subjects with bipolar disorder

	Age onset <40 n=43	Age onset ≥40 n=18	χ^2 or t Statistic (df)	p
Age (years)	66.6 (6.4)	70.0 (8.0)	1.73 (59)	0.088
Men (%)	33%	39%	0.23 (1)	0.64
Caucasian (%)	93%	88%	0.37 (1)	0.55
African American (%)	5%	12%		
Bipolar I (%)	81%	61%	2.82 (1)	0.093
Bipolar II (%)	19%	39%		
Age onset (years)	24.0 (7.8)	49.9 (7.4)	N/A	N/A
Lifetime duration illness (years)	42.7 (9.8)	20.0 (10.7)	N/A	N/A
Family history of psychiatric illness (unipolar and bipolar mood disorders, psychotic disorders, and anxiety disorders)	n=42 74%	n=17 47%	2.86 (1)	0.04
Family history of bipolar disorder	36%	18%	1.86 (1)	0.17
Anxiety disorder (%)	47%	22%	3.14 (1)	0.077
Substance abuse (%)	40%	17%	3.01 (1)	0.083
Suicide attempt (%)	28%	24%	0.10 (1)	0.76
Prior psychiatric hospitalization (%)	21%	6%	2.19 (1)	0.14
CIRS-G Total	8.9 (3.8)	7.9 (4.1)	0.88 (59)	0.38
CIRS-G Count	5.7 (2.0)	4.7 (2.0)	1.67 (59)	0.10
Prior medical hospitalization (%)	40%	44%	0.13 (1)	0.72
Folstein mini-mental state exam mean (SD)	n=30 28.3 (1.7)	n=11 28.5 (1.5)	0.43 (39)	0.67
Outcome path				
Length of follow-up (days) mean (SD)	592 (202)	613 (203)	0.49 (1)	0.481
Completed study (%)	65%	89%	3.57 (1)	0.059
Days well mean (%) (SD)	77% (20)	82% (27)	2.86 (1)	0.091
Days depressed mean (%) (SD)	22% (20)	13% (25)	5.25 (1)	0.022
Days manic mean (%) (SD)	6% (16)	1% (4)	2.74 (1)	0.098
Psychiatric hospitalizations # (%)	9 (14.7%)	1 (1.6%)	Fisher's Exact	0.255
Medical hospitalizations # (%)	17 (27%)	8 (13%)	Fisher's Exact	0.779