Journal of Psychiatric Research 44 (2010) 1170–1175

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Association between age of onset and mood in bipolar disorder: Comparison of subgroups identified by cluster analysis and clinical observation

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ARTICLE INFO

Article history:
Received 6 January 2010
Received in revised form
29 March 2010
Accepted 7 April 2010

Keywords:
Bipolar disorder
Age of onset

ABSTRACT

Background: This study compared subgroups identified by cluster analysis and clinical observation by evaluating the association between the age of onset of bipolar disorder and self-reported daily mood ratings.

Methods: Two hundred and seventy patients with bipolar disorder provided daily self-reported mood ratings for about 6 months returning 55,188 days of data. The age of onset subgroups were determined both using previously defined cutoff values based upon clinical observation ($\leq$12 years, 13–19 years, 20–29 years, >29 years), and model-based cluster analysis. Demographic characteristics were compared in the age of onset subgroups. Univariate general linear models with age of onset subgroups and other demographic variables as fixed factors and covariates were used to analyze the percent of days depressed, euthymic and hypomanic/manic.

Results: Using the predetermined subgroups, demographic differences were found between the four subgroups in the diagnosis of bipolar I/II, years of illness, age and use of lamotrigine. Post-hoc pairwise comparison found that patients with an age of onset less $\leq$ 12 years spent more days hypomanic/manic: 16.4 percent versus 8.0 for patients with an age of onset between 13 and 19 years ($p = 0.006$) and 8.2 percent for patients with an age of onset between 20 and 29 years ($p = 0.031$). The majority of the additional days of hypomania/mania occurred outside of an episode. Model-based cluster analysis found a mixture of 2 distributions of onset with peaks at age 15.1 years (SD = 4.7) and 27.5 years (SD = 10.2). Analysis of these two subgroups detected no significant differences in demographic characteristics or mood ratings.

Conclusion: Age of onset subgroups arising from clinical observation may be more useful than those determined by cluster analysis.

1. Introduction

There is considerable variation in the presentation, clinical course, and outcome in bipolar disorder. The age of onset of bipolar disorder shows familial aggregation and may help to distinguish homogeneous phenotypes to better explain this complexity (Kassem et al., 2006; Leboyer et al., 2005; Lin et al., 2006). Patients with an early age of onset have a stronger family history and a poorer clinical course (Geller et al., 2002; Leverich et al., 2007; Perlis et al., 2004, 2009; Schürhoff et al., 2000; Strober et al., 1988; Winokur and Kadrmas, 1989) and may be more likely to develop comorbidities including anxiety disorders, substance abuse and Axis II disorders (Carter et al., 2003; Goldberg and Garno, 2009; Goldstein and Levitt, 2006). An early age of onset may also be a useful diagnostic criterion to distinguish bipolar spectrum disorders from unipolar depression (Benazzi and Akiskal, 2008).

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doi:10.1016/j.jpsychires.2010.04.009

While most of the published results were obtained by comparing characteristics among age of onset subgroups, varying criteria were used to group the data.

Two general approaches have been utilized to identify subgroups based on the age of onset. Some researchers use clustering methodology, an analytical technique to determine the optimal number of distinct subgroups for a continuous variable in a sample, in this case the age of onset (Bellivier et al., 2001; Hamshere et al., 2009; Lin et al., 2006). Other researchers categorize data using predetermined cutoff values that arose from clinical observation (Leboyer et al., 2005; Leverich et al., 2007; Perlis et al., 2004; Post et al., 2008). The aim of this study was to analyze one dataset using both approaches to group the data. To compare the results using subgroups identified by model-based clustering and predetermined cutoff values, this study evaluated the association between the age of onset and daily self-reported mood ratings in patients with bipolar disorder.

2. Methods

2.1. Participants and data collection

Data were obtained from adult outpatients in the US with a DSM-IV diagnosis of bipolar disorder who volunteered and provided informed written consent. All patients received treatment as usual throughout the study, and were willing to self-report mood and sleep daily for at least 5 months. The diagnosis was made in a clinical interview by the prescribing psychiatrist. The naturalistic design with minimal exclusion criteria was selected to better reflect routine clinical practice and patient variability.

Patients recorded mood daily using the previously validated ChronoRecord software on a home computer (Bauer et al., 2004, 2008), as detailed elsewhere (Bauer et al., 2004, 2009). ChronoRecord includes a 100-unit visual analogue scale to rate mood between the most extreme mania and depression the patient ever experienced. Based upon the validation studies comparing the self-ratings with clinician ratings on the Hamilton Depression Rating Scale (HAMD) and the Young Mania Rating Scale (YMRS) (Bauer et al., 2004, 2008), a mood entry less than 40 was considered depression, 40–60 euthymia, and greater than 60 hypomania/mania. The self-ratings of mania reflect activation levels for either euphoric or dysphoric mood (Bauer et al., 2004).

The age of onset was defined as the self-reported patient's perception of when they experienced their first episode of depression, mania or hypomania.

2.2. Age of onset subgroups

Two methods were used to define subgroups in the sample based on the age of onset. The first method was model-based cluster analysis, which uses a statistical probability model to determine both the number and composition of the clusters (Fraley and Raftery, 1998, 2002). In contrast, traditional cluster analysis is based on heuristic techniques such as hierarchical or relocation algorithms (Fraley and Raftery, 1998, 2002). Model-based clustering assumes the sample is a mixture of one or more normal distributions and does not specify in advance the number of distributions, nor the shape, volume or orientation of the distributions (Fraley and Raftery, 1998, 2002, 2006). The best fitting model and number of clusters are selected using the Bayesian Information Criteria (BIC), with the model with the smallest BIC being optimal. MCLUST 3.3.1 for R 2.9.1 software (Fraley and Raftery, 2006) was used for all model calculations.

The second method created four predetermined age of onset subgroups as defined by prior clinical research: ≤12 years, between 13 and 18 years, between 19 and 29 years, and ≥30 years (Leverich et al., 2007; Post et al., 2008). This clinical criterion has been used in several recent studies (Larsson et al., 2009; Oedegaard et al., 2009).

2.3. Statistics

For each patient, the percent of days with hypomania/mania, depression and euthymia and the percent of days with missing mood data were determined. Episodes of hypomania, mania and depression were determined for each patient based on the DSM-IV length criteria, using a published algorithm to calculate episodes from daily self-reported mood data (Denicoff et al., 1997). To be considered using a medication, a patient had to take any dose of the drug for at least 50% of the days. The Pearson χ^2 test was used to compare categorical demographic variables and medications taken using the age of onset subgroups determined both by model-based cluster analysis and from the predetermined cutoff values. A univariate general linear model (GLM) was used to compare all continuous demographic variables with each type of age of onset subgroups as a fixed factor. Continuous demographic variables that showed a statistically significant ($p < 0.05$) difference among the subgroups were analyzed for collinearity using a correlation analysis. If continuous variables were significantly correlated, a single representative variable was chosen for inclusion in the model.Univariate GLMs with each type of age of onset subgroups as a fixed factor were used to estimate the percent of days in episodes, the mean percent of days with hypomania/mania, depression and euthymia, and the mean percent of days with missing mood data. For the age of onset subgroup to be significant in any GLM estimation, both the corrected model F-statistic and the pairwise age of onset subgroup *t*-statistic had to be significant at the 0.05 level. The Sidak method was then used to adjust significance levels for multiple comparisons for all pairwise age of onset subgroup *t*-statistics. SPSS version 17.0 was used for all calculations.

3. Results

Data was available from 292 patients but the age of onset was missing for 22 who were excluded from the analysis. The remaining 270 patients returned 55,188 days of data (mean 189, SD = 130). The 270 patients spent 67.2% of days euthymic, 23.0% of days depressed, and 9.8% of days hypomanic/manic.

3.1. Age of onset subgroups

Using the model-based cluster analysis, the best fitting model consisted of two normal distributions with unequal variance. The first subgroup had a mean age of onset of 15.1 years (SD = 4.7) and included 184 patients (68.1%), and the second subgroup had a mean age of onset of 27.5 years (SD = 10.2) and included 86 people (31.9%). Using the four predetermined age of onset subgroups, there were 52 patients (19.3%) with an age of onset ≤ 12 years, 105 patients (38.9%) with an age of onset between 13 and 19 years, 66 patients (24.4%) with an age of onset between 20 and 29 years, and 47 patients (17.4%) with an age of onset ≥ 30 years. See Fig. 1.

3.2. Demographic differences

No significant differences in the distribution of any demographic variables or medication use were found using the two age of onset subgroups determined by model-based clustering. In contrast, significant differences in the distribution of demographic variables and medication use were found using the four predetermined age of onset subgroups, as shown in Table 1. There was a significant

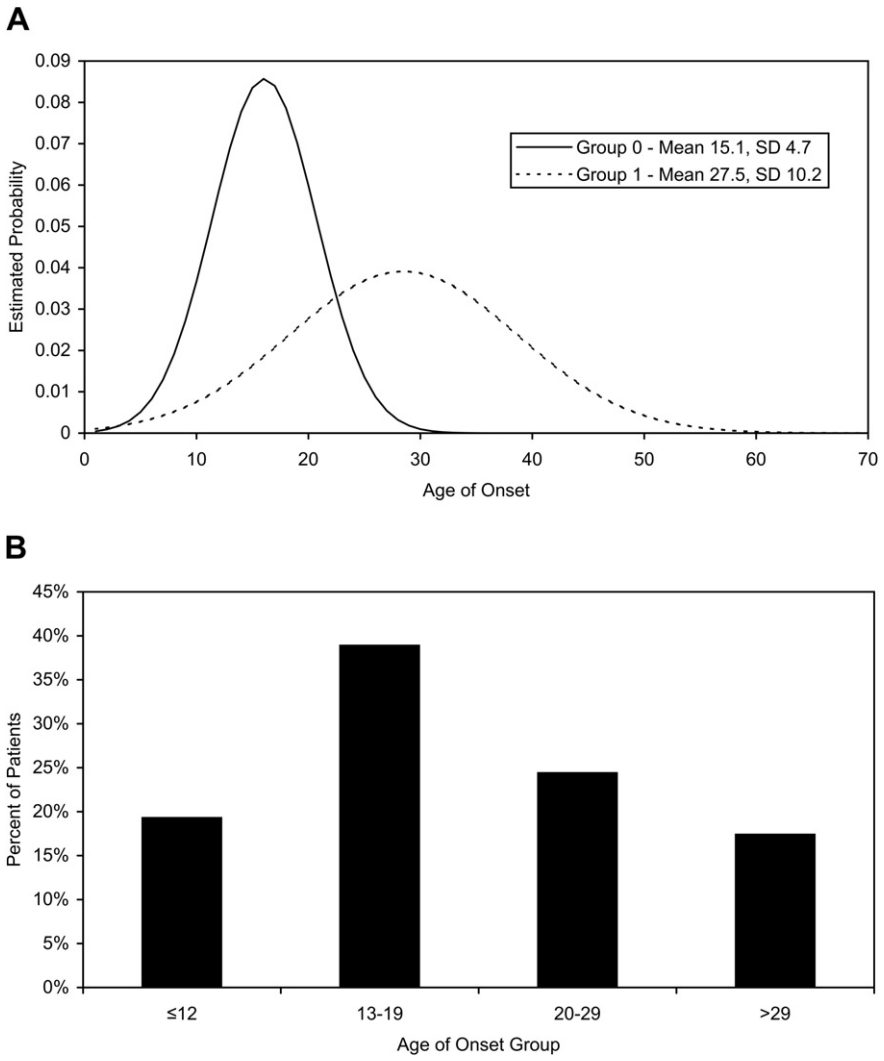

Fig. 1. A) Theoretical distribution of age of onset based on model-based cluster analysis. (B) Distribution of age of onset based on predetermined clinical subgroups.

difference among the subgroups in the diagnosis of bipolar I/II, years of illness, age, and taking lamotrigine. Correlation analysis showed that age was significantly correlated with years of illness ($r = 0.618$, $p < 0.01$). Considering the medications taken for at least 50% of study days, there was no significance difference among the subgroups in the use of lithium, valproate, benzodiazepines, any antidepressant, any antipsychotic, carbamazepine or sleep medications.

The model used to analyze the percent of days in episodes and percent of days with hypomania/mania, depression or euthymia included age of onset subgroup, diagnosis, taking lamotrigine, and gender as fixed factors, and years of illness as a covariate. Gender was included *a priori* due to differences noted in prior research (Kennedy et al., 2005; Robb et al., 1998; Viguera et al., 2001). This same model was used with age of onset subgroups determined both by model-based cluster analysis and from the predetermined cutoff values.

For all 270 patients, the mean percent of days with missing mood data was 7.1%, equivalent to missing 13 days over 6 months. There was no significant difference in the mean percent of missing data by age of onset subgroup ($p = 0.526$ using the four predetermined subgroups).

3.3. Association with mood

There were no significant differences between the two subgroups from the model-based cluster analysis in the mean percent of days depressed, euthymic or hypomanic/manic or in any episode. Using the four predetermined subgroups, although there were no significant differences in the mean percent of days depressed, euthymic or in any episode, there was a significant difference in the mean percent of days hypomanic/manic, and the percent of days hypomanic/manic outside of an episode. The results from the pairwise comparisons are shown in Table 2. Considering all days of hypomania/mania, patients with an age of onset of $\leq$12 years experienced 8.4% more symptomatic days than those with an age of onset between 13 and 19 years, 8.2% more symptomatic days than those with an age of onset between 20 and 29 years, and 5.9% more days than those with an age of onset $>$29 years. Considering days of hypomania/mania that were outside of an episode, patients with an age of onset of $\leq$12 years experienced 9.2% more symptomatic days than those with an onset between 13 and 19 years, 9.3% more symptomatic days than those with an age of onset between 20 and 29 years, and 5.2% more days than those with an age of onset $>$29 years.

4. Discussion

In this study, the predetermined age of onset subgroups based on clinical observation were more useful than the subgroups derived from model-based clustering. No differences in mood were

Table 1
Patient demographics and significantly different medications[a] by predetermined age of onset subgroups ($n = 270$).

		Age of onset subgroup									Test	df	p
		≤12		13–19		20–29		>29		Total			
		n	%	n	%	n	%	n	%	N			
Gender	Male	6	12	27	26	19	29	13	28	65	$X^2 = 5.758$	3	0.124
	Female	46	88	78	74	47	71	34	72	205			
Bipolar I	Yes	25	48	56	53	48	73	32	68	177	$X^2 = 10.711$	3	0.013
	No	27	52	49	47	18	27	15	32	93			
Married	Yes	26	50	44	45	22	34	25	56	117	$X^2 = 5.464$	3	0.141
	No	26	50	54	55	42	66	20	44	142			
Working full time	Yes	23	48	55	53	33	51	14	30	125	$X^2 = 7.404$	3	0.060
	No	25	52	49	47	32	49	33	70	139			
Any college	Yes	45	88	99	94	60	92	40	85	244	$X^2 = 4.006$	3	0.261
	No	6	12	6	6	5	8	7	15	24			
Days of data		187 SD = 108		176 SD = 107		225 SD = 159		202 SD = 139			$F = 0.348$	3266	0.790
Age		35 SD = 12.8		35 SD = 10.1		37 SD = 8.4		47 SD = 8.3			$F = 17.805$	3266	<0.001
Years of illness		26 SD = 13.4		19 SD = 10.0		14 SD = 9.3		10 SD = 8.1			$F = 23.336$	3266	<0.001
Daily medication count		2.5 SD = 1.4		2.9 SD = 1.6		2.7 SD = 1.5		3.4 SD = 1.4			$F = 3.233$	3266	0.023
Significantly different medications													
Oxcarbazepine	Yes	9	17	8	8	12	18	14	30	43	$X^2 = 12.481$	3	0.006
	No	43	83	97	92	54	82	33	70	227			
Lamotrigine	Yes	20	39	46	44	30	46	9	19	105	$X^2 = 9.977$	3	0.019
	No	32	61	59	56	36	54	38	81	165			

[a] Taking any dosage of the medication for ≥ 50% of days.

detected using the subgroups derived from clustering methodology. In contrast, using the predetermined subgroups, patients with an age of onset of ≤12 years experienced more hypomania/mania than patients with an age of onset between 13 and 30 years. Although most of the increase in symptomatic days occurred outside of an episode, subsyndromal or residual symptoms of mania are associated with an increased risk of relapse (Perlis et al., 2006; Judd et al., 2008) and poorer objective functioning (Piccinni et al., 2007). While the patients with an age of onset of ≤12 years did not differ in employment rate or marital status, these variables were collected at a single time point and do not measure ongoing social functioning. The association between an early age of onset and an increased frequency of hypomania/mania is in agreement with prior research (Goldstein and Levitt, 2006; Leverich et al., 2007; Perlis et al., 2004), and provides further evidence that patients with an early onset may suffer a worse outcome. The patients with an age of onset of ≤12 years did not experience significantly more depression, which is consistent with some (Perlis et al., 2004) but not all prior results (Leverich et al., 2007).

No demographic differences were detected using the subgroups derived from clustering methodology. However, using the predetermined subgroups, the demographic characteristics of patients with early and later onset were also consistent with prior reports including a significant difference in the diagnosis of bipolar I/II (Baldessarini et al., 2010; Carter et al., 2003; Perlis et al., 2009), an association between an earlier onset and a longer duration of illness (Goldstein and Levitt, 2006; Perlis et al., 2004), and little gender difference (Baldessarini et al., 2010; Carter et al., 2003; Leverich et al., 2007; Perlis et al., 2004). Alternatively, some researchers have reported a younger age of onset in males (Kennedy et al., 2005; Viguera et al., 2001) and no diagnostic differences between bipolar I/II (Leverich et al., 2007; Perlis et al., 2004).

The current study results are also noteworthy since the distribution of the age of onset in this sample was consistent with prior research that used either methodological approach to identify age of onset subgroups. Several studies of patients in the US used the same four age of onset subgroups and reported a very similar overall distribution (Leverich et al., 2007; Post et al., 2008). Moreover, in this study, the percent of patients with an age of onset of less than 19 years was 58.2%, consistent with prior findings from US studies of between 59% and 66%. (Leverich et al., 2007; Lish et al., 1994; Perlis et al., 2004; Post et al., 2008). The result of the model-based cluster analysis in this sample, with peaks for the age of onset at 15.1 and 27.5 years, was also similar to previous research that used a type of cluster analysis. For patients in the US with bipolar I, II or schizoaffective disorder, peaks for age of onset were found at 16.6, 26 and 34.7 years (Lin et al., 2006). For patients in France with bipolar I disorder, peaks for the age of onset were found at 16.9, 26.9 and 46.2 years (Bellivier et al., 2001). In a large sample of 1369 patients with bipolar I disorder in the UK (Hamshere et al.,

Table 2
Pairwise comparison of mean percent of days hypomanic/manic and mean percent days hypomanic/manic not in an episode by predetermined age of onset subgroups ($n = 270$).

	Mean percent of days				p Value[a]					
	≤12	13–19	20–29	>29	≤12 vs. 13–19	≤12 vs. 20–29	≤12 vs. >29	13–19 vs. 20–29	13–19 vs. >29	20–29 vs. >29
Percent days hypomanic/manic[b]	16.4	8.0	8.2	10.5	0.006	0.031	0.339	>0.999	0.924	0.962
Percent days hypomanic/manic not in an episode[c]	15.8	6.6	6.5	10.6	0.001	0.003	0.396	>0.999	0.470	0.483

[a] t-Statistic with Sidak adjustment for multiple comparisons.
[b] t-Statistic for the diagnosis coefficient in the GLM not significant ($p = 0.184$).
[c] t-Statistic for the diagnosis coefficient in the GLM not significant ($p = 0.363$).

2009), peaks were found at 17.9, 29.7, and 48.0 years with 11% of this sample having an age of onset between 40 and 73 years. Although only two peaks were found in this study, the ages are very similar to the two younger peaks reported in the prior studies. Furthermore, only 3.6% of the present sample reported an age of onset $\geq$ 40 years with the oldest onset at 62 years. This suggests that the current finding of two peaks does not conflict with prior findings of three peaks in samples containing a larger percentage of patients with an older age of onset.

There were several methodological limitations to this study. The age of onset data was obtained entirely from patient memory and thus subject to recall bias, although a retrospective approach has often been used in prior research (Baldessarini et al., 2010; Goldstein and Levitt, 2006; Lin et al., 2006; Perlis et al., 2004, 2009). The current sample size was relatively small but provided sufficient power for model-based cluster analysis using a single variable (Fraley and Raftery, 2002, 2006). The sample included few patients with an older age of onset so conclusions about patients with an age of onset over 29 years could not be made. Since an early age of onset occurs far more frequently in the US than Europe (Hamshere et al., 2009; Post et al., 2008; Soutullo et al., 2005), a large sample in the US would be needed to include patients with an onset late in life. The sample included patients with bipolar I and II disorder. However, there is considerable variation in the symptoms and course of illness within both diagnostic categories (Akiskal et al., 2000; Angst et al., 2004; Ketter et al., 2004; MacQueen et al., 2005; Benazzi, 2007). Medication adherence and substance abuse data were not included in this analysis. Additional limitations include the use of self-reported mood ratings, the need for daily patient access to a computer, the relatively short length of the study period, and fewer males in the sample.

In conclusion, the age of onset subgroups arising from clinical observation were more useful than those determined by cluster analysis for identifying differences in mood and demographic characteristics. Although the natural clustering of the age of onset of bipolar disorder was detected by model-based analysis, the subgroups were indistinguishable. However, many other variables that aggregate within families have been detected in clinical, cognitive, epidemiologic and brain imaging studies of bipolar disorder (Craddock and Sklar, 2009; MacQueen et al., 2005). Since it is unlikely that the age of onset alone will be sufficient to distinguish homogeneous subgroups, this study highlights the importance of clinical insight to the ongoing process of refining the phenotypes for bipolar disorder.

Funding

This project was funded entirely by local university funds. The local funding sources had no involvement in the study design, collection, analysis and interpretation of data, in writing the report, and in the decision to submit for publication.

Contributors

All authors contributed to and approved the final manuscript. Authors Bauer and Glenn designed the study. Authors Bauer, Rasgon, Marsh, Sagduyu, and Munoz were involved with data collection, authors Lewitzka and Schmid additionally in data interpretation. Author Glenn provided data analysis. Authors Bauer and Glenn wrote the draft manuscript.

Conflict of interest

The ChronoRecord Association is a 501(c)(3) nonprofit organization that aims to increase understanding of mood disorders (www.chronorecord.org). None of the authors receive financial compensation from the Association. Tasha Glenn and Peter C Whybrow share a patent for ChronoRecord software. Michael Bauer, Natalie Rasgon, Rodrigo Munoz, and Peter C Whybrow are on the Medical Advisory Board.

Michael Bauer has received grant/research support and/or has been a consultant and/or received speaker honoraria from the following companies: AstraZeneca, Lilly, GlaxoSmithKline, BMS, Otsuka, Pfizer, Servier, Janssen-Cilag, and Lundbeck.

Natalie Rasgon has received grant/research support and/or has been a consultant and/or received speaker honoraria from the following companies: Abbott Laboratories, Inc., Bayer HealthCare Inc., Bristol-Myers Squibb Company, Forest Laboratories, GlaxoSmithKline, Pfizer Inc., Wyeth-Ayerst Pharmaceuticals.

Kemal Sagduyu has received speaker honoraria from Merck.

There are no other conflicts of interest.

Acknowledgements

There are no acknowledgements.

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