Journal of Affective Disorders 201 (2016) 88–94

Contents lists available at ScienceDirect

Journal of Affective Disorders

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

Research paper

Admixture analysis of age at onset in first episode bipolar disorder

Behdin Nowrouzi [a,f], Roger S. McIntyre [b,c], Glenda MacQueen [d], Sidney H. Kennedy [b,c], James L. Kennedy [a,b], Arun Ravindran [a,b], Lakshmi Yatham [e], Vincenzo De Luca [a,b,*]

[a] Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[b] Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
[c] University Health Network in Toronto, Ontario, Canada
[d] University of Calgary in Calgary, Alberta, Canada
[e] University of British Columbia, Vancouver, British Columbia, Canada
[f] Centre for Research in Occupational Safety and Health, Laurentian University, Sudbury, Ontario, Canada

ARTICLE INFO

Article history:
Received 22 November 2015
Received in revised form
6 March 2016
Accepted 11 April 2016
Available online 27 April 2016

Keywords:
Bipolar disorder
Age at onset
Admixture analysis
Recall bias
Finite mixture model

ABSTRACT

Background: Many studies have used the admixture analysis to separate age-at-onset (AAO) subgroups in bipolar disorder, but none of them examined first episode patients.
Objective: The purpose of this study was to investigate the influence of clinical variables on AAO in first episode bipolar patients.
Methods: The admixture analysis was applied to identify the model best fitting the observed AAO distribution of a sample of 194 patients with DSM-IV diagnosis of bipolar disorder and the finite mixture model was applied to assess the effect of clinical covariates on AAO.
Results: Using the BIC method, the model that was best fitting the observed distribution of AAO was a mixture of three normal distributions. We identified three AAO groups: early age-at-onset (EAO) (μ=18.0, σ=2.88), intermediate-age-at-onset (IAO) (μ=28.7, σ=3.5), and late-age-at-onset (LAO) (μ=47.3, σ=7.8), comprising 69%, 22%, and 9% of the sample respectively. Our first episode sample distribution model was significantly different from most of the other studies that applied the mixture analysis.
Limitations: The main limitation is that our sample may have inadequate statistical power to detect the clinical associations with the AAO subgroups.
Conclusions: This study confirms that bipolar disorder can be classified into three groups based on AAO distribution. The data reported in our paper provide more insight into the diagnostic heterogeneity of bipolar disorder across the three AAO subgroups.

1. Introduction

Bipolar disorder (BD) refers to a group of disorders, which are characterized by depressive and manic or hypomanic or mixed episodes (Phillips and Kupfer, 2013). Initiatives to define the disorder have been based on the subtype of bipolar disorder (BD type I versus BP type II), comorbidity pattern (panic attacks, suicide ideation, addiction or hyperactivity), sex differences and course pattern (rapid cycling or seasonal) (Leboyer et al., 2005).

Age at onset (AAO) has been proposed as a key clinical variable in defining more homogeneous subgroups of bipolar disorder patients (Bellivier et al., 2001). Usually, AAO in bipolar disorder is not normally distributed. A significant setback of previous studies has been to use cutoff points, with subjective definitions of early and late onset.

The admixture analysis is a statistical approach that has been developed and used to overcome this challenge (Thode Jr. et al., 1988).

Numerous studies have used the admixture analysis to separate AAO subgroups in bipolar patients, but few have examined first episode patients.

The application of this statistical approach by several researchers has indicated that bipolar disorder aggregated into three age-at-onset subgroups: early age-at-onset (EAO), intermediate-age-at-onset (IAO), and late-age-at-onset (LAO). There are many studies that have adopted the admixture approach (Bellivier et al., 2003, 2011; Hamshere et al., 2009; Azorin et al., 2013; Manchia et al., 2008; Tozzi et al., 2011; Lin et al., 2006; Severino et al., 2009; Manchia et al., 2010; Grigoroiu-Serbanescu et al., 2014; Javaid et al., 2011; Golmard et al., 2015) in order to demonstrate that the theoretical model best fitting the observed distribution of AAO in

* Corresponding author at: Centre for Addiction and Mental Health, 250 College Street, Room R340, Toronto, ON, Canada M5T 1R8.
E-mail address: Vincenzo_deluca@camh.net (V. De Luca).

http://dx.doi.org/10.1016/j.jad.2016.04.006
0165-0327/

bipolar disorder is consistent with the existence of three AAO subgroups. However, most of these studies have assessed chronic bipolar patients. On the other hand, there is a recent report (Golmard et al., 2015) that specifically analyzed bipolar subjects with onset before 30 and controlled for the age at assessment. Also, Ortiz et al. (2011), within the main analysis, performed a sub-analysis in bipolar subjects considering only patients with mania or depression as their first episode.

The implementation of these statistical approaches in first-episode bipolar patients is warranted. Therefore, the aim of the current study is to apply the admixture analysis in bipolar patients with no more than five years of illness.

2. Methods

A sample of 194 unrelated first-episode (less than 5 years of illness) bipolar patients were recruited at four different clinical sites in Canada: Center for Addiction and Mental Health in Toronto, Ontario (n=52); University Health Network in Toronto, Ontario (n=57); University of Calgary in Calgary, Alberta, Canada (n=8); University of British Columbia in Vancouver, British Columbia (n=77). The diagnosis of bipolar was based on fulfilling the DSM-III-R or DSM-IV criteria. This study was approved by the ethical review committees of the clinical centers involved in the study.

We considered the following potential covariates for the analyses: age, sex, ethnicity (Caucasian versus others), duration of illness, street drug use, cannabis use and alcohol use, suicide attempt, family history of psychiatric disorders. The power for the analysis of the clinical covariates was determined following the method described by Cohen (1992). With a sample size of 194 subjects and a significance level of 0.05 and assuming an effect size d of 0.4 for the covariates under investigation, we can achieve a power of 80% to estimate a significant effect on AAO. G*Power 3.1 was used to calculate the power for this sample (Faul et al., 2009).

To determine whether the best fitting model of AAO in our bipolar sample is defined by three normal distributions, we analyzed the AAO using MCLUST (Normal Mixture Modeling for Model-Based Clustering, Classification, and Density Estimation) (MCLUST Version 3, 2006; Fraley and Raftery, 1999, 2003). We considered a range of number of AAO groups (one to nine). The number of groups that best fitted our data was selected as that number which maximized the Schwarz's Bayesian information criteria (BIC). The BIC permitted the comparison of models with different numbers of parameters owing to different numbers of normal distributions. The BIC is an increasing function of the error of variance and an increasing function of the number distributions. Furthermore, unexplained variation in the dependent variable and the number of explanatory factors increase the value of BIC, therefore the best fitting model was chosen according to the lowest value of BIC. We have also calculated the Akaike information criterion (AIC) (Di and Liang, 2011; Chen and Chen, 2001) to confirm the model selection obtained using the BIC.

Once the number, mean and standard deviation of normally distributed groups had been modeled, the theoretical AAO function could be determined. The theoretical AAO function defined the AAO probability density across different ages. Each patient's probability of belonging to each AAO subgroup was calculated using the theoretical AAO function (Hamshere et al., 2009). Then, we allocated each individual into one of the theoretical distribution groups such that the probability of membership was maximized. Furthermore, the theoretical AAO function was used to locate the cut-off age between early and late onset subgroups.

We used the Finite Mixture Modeling (FMM) statistical package from STATA version 11.0 (FMM: stata module to estimate finite mixture models, 2009) in order to analyze the existence of a theoretical model of finite mixture components of AAO that considered the possible influence of the clinical covariates. The finite mixture model offers an intuitively feasible representation of heterogeneity in a usually small number of finite mixtures latent classes (Deb et al., 2011). Estimates of such finite mixture models may provide robust numerical approximations even if the principal mixing distributions is continuous (Heckman and Singer, 1984; Laird, 1978). This statistical analysis fits a finite mixture regression model using maximum likelihood estimation, in which the mixing probability may be specified with clinical covariates. We suggest that the complexities of the relationship are not accurately addressed by traditional methodology, which may have led investigators to draw incorrect conclusions about the effect of clinical covariate on bipolar AAO.

For the comparison of our distribution with those reported in other studies, a replicate of the observations in our sample was generated according to the best fitting theoretical model for the comparative analysis using the two-sample Kolmogorov-Smirnov test. In this test, the largest absolute difference value *D* among the empirical cumulative distribution of the present study and those obtained in previously published studies was used to determine whether the function obtained in this study was consistent with those obtained in previously published studies. A significant p-value test rejects the hypothesis that there is no difference between two AAO distributions.

Table 1
Demographics of subjects (n=194).

	N (%)
Sex	
Female	97 (50.0)
Male	97 (50.0)
Age (Mean ± S.D.)	25.2 ± 9.51
Distribution of subjects by site	
Calgary	8(4.1)
Toronto(CAMH)	52(26.8)
Toronto (UHN)	57(29.4)
Vancouver	77(39.7)
Ethnicity	
European Caucasian	141(72.7)
Others	53(27.3)
Age of onset (Mean ± S.D.)	23.0 ± 9.60

Duration of illness < =5 years.

3. Results

3.1. Sample description

One hundred ninety four (97 males and 97 females) were included. The participants came from different ethnic backgrounds and 141 subjects were White European. This study included only bipolar type I and bipolar type II and did not extend to bipolar disorder NOS subjects. The sample included 155 bipolar type I and 39 bipolar type II subjects. There were 83 subjects with with a 1st episode characterized by depression, nine subjects with a 1st episode characterized by hypomania, 76 subjects with a 1st episode characterized by mania and 26 subjects with a 1st episode