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Ethnicity and Age at Onset in Bipolar Spectrum Disorders

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ABSTRACT

Introduction: To determine the influence of ethnicity on the age at onset (AAO) and further understand the significance of AAO as a clinical marker of bipolar and schizoaffective disorders.

Methods: Admixture analysis was used to identify sub-groups characterized by differences in AAO. Differences in clinical features were analyzed for these sub-groups using multivariate logistic regression. Comparisons were made with previous studies using the 2-Sample Kolmogorov-Smirnov Test.

Results: Admixture analysis yielded a combination of 2 normal theoretical distributions with means (SD) of 16.9 (3.6) for the early-onset sub-group and 24.4 (9.2) years for the late-onset sub-group. The sub-groups were divided by a cut-off of 22 years. There were significant differences between the early and late onset bipolar patient populations regarding substance abuse comorbidity (P=.044) and psychotic features (P=.015). Ethnicity did not have a significant influence on the AAO.

Discussion: The associations between early-onset and higher incidence of psychosis and

FOCUS POINTS

- Conducting admixture analysis yielded a combination of two normal theoretical distributions for age at onset of bipolar spectrum disorders, categorized as early and late-onset groups.
- In comparing the onset ages of white and non-white patients, ethnicity was not found to be a significantly influential factor.
- Studying the clinical characteristics of our patient population, this work reinforced the results of prior work in that an early age at onset is a predictor of poor outcome in bipolar spectrum disorders and frequently comorbid with substance abuse disorders.
- The findings also warn against misdiagnosis of early-onset bipolar disorders as schizophrenia due to the frequent presentation of psychosis in both cases.
- Future work should focus on obtaining a more ethnically diverse sample and minimizing reliance on retrospective self-reported data for age at onset, thereby reducing recall bias.

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substance abuse in our sample are consistent with other studies exploring the AAO in bipolar disorder.

Conclusion: Our findings support the notion of AAO as a clinical marker for the underlying heterogeneity of bipolar spectrum disorders. In particular, we found a strong overlap of early AAO with clinical features associated with greater severity and poor outcome.

INTRODUCTION

Our study aimed to determine the influence of ethnicity on the age at onset (AAO) and further understand the significance of AAO as a clinical marker of bipolar and schizoaffective disorders. Both populations were studied together to encompass a broader spectrum of mood-related illnesses. We applied admixture analysis to identify sub-groups characterized by differences in AAO, evaluated differences in the clinical presentation of these sub-groups, and conducted statistical comparisons with previous studies.

Background

It has been demonstrated that the AAO of bipolar disorder has implications for the clinical, familial, as well as underlying genetic features of this illness.[1] With lifetime prevalence between 0.5% and 1.5%, and mean AAO of ~21 years of age, bipolar disorder is a complex disease that strikes male and female patients and all ethnic groups at nearly equal rates.[2,3]

The AAO of certain complex diseases has been shown to reflect the underlying genetic heterogeneity of the illnesses. This has proven to be the case with Alzheimer's disease and breast cancer.[4,5] Given the broad and complex clinical spectrum presented by bipolar disorder, several studies have attempted to delineate sub-groups of patients based on differences in AAO and homogeneity of clinical features within these groups.[1,6,7] The existing literature contains mixed results where different diagnostic subtypes of bipolar disorder (type I and type II) are studied with respect to differences in AAO.

Some studies have demonstrated that differences in AAO do not correspond with the subtypes of bipolar disorder, whereas others maintain that type II has, on average, a later onset. Studies have also shown that AAO may have a strong heritable component, as demonstrated by a close association between the severity and earlier AAO, and consistency in the time of onset where multiple siblings are affected.[8,9] With respect to the relationship between AAO and the presence of psychotic episodes and suicidality, symptoms frequently observed in bipolar disorder, both features were more likely to be found in patients with earlier AAO.[10,11] In studies, such as the one conducted by Carter and colleagues,[12] subjects with AAO <18 years of age were found to be more likely to have a rapid cycling course of the disorder and concurrent anxiety disorders. In a large United States sample, Perlis and colleagues[13] replicated the association between an earlier onset of bipolar disorder and greater recurrence of the disorder as well as higher rate of comorbidity with anxiety disorders. More recently, evidence for three normal distributions for AAO in bipolar disorder was found.[14] Tondo and colleagues[15] combined bipolar disorder and unipolar depression subjects and found an overall earlier onset in the bipolar patients. A broader clinical implication of this finding was that earlier AAO may be helpful in distinguishing the course of bipolar disorder from a unipolar course in patients with mood symptoms.

METHODS

The studied sample consisted of 353 individuals diagnosed with bipolar disorder (n=318) or schizoaffective disorder (n=35), previously recruited for a genetics study. The sample was recruited through newspaper advertisements and hospital clinic referrals from the Toronto region and included mainly unrelated individuals; however, there were 32 affected first degree relatives and four affected second degree relatives. Interviewers provided a detailed description of the study to each of the participants and obtained written informed consent from the probands and any involved family members. The diagnostic Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (SCID) was conducted by trained research assistants on each participant. The Family Interview for Genetics Studies (FIGS) was used to draw retrospective life-charts and obtain a detailed family history of mood disorders (unipolar, bipolar, and schizoaffective disorders). When available, the psychiatric family history provided by probands was verified by family members and reviewing medical records.

The AAO was defined as the age at which a

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patient was first reliably diagnosed with a major mood episode or mood-related psychotic symptoms,[1] and was verified by data from the SCID, medical records, and other family members when available. Participants were categorized into ethnic groups of White Caucasian and non-White. The following types of data were extracted from the SCID and verified by reviewing medical records upon availability: axis I comorbidity, lifetime substance and alcohol abuse, lifetime suicide attempt, and severity of suicidal behavior (ranging from 1 to 4; 1=thoughts of death, 2=suicidal ideation, 3=suicide plan, 4=suicide attempt). Abuse or dependence for different drugs (sedatives-hypnotics-anxiolytics, stimulants, opioids, hallucinogens, cocaine, and cannabis) was considered as a single predictor. Admixture analysis was used to determine the best-fitting theoretical model for the observed distribution of AAO. In order to choose the best fitting model, we applied the χ^2 goodness of fit test using χ^2 fit command implemented in denormix module of the software STATA (release 8, StataCorp, College Station, TX).

The best fitting model is chosen based on the highest *P*-value of the χ^2 test, which indicates that the theoretical model does not deviate from the empirical distribution function of AAO in our sample.

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. Patients were then assigned to the distribution they had the highest probability of belonging to. The theoretical AAO function was used to calculate these probabilities and to locate cut-off points.

The largest absolute difference value between the empirical cumulative distribution function of the present study with those obtained in previously published studies was used to determine whether the fitted function obtained in this study was consistent with those obtained in previously published studies.[3] A significant *P*-value test rejects the hypothesis that the two AAO distributions are equal.

Pearson χ^2 test was used to compare early and late-onset sub-groups with respect to the following clinical variables: ethnicity, age at interview, gender, presence of bipolar I diagnosis, presence of psychosis, lifetime suicide attempt, suicide behaviour severity, substance use, alcohol use, family history of mood disorder, and axis I comorbidity.

Multivariate logistic regression analysis was also used in order to analyze the combined effect of the above variables on the AAO. Here, the AAO was the designated dependent variable with the following covariates: ethnicity, age at interview, gender, axis I comorbidity, family history of a mood disorder, lifetime suicide attempt, substance use, and alcohol use. All analyses were conducted using DENORMIX: STATA Module 8 SE and SPSS 15.0 for Windows. All tests were 2-tailed and we did not correct for multiple testing because the analysis is exploratory in nature. In reporting the odds ratios (ORs) the late onset was considered as baseline group.

RESULTS

A total of 353 bipolar and schizoaffective patients (137 male, 216 female) were included in the study (Table 1). The mean (SD) age at contact was 35 (10.69) years and 36 (10.67) years for male and female patients, respectively. The overall mean (SD) AAO was 20.22 (7.61) years (Figure 1).

TABLE 1.
Demographics and Clinical Descriptives of Patients with Bipolar and Schizoaffective Disorders

Descriptives	Total Sample (n=353)
Gender	
Male	137 (38.8%)
Female	216 (61.2%)
Lifetime Suicide Attempt *	
Absent	276 (78.2%)
Present	75 (21.2%)
Psychotic Features†	
Absent	128 (36.3%)
Present	182 (51.6%)
Age at Onset, Mean Years (SD)	
Male	21 (7.81)
Female	20 (7.46)
Age at Interview, Mean Years (SD)‡	
Male	35 (10.69)
Female	36 (10.67)

* Data was not available for 2 patients.
† Data was not available for 43 patients.
‡ Data was not available for 18 patients.

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Admixture analysis yielded a combination of two normal theoretical distributions. This best-fitting two-component model had means (SD) of 16.9 (3.6) years and 24.4 (9.2) years for the early and late-onset distributions, respectively. When we analyzed the bipolar sample (n=318) excluding the schizoaffective patients we found similar results with two components of mean ages at 16.5 (3.1) years and 23.7 (8.9) years. Furthermore, the secondary analysis in the unrelated individuals only showed that the two component model had means and standard deviations of 16.9 (3.5) and 23.7 (9.1) which is very close to the overall sample results.

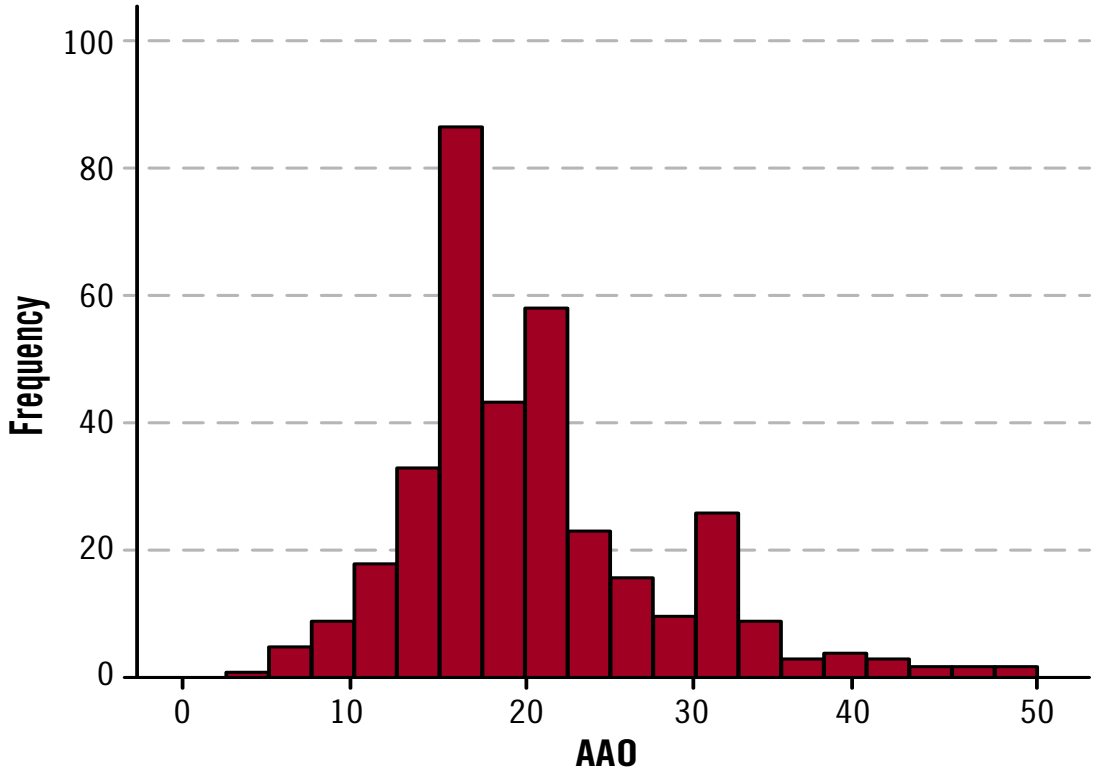
The two sub-groups were divided by AAO with 22 years of age as an ideal cut-off, characterized by the point at which the two curves intersect (Figure 2). Thus, patients who had onset at ≤21 years of age were considered in the early-onset group and those with onset at ≥22 years of age were included in the late-onset group.

Using the absolute difference method we found a value of .0455 when comparing our theoretical cumulative AAO distribution with that of Lin and colleagues (*P*=1.00).[7] On the other hand, a significant difference of .3030 existed between our distribution and the theoretical distribution of Manchia and colleagues(*P*=.003).[3]

Finally when comparing our cumulative distribution with those generated using the normal distribution parameter estimates reported by Hamshere and colleagues[16] and Bellivier and colleagues[6] we found that the absolute values of difference between age at onset were .2424 (*P*=.034) and .2273 (*P*=.056) respectively (Figure 3). However the absolute difference between Hamshere and colleagues[16] and Bellivier and colleagues[6] was very small confirming the finding that these two distributions are very similar (Figure 3).

The early-onset subgroup (<22 years of age) was comprised of 233 patients (66%), while the late-onset (≥22 years of age) included 120 patients (34%). Of the early-onset subgroup, 61% were

FIGURE 1.
Frequency curve for AAO in years for patients with bipolar and schizoaffective disorders (n=353). The mean(±SD) AAO is 20.22±7.60 years



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diagnosed with bipolar type I, compared to 71% in the late-onset subgroup.

Using the Pearson Chi-square test, the analyses did not yield a statistically significant influence of ethnicity on the AAO (chi-sq=2.66 1 df *P*=.102). This suggested that White Caucasian patients did not have a significantly different time at onset than that of the other ethnic groups (Table 2).

Looking at the clinical characteristics of onset sub-groups, we found a slightly significant influ-

FIGURE 2.
Theoretical distributions for ages at onset for 353 patients with bipolar and schizoaffective disorders with early-onset and late-onset

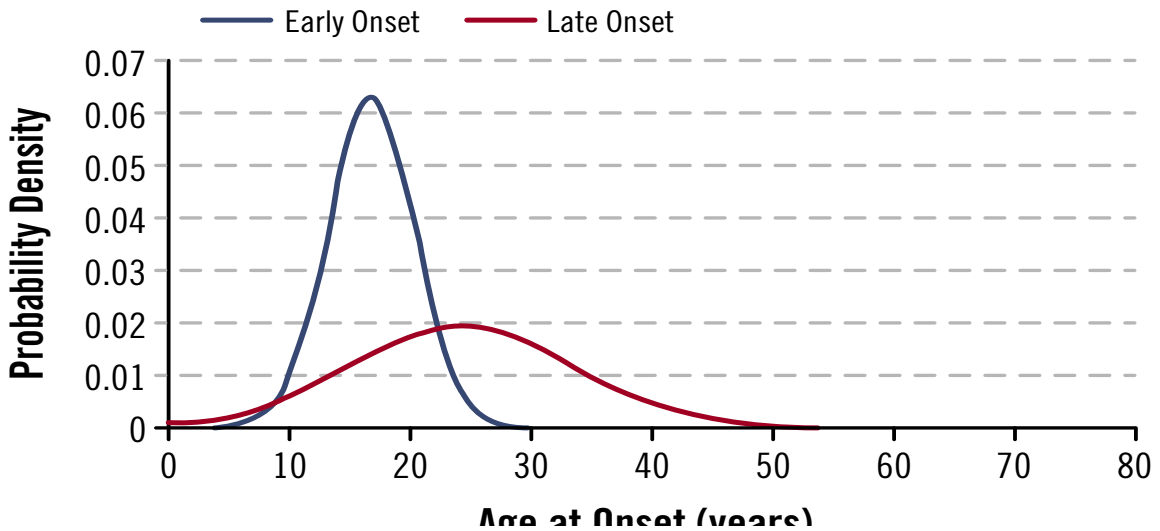

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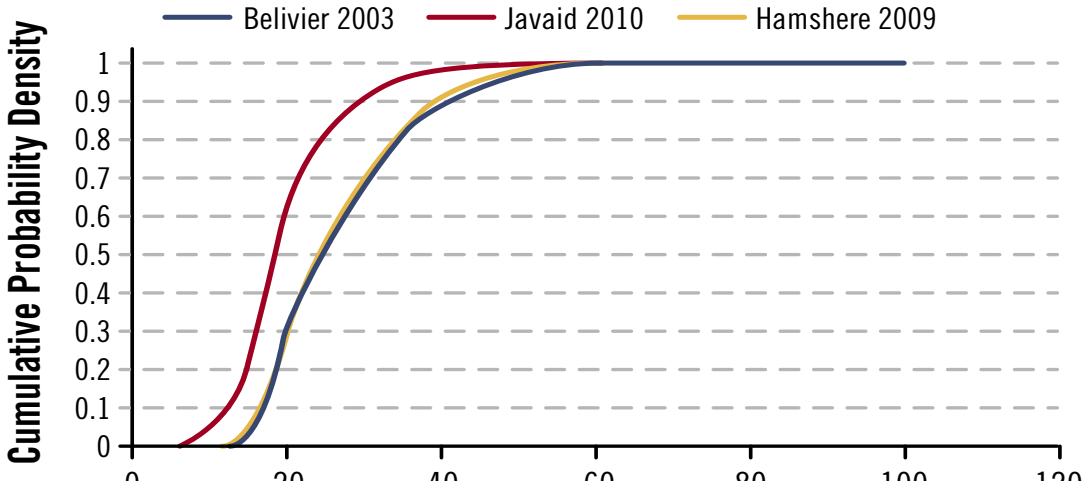
FIGURE 3.
Comparison between the cumulative distribution functions fitted to age at onset in our sample and samples by Hamshere and colleagues[16] and Bellivier and colleagues.[6] The maximum difference between the cumulative distributions of Hamshere and colleagues[16] and Bellivier and colleagues[6] is 0.0758 with a corresponding *P* of .989



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ence of substance abuse on the early-onset group was found (chi-sq=4.057 1 df *P*=.044). A highly significant association between psychosis and early-onset was also observed (chi-sq=5.888 1 df *P*=.015). Thus, substance abuse was found more frequently in cases of early-onset, and psychosis was consistent with an earlier onset. The only notable effect of ethnicity on clinical features was with respect to lifetime suicide attempt. We found a slight trend with more frequent suicide attempts in non-White individuals (chi-sq=2.746 1df *P*=.097).

An independent-samples t-test was conducted to compare age at interview for the early-onset and late-onset sub-groups. Assuming equal variance, there was a significant difference in this age for early and late-onset groups (t (351)=4.784, *P*<.001). These results suggest that age at interview may have been a confounding variable with respect to the AAO therefore we reanalyzed the clinical outcomes incorporating the age at interview as covariate in a logistic regression model. After the correction the association between early onset and psychoses was still significant (*P*=.013) and the association between early onset and substance abuse remained significant too (*P*=.049).

We applied a step-wise backward logistic regression model incorporating the following variables: gender, ethnicity, age at interview, axis I comorbidity, family history of mood disorder, lifetime suicide attempt, presence of psychosis, substance abuse and alcohol abuse were considered together. After the step-wise removal the best-fitting model in predicting the early onset included the presence of psychoses (*P*=.017; OR=1.8 95% CI 1.11-2.92) and Axis I comorbidity (*P*=.035; 95% CI 1.04-3.44). However when we analyzed the probability of belonging to the early onset as dependent variable in a linear regression model incorporating psychosis and axis I comorbidity as predictors we lost the significant effect (*P*=.546) and (*P*=.212) respectively.

DISCUSSION

The present study aimed to determine the role of ethnicity as a contributive factor in the AAO of individuals with bipolar disorder and schizoaffective disorder. We found two sub-groups of patients from our studied sample divided by the AAO into an early-onset group with a mean AAO of 16.9 years of age and a late-onset group with a mean AAO of 24.4 years of age. Twenty-two years of age was deemed as an ideal cut-off point for dividing the two subgroups by the mean of the admixture analysis.

Our findings demonstrated that ethnicity did not have a notable influence on the AAO of patients with bipolar and schizoaffective disorders as White-Caucasians and non-Whites did not

TABLE 2.
Clinical Variables in Patients with Early and Late AAO

	Early Onset (<Age 22; n=233)	*Late Onset (≥Age 22; n=120)*	*P*
Ethnicity (Non-White:White)*	24:203 (10.3%)	6:108 (5%)	.102
Mean Age at Interview in Years±SD†	34±10.94	39±9.14	<.001
Gender (Female:Male)	147:86 (63.1%)	69:51 (57.5%)	.307
Bipolar I Disorder (Yes:No)	142:91 (60.9%)	85:35 (70.8%)	.052
Psychosis (Yes:No)‡	132:101 (56.7%)	50:70 (41.7%)	.015
Lifetime Suicide Attempt (Yes:No)§	46:185 (19.7%)	28:90 (23.3%)	.517
Suicide Behavior Severity, Mean±SD	2.01±1.35	2.00±1.57	.154
Substance Abuse (Yes:No)	27:206 (11.6%)	6:112 (5%)	.044
Family History (Yes:No)‖	189:38 (81.1%)	93:25 (77.5%)	.515
Alcohol Abuse (Yes:No)	52:181 (22.3%)	23:97 (19.2%)	.493
Axis I comorbidity (Yes:No)	64:169 (27.5%)	22:98 (18.3%)	.058

* Data was not available for 12 patients; † Data was not available for 18 patients; ‡ Data was not available for 43 patients; § Data was not available for 2 patients; || Data was not available for 8 patients.

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show significant differences in their ages at onset. However, a slight trend was found for ethnicity and age at onset (P=.10) and the test may not have been significant because of the lack of power.

It is probable that the differences in clinical features observed amongst various ethnic groups can be attributed to socio-cultural factors as well as genetic predispositions. For example, Richardson-Vejlgaard and colleagues[17] found significant differences in cultural attitudes towards suicide amongst white, black, and hispanic patients with mood disorders. It follows that such cultural variations likely influence the way mood disorders are experienced in these populations.

Even though ethnicity is an important confounding factor in genetic studies, clinical studies investigating the effect of ethnicity as risk factor for course and severity of bipolar disorder can provide valuable information to the clinicians in the assessment and the follow-up.

Our study confirmed the claim in the literature that an earlier onset of bipolar and schizoaffective disorders is strongly characterized by psychosis and substance abuse. This is consistent with Perlis and colleagues[13] who found substance abuse to be associated with age at onset prior to 18 years of age. Furthermore, previous work has described substance abuse, specifically cannabis abuse, to act as a component that may interact with other factors to trigger a psychotic episode, increase the risk of psychotic disorder, or exacerbate psychotic symptoms via the interaction between cannabinoids and several neurotransmitter systems.[18] Similarly, we found that substance abuse, the most common of which was cannabis abuse, has a slightly significant effect by itself and also in combination with other variables to influence an earlier AAO of mood disorders. Thus, substance abuse should be considered only a partial risk factor and not necessarily or sufficiently influential on AAO alone.

Clinically, it is crucial to consider the heterogeneity in the clinical presentations of earlier and later onset to avoid misdiagnosis. Literature supports that bipolar disorder is commonly misdiagnosed as schizophrenia, especially in non-White populations, as patients with early-onset bipolar disorder frequently present psychotic symptoms.[19,20] Thus, early and accurate detection of bipolar disorder or schizoaffective disorder is essential, particularly when considering the impact on treatment outcome and the strong association between suicidality and untreated bipolar disorder.[21] Tondo and colleagues[15] applied a similar strategy in order to differentiate clinical courses of unipolar depression from bipolar disorder.

Moreover, the presence of psychotic symptoms in early-onset bipolar patients has previously been associated with greater severity, poor functioning, and poor outcome.[22] We found similar associations in our study and these are further supported as other studies have also shown earlier AAO to be implicated with more severe clinical presentation of bipolar disorder, a greater likelihood of comorbidity with substance abuse, Axis I disorders, suicidal ideation and/or behaviour, and an overall poorer prognosis.[23,24]

Expanding upon the study by Manchia and colleagues[3] on a homogenous Sardinian population, we took the innovative approach of grouping both schizoaffective-bipolar and schizoaffective-depressive subtypes with the bipolar patients. This was done in order to obtain a larger sample size and observe if distinct early-onset and late-onset distributions would emerge in a larger pool of this mixed patient population. We found distinct theoretical AAO distributions in a mixture of these two psychiatric populations as well.

When comparing our findings with those of previous studies conducted on AAO sub-groups, we have found two theoretical distributions (early- and late-onset) whereas other researchers found three (early-, intermediate-, and late-onset).[1,3,6,7] However, there existed a great deal of variation in the mean AAO of each sub-group, as well as the percentage composition of the sub-groups, within those studies with tri-modal distribution. In addition, the cut-off point used by these studies separating the early and intermediate-onset was in the early 20s and thus, similar in nature to ours. On the other hand, the cutoff of 18 between the two subgroups in Carter and colleagues[12] was chosen a priori ignoring the onset distribution. Using systematically the maximum difference method we compared our theoretical distribution with others investigating a US[7] population and we did not find statistical difference however we found a statistically significant difference when we compared our sample with bipolar samples from European populations. In fact, using two different statistical strategies and after plotting our distribution and the distribution of Hamshere and colleagues[16] we show significant difference with Hamshere distribution shifted to the right due to the later onset of the third component (Figure 3). On the other hand, Hamshere and colleagues[16] found the same cutoff

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of 22 years to separate the early onset from the later onset in their sample.

As in other studies of this nature, our study has the limitation of relying on data which is mainly obtained by retrospective self-reports. Our measures of AAO were primarily obtained through this means and are therefore potentially affected by recall bias. For example, it is easier to recall a more precise time of onset if the assessment takes place soon after the onset, as opposed to many years later, making the onset age more difficult to recall.

The lack of independence between the AAO and the age at interview found in the above results suggests that such a bias is likely to be present. Lin and colleagues[7] have raised the issue of age at assessment acting to confound the AAO. Their solution is that AAO be obtained in broader age-categories rather than ages in years as the former may be more accurately differentiated. Of course, this requires that these age-categories have reliable cut-off points dividing them. We attempted to overcome this limitation in our study by verifying self-report measures by interviews of other family members and medical records. However, these were unfortunately not always available for all patients.

Another limitation is that our sample may not have been reflective of the ethnic differences present with respect to the AAO in the psychiatric populations of our interest. The trend in our findings suggesting more frequent suicide attempts in non-White patients may be a biased result of this constraint. Historically, non-White ethnic groups have been less likely to self-report mental illness and participate in research studies.[25] Lack of access to services, limited knowledge of treatment options, as well as cultural norms are among a number of factors that may be responsible for the disparities. Eradicating disparities in the availability of services to ethnic minorities and spreading awareness of the importance of treatment and research are possible solutions for this constraint as well as many others.

CONCLUSION

Our findings support the idea of AAO as a clinical marker for the underlying heterogeneity of bipolar spectrum disorders. In particular, we found a strong overlap of an early-onset diagnosis with clinical features, such as substance abuse and the presence of psychosis, that have been previously associated with poor outcome. A significant influence of ethnicity on the AAO was not found. ***CNS***

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