

Brief communication

Birth-cohort and dual diagnosis effects on age-at-onset in Brazilian patients with bipolar I disorder

da Silva Magalhães PV, Gomes FA, Kunz M, Kapczinski F. Birth-cohort and dual diagnosis effects on age-at-onset in Brazilian patients with bipolar I disorder.

Objective: Substance use disorders and birth-cohort have been associated with an earlier onset in bipolar disorder (BD). This study aimed at evaluating the inter-relations of these factors in age-at-onset in bipolar illness.

Method: Two-hundred and thirty patients with bipolar I disorder were cross-sectionally evaluated. Patients were categorized into four age groups for analysis. Lifetime comorbidity and age-at-onset were derived from the Structured Clinical Interview for DSM-IV.

Results: There was a strong linear association between age group and age-at-onset. Lifetime alcohol and drug use disorders were also associated with age-at-onset. Illicit drug and alcohol use disorders and age group remained significant in the multivariate model. No interactions appeared.

Conclusion: Both age group and dual diagnoses had strong and independent impacts on age-at-onset in out-patients with BD. Substance abuse may be partly accountable for earlier symptom onset, but other features of BD in younger generations are still in need to be accounted for.

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Key words: bipolar disorder; age-at-onset; substance use disorders; birth-cohorts; cohort effect

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Significant outcomes

- Age-at-onset was strongly associated with birth-cohort. Younger age groups were associated with an earlier age-at-onset.
- Both alcohol and other substance use disorders were also associated with an earlier age-at-onset.
- These effects were largely independent.

Limitations

- Cross-sectional design in a tertiary care facility.
- Possibility of recall and survival bias.
- Order of onset of bipolar disorder and substance use disorders not available.

Introduction

There has been increasing interest in studying age-at-onset in bipolar illness. The age when symptoms begin has been proposed as a marker of disease heterogeneity (1). It may also provide clues to illness course in vulnerable individuals (2). Earlier age-at-onset of bipolar disorder (BD) has been

associated with suicide attempts, psychotic features and greater comorbidity (3, 4), making for a more severe illness subgroup.

More recent studies have revealed a lower age-at-onset in younger generations of patients with BD. These cohort effects have been shown in clinical and community samples (5, 6). The term cohort effect is used here to specify illness

variations such as age-at-onset over time among individuals defined by shared temporal or life experience. When related to year of birth, then it is a birth-cohort effect. Although changes in nosology may be partly responsible for such earlier onsets, other suggestions have been examined in the past few years. Heightened genetic vulnerability and increased exposure to drugs of abuse have been investigated as possible pathways (2).

An 'unstable DNA' hypothesis has been proposed for the major psychoses (7). Through a direct genetic means, younger ages-at-onset would be related to expansion of unstable genomic triplets. The phenomenon is termed genetic anticipation, a pattern of inheritance including also increased severity of symptoms in younger generations (8). A few studies have appeared in support in BD, but no triplet has been firmly identified (9). Furthermore, there is no accepted biological mechanism for anticipation in complex diseases (8).

A cohort effect might also occur if newer generations are differentially exposed to factors affecting illness diagnosis or course. Substance use disorders (SUDs) are over-represented in BD and have been related to worse illness courses (10). There have been hints that SUDs may be rising in BD (11). This way, a greater prevalence of comorbidity might explain the association of birth-cohort and age-at-onset.

Aims of the study

Whether the pathways above coexist is not currently established. Studies have usually probed the effect of either dual diagnosis or birth-cohort on age-at-onset. In this report, we evaluate in tandem the impact of birth-cohorts and psychiatric comorbidity on age-at-onset in Brazilian patients with bipolar I disorder.

Material and methods

Participants

Two-hundred and thirty patients with bipolar I disorder were consecutively recruited for this cross-sectional study. Subjects were either out-patients from the Bipolar Disorder Program at the Hospital de Clínicas de Porto Alegre ($n = 198$) or in-patients at the University Hospital at the Universidade Federal de Santa Maria ($n = 32$). All had a clinical diagnosis of BD type I confirmed with the Structured Clinical Interview for DSM-IV (SCID). Only those unable to provide consent were excluded. Participants gave written informed con-

sent before entering the study, which was approved by the local ethics committee.

Instruments

Lifetime comorbidity, clinical and age-at-onset data were derived from the SCID. This method of obtaining age-at-onset has been used by others and has been found to have validity when compared with self-report (12). Although there is more than one way of defining age-at-onset, here it is the age when symptoms first appeared. This approach was also taken in similar studies (5). Illicit drug use disorders included abuse or dependence of cannabis, stimulants, opiates, inhalants and hallucinogens.

Statistical analyses

Four age groups were created for analysis. The first was from 18 to 29, then 30–39, then 40–49, then 50 or older. We log-transformed age-at-onset for parametric analysis, as performed by Chengappa et al. (5). Age groups were tested for linearity regarding discrete variables with ANOVA and dichotomous variables with chi-squared tests. Multivariate ANOVA was used to assess independent effects of age-at-onset and SUDs. All tests are two-tailed.

Results

Two-hundred and thirty patients were included. Women comprised 69.4% of the sample. Median age was 42 years (IQR 32.5–50) and age-at-onset, 23 years (IQR 16.75–35). Median age-at-onset was 35 years (IQR 22) for the oldest age group (50 or older), 29 years (IQR 22) for the 40–49 age group, 21 years (IQR 13) for the 30–39 age group and 17 years (IQR 5) for the 18–29 group. Twenty-nine per cent had lifetime comorbidity with alcohol use disorders and 21% with illicit drug use disorders.

There was a strong linear association between age group and age-at-onset ($F = 62.64$, $df = 3$, $P < 0.001$). Alcohol ($F = 14.11$, $df = 1$, $P < 0.001$) and drug use disorders ($F = 20.80$, $df = 1$, $P < 0.001$) were also associated with age-at-onset.

In the multivariate ANOVA model, both illicit drug ($F = 5.18$, $df = 1$, $P = 0.024$) and alcohol use disorders ($F = 4.07$, $df = 1$, $P = 0.045$) and age group ($F = 17.16$, $df = 3$, $P = 0.001$) remained significant. Adjusted R^2 for the model was 0.25. Finally, we tested for interactions between these factors. None appeared ($P > 0.5$ for all two and three-way), attesting for the independence of com-

orbidity and birth-cohort effects on age-at-onset (Fig. 1).

Discussion

Secular trends can have modifying effects in illness onset and course (8). In this report, both age group and dual diagnoses had an impact on age-at-onset in out-patients with BD. These effects were strong and independent.

Not many studies have evaluated the presence of a birth-cohort effect in BD. In a sample from the Stanley Center Bipolar Registry, Chengappa et al. (5) similarly found strong correlations between age-at-onset and birth-cohort. Increased representation of BD in younger subjects has been found in one clinical database (13) and in a population study (6). This could be explained by many different causes. Although we do not directly address the issue of anticipation (i.e. we cannot rule this effect out), its importance in polygenic diseases has been discredited.

As a more plausible mechanism, rising comorbidity with SUDs might explain the earlier unveiling of BD symptoms. Studies have consistently shown a lower age-at-onset related to substance misuse (3, 14, 15). Various mechanisms may underlie this co-occurrence (10). One possibility is for a causative effect through behavioral sensitization or kindling (16). This suggests that substance abuse would be an additional risk factor needed to reveal BD in vulnerable individuals (17). Through this, greater prevalence of dual diagnoses in more recent cohorts could be responsible for the triggering of early onset BD.

Shared vulnerability would be another possibility. Studies have shown a familial association between BPD and SUD (18, 19). As a whole, they raise the question of whether the two share genetic or other etiologic factors. As such, genes

that might be associated with both disorders as well as environmental issues might precipitate both conditions (16). If this is the case, other mechanisms for increased vulnerability might be in play. Rising fertility of those more severely affected has been proposed as one means (20). The hypothesis put forward is that widespread use of lithium may be responsible for better functional outcomes, including ability to procreate. If this holds true, newer generations might have more severe diseases.

We are unable to test which of these hypotheses is a better explanation with a cross-sectional design. Cohort studies examining competing hypotheses are needed. Likely biases operating towards our findings are recall and mortality bias. Through recall bias, younger cohorts are likely to remember more accurately age-at-onset. In addition, as BD is a condition with high all-cause mortality. It is possible, thus, that survivors have less severe illnesses, making for the appearance of a cohort effect. Bipolar illness, yet, is often longitudinally associated with increasing severity and disability. Thus, an effect in the opposite direction might be expected. The order of onset of BD and SUDs could be an additional source of illness heterogeneity. Those in which SUDs had an onset prior to BD have been described as having less severe features (17). Therefore, separating different populations of comorbid BD and SUDs based on onset might be relevant. If present, however, such variation would increase error and operate in opposition to the findings in this report.

In this group of patients from a specialized facility, we found independent effects for both birth-cohort and dual diagnosis on age-at-onset. Substance abuse may be partly liable for earlier symptom onset, but other features of BD in younger generations are still in need to be accounted for.

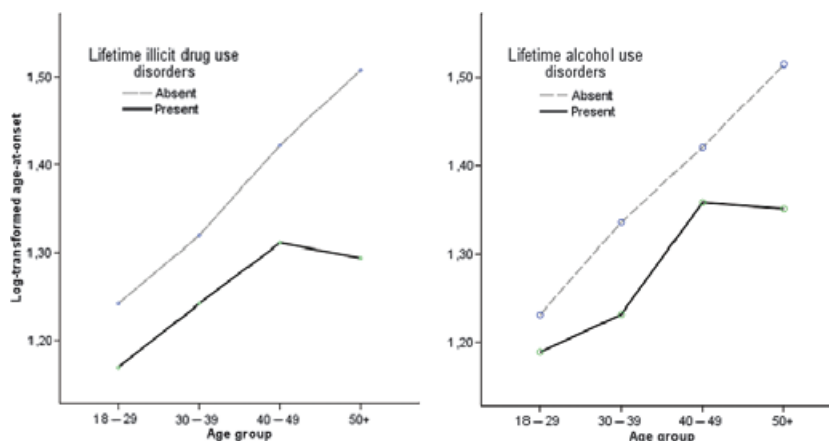


Fig. 1. Multivariate relationship between birth-cohorts, substance use disorder and age-at-onset of bipolar I disorder (n = 230).

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Declaration of interests

Dr Kapczinski has received grant/research support from Astra-Zeneca, Eli Lilly, the Janssen-Cilag, Servier, CNPq, CAPES, NARSAD and the Stanley Medical Research Institute; has been a member of the speakers boards for Astra-Zeneca, Eli Lilly, Janssen and Servier; and has served as a consultant for Servier. The other authors declare they have no conflict of interest in the matter.

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