



Full length article

Alcohol use and bipolar disorders: Risk factors associated with their co-occurrence and sequence of onsets



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ARTICLE INFO

Keywords:

Bipolar disorder
Alcohol use disorder
Comorbidity
Sequence of onsets

ABSTRACT

Background: Little is known about the sequence of onsets in patients affected by comorbid alcohol use and bipolar disorder. This study examines the risk factors associated with their co-occurrence and order of onset.

Method: The demographic, clinical, and temperament characteristics as well as the course of illness were analyzed within our sample of 1090 DSM-IV bipolar I manic patients. Our sample was categorized according to the presence of comorbid alcohol use disorder and the sequence of onsets of bipolar and alcohol use disorders i.e., alcohol first (AUD-BD) and bipolar first (BD-AUD).

Results: Regression analyses revealed that alcohol use disorder (52.5%) was associated with the male gender, additional substance use disorders, as well as an irritable and a hyperthymic temperament. The AUD-BD group (6.6%) was older than the BD-AUD group (45.8%) and showed higher rates of comorbid sedative use, organic, and anxiety disorders with higher levels of irritable temperament, and a bipolar subtype characterized by depressive polarity at onset. The BD-AUD group had high levels of hyperthymic temperament with higher rates of comorbid stimulant use disorder and a manic polarity at onset.

Conclusions: In the AUD-BD group, alcohol might have been used to reduce stress and tension caused by the presence of an irritable temperament as well as anxious and organic disorders, leading to first depressive episode. In the BD-AUD group, stimulant use might have triggered the first manic episode, and alcohol abuse result from mania severity.

1. Introduction

There exists abundant evidence in the literature reporting the role of factors associating comorbid alcohol use disorder (AUD) with bipolar disorder (BD) patients (reviewed in Strakowski et al., 2000; Frye and Salloum, 2006; Goodwin and Jamison, 2007; Salloum and Ruiz, 2015). The diversity of these factors within this comorbidity has fueled numerous explanatory models that were proposed to account for such a comorbidity (Winokur et al., 1995; Strakowski et al., 2000; Goodwin and Jamison, 2007). The ascertainment bias hypothesis (i.e., having a combination of diseases increases the probability of seeking treatment) (Berkson, 1946) does not seem to be adequate, as the frequent association of BD and AUD was based not only on data from clinical facilities, but also on population surveys (Regier et al., 1990; Kessler et al., 1997). Another hypothesis is that the patient has two diseases, BD and

AUD, which would be “true” comorbidity (Winokur et al., 1995; First, 2005). However, this is unlikely since the association is considerably more frequent than would be expected by chance alone (Helzer and Pryzbeck, 1988). The self-medication hypothesis (i.e., AUD results from the use of alcohol to cope with the symptoms of BD) (Reich et al., 1974; Khantzian, 1985), as well as that of common genetic (Winokur et al., 1998) and neurobiological (Rakofsky and Dunlop, 2013) mechanisms, appears to be more plausible (Camacho and Akiskal, 2005; Farren et al., 2012; Carmiol et al., 2014). It has also been proposed that mania could be induced by alcoholism (Sonne et al., 1994), and conversely that alcohol intake may directly result from manic behavior (Liskow et al., 1982). In accordance with this hypothesis, patients with comorbid AUD and BD were divided into two subtypes: BD preceded by AUD (AUD-BD or Primary AUD), and BD followed by AUD (BD-AUD or Secondary AUD) (Winokur et al., 1995). However, the literature addressing the

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<http://dx.doi.org/10.1016/j.drugalcdep.2017.07.005>

Received 12 March 2017; Received in revised form 5 July 2017; Accepted 7 July 2017

Available online 03 August 2017

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order of onset of AUD and BD remains scarce (Winokur et al., 1995; Strakowski et al., 1996, 2005; Pacchiarotti et al., 2009), and the results of the studies may be affected by their small sample size. So far, the main findings reported that AUD-BD occurred in older patients and was a less severe subtype of BD, as compared to BD-AUD. This suggests that AUD-BD and BD-AUD could represent two distinct phenotypes of BD, and for this reason it is important to look at the order of onset in this comorbid population. More recently, it was suggested that affective temperaments could play a role in the development of alcohol abuse, both in normal (Unselde et al., 2012) and bipolar populations (Singh et al., 2015). As affective temperaments are likely to be vulnerability factors for the outbreak of BD (Savitz and Ramesar, 2006), we hypothesized that AUD-BD and BD-AUD could differ according to their respective temperamental propensities.

The Epidemiology of Mania (EPIMAN) II-Mille study is one of the largest observational studies conducted in patients suffering from bipolar I disorder. This large-scale study offers a unique opportunity to examine specific aspects of this pathology. The aims of the current investigation were (1) to assess the prevalence rates of AUD, AUD-BD and BD-AUD in a large sample of bipolar I patients, (2) to determine and compare their clinical characteristics to those of bipolar I patients without such a comorbidity (BD-O: BD Only), (3) to evidence risk factors associated with the co-occurrence and sequence of onsets of BD and AUD, with a particular focus on temperamental components.

2. Material and methods

2.1. Study population

Patients included in the study were hospitalized due to a manic episode of bipolar I disorder. Diagnosis was made using the French version of the Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-P) (First et al., 1997; Bordeleau, 1997).

2.2. Study design

EPIMAN II Mille implemented in France, was a multisite study conducted at 19 medical centers between December 2000 and April 2002. It was a naturalistic study, carried out under the conditions of clinical practice, in order to have high clinical representativeness. In particular, patients with complex (i.e., highly comorbid) disorders could be included, as they usually occur in clinical practice. The primary aim of the study was to characterize the different subtypes of bipolar I disorder and estimate their prevalence. Our objective was to enroll 1000 patients. To reach this goal, each of our 317 psychiatrists had to recruit at least 2 consecutive patients (with a maximum of 6). All psychiatrists had considerable clinical experience in studies involving bipolar patients and worked in public, university, or private hospitals. The study exceeded the initial target of 1000 patients with the final inclusion of 1090 patients. This large sample size gave us the opportunity to study the factors that could be associated with the co-occurrence of bipolar and alcohol use disorders, as well as their sequence of onset.

2.3. Clinical assessments

Upon clinical admission, sociodemographic characteristics and mental illness history were collected. Symptom intensity was rated using several scales; mania was assessed by the Mania State Rating Scale (MSRS) (Beigel et al., 1971; Akiskal et al., 2003); depression was rated using the Montgomery Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979; Pellet et al., 1981) and a newly derived depression checklist less affected by manic symptoms (Akiskal et al., 2000); psychotic symptoms were recorded on the Scale for Assessment of Positive Symptoms (SAPS) (Andreasen, 1984; Boyer and Lecrubier, 1997); and mood disturbances were self-reported through

the Multiple Visual Analog Scales of Bipolarity (MVAS-BP) (Ahearn and Carroll 1996; Akiskal et al., 2001). Most scales were used in their respective French versions as validated in our prior EPIMAN study (Akiskal et al., 1998; Azorin et al., 2000). The MADRS and SAPS scales had been validated by others as referenced above.

After a marked improvement of the manic episode at an average of 21 days post-admission, comorbidity for AUD was assessed using the SCID-P (First et al., 1997; Bordeleau, 1997). Comorbidity for other Axis I disorders was assessed using the same method. Comorbid cocaine and amphetamine-like use disorders were grouped under the category of stimulant use disorders; and opioid use under sedative use disorders. Using a medical history form, patients were also asked whether they ever had any general medical disorder during lifetime. If the illness was diagnosed by a physician, they were scored as positive. Ages at onset of bipolar and comorbid disorders were obtained from structured interviews with the patients and their relatives, and from their medical records. Age at onset was defined as the age the patient first met the DSM-IV criteria for the corresponding Axis I disorders. However, age of onset for general medical disorders was defined based on their medical records. The interviews were conducted by the psychiatrists who recruited the patients in each center. The ages of disorder onset were retrospectively reported during the interviews, but also independently assessed through medical records. Ages of onset reported during the interviews with the patients and from medical records were available for each recruited patient. However, ages of onset reported by relatives during interviews could not be obtained for 41 patients. Validity of age of onset was assessed by comparing the ages of onset reported in the patient interview with those reported in the family interview and the medical record. For both AUD and BD, the values were highly correlated ($p < 0.001$), and the ages of onset reported in the patient interview were within 1 year of the ages of onset reported either in the family interview or the medical record. Hence, using the ages of onset reported by the patient appears to be a reasonable estimate of the order of onset in this data set. The order of onset was established by two of the authors (RB and MA). Any disagreements were resolved by a third author (JMA), based on all available data. The presence of stressful events before current episode and bipolar illness onset was assessed through interviews with patients and their families as well as hospital records, following the guidelines for assessment of DSM-IV Axis-IV (American Psychiatric Association, 1994). Finally, affective temperaments (hyperthymic, depressive, cyclothymic and irritable) were self-reported in four separate questionnaires (Hantouche et al., 2001). These four yes-or-no type questionnaires represent the French version of TEMPS-A (Temperament Evaluation of Memphis, Pisa, Paris and San Diego, auto-questionnaire version), and are designed to quantify temperament in psychiatric patients and healthy subjects.

The study was reviewed and approved by the appropriate ethics committee, and patients participated with informed, voluntary, written consent.

2.4. Statistical analyses

Characteristics of bipolar patients were examined for association with alcohol use disorder. For categorical variables, χ^2 or Fisher's exact tests were used to compare three groups: AUD-BD, BD-AUD, and BD-O. For continuous variables, the appropriate tests of analysis of variance (parametric or nonparametric) were used to compare the three groups. For all analyses, if the overall test was found to be statistically significant ($p \leq 0.05$), pairwise post hoc comparisons were conducted. For pairwise comparisons, Bonferroni correction for multiple comparisons was performed.

Stepwise logistic regression models were then used to identify risk factors associated with alcohol use disorder (BD with AUD vs BD-O; AUD-BD vs BD-AUD; AUD-BD vs BD-O; AUD-BD vs others; BD-AUD vs BD-O; BD-AUD vs others). Odds ratios with 95% confidence intervals were used for observed associations.

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