Research paper

Possible predictors of age at illness onset and illness duration in a cohort study comparing younger adults and older major affective patients

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ABSTRACT

Background: Major affective conditions are associated with significant disability and psychosocial impairment. Whether specific socio-demographic and clinical characteristics may distinguish subgroups of patients in terms of prognosis and illness trajectories is a matter of debate.

Methods: The sample of this naturalistic cohort study included 675 currently euthymic patients with major affective disorders of which 428 (63.4%) were diagnosed with unipolar and 247 (36.6%) with bipolar disorders.

Results: Younger adults with a longer duration of untreated illness and residual inter-episodic symptoms were more likely to be single or divorced, students, with an earlier age of first treatment/hospitalization, longer duration of substance abuse and duration of illness than older patients who were, conversely, more likely to be widowed and retired. Multivariate analyses showed a significant positive contribution to age at illness onset by marital status, nonpsychiatric medications, substance abuse, psychiatric diagnosis (bipolar *vs.* unipolar), age at first treatment/hospitalization, duration of illness, and current age. According to a further analysis, we also found a significant positive contribution to duration of illness by marital status, educational level, positive history of psychiatric conditions in family, substance abuse, psychiatric diagnosis (bipolar *vs.* unipolar), age at illness onset, age at first treatment, and certain cardiovascular disorders.

Conclusions: There are substantial socio-demographic and clinical differences that may help to distinguish specific subgroups of patients; however, additional studies are requested to replicate these results and further investigate the main factors underlying our findings.

1. Introduction

Major affective conditions including major depressive disorder (MDD) and bipolar disorder (BD) are associated with significant disability and psychosocial impairment over the life course (Rush, 2003; Andlin-Sobocki et al., 2005). Although these invalidating conditions are associated with higher medical costs, morbidity, and mortality (Katon and Sullivan, 1990), they are often not adequately recognized or diagnosed due to the complexity and heterogeneity of their clinical presentations. This heterogeneity is likely related to the presence of a shared genetic vulnerability as well as the interplay of physical and psychosocial factors across the life span (Nivoli et al., 2014).

Based on existing findings from the current literature, beyond their different symptomatic presentation, BD may be distinguished from MDD according to the presence of some key clinical characteristics related to the short- and long-term course, and illness trajectory that account for significant differences in terms of management and treatment. These differences mainly regard socio-demographic features such as marital and socio-economic status, and educational level but also clinical characteristics such as age at first illness onset, age at first treatment/hospitalization, number of episodes with/without psychotic features, positive family history for psychiatric conditions, or suicidal

behavior (Ghanbari Jolfaei et al., 2016; Goodwin and Jamison, 1990; McMahon et al., 1994; Winokur et al., 1993; Peselow et al., 1982).

Most of the differential characteristics of major affective disorders seem to depend on the complex interplay with the biopsychosocial context (Schotte et al., 2006) but they may significantly vary even according to specific illness variables. For instance, age at onset of the first major depressive episode may significantly influence the symptoms and clinical course of subsequent episodes; thus, this feature has been proposed as an important indicator to split heterogeneous MDD subjects into more homogenous subgroups and also for subtyping/phenotyping patients with MDD (Zhu et al., 2012; Jaffee et al., 2002). According to existing evidence, early adult onset MDD patients (*i.e.* with a first depressive episode presenting not later than 44 years of life) were more likely to have a more severe and chronic condition, a predominance of female gender, longer illness duration, higher number of episodes, higher suicidal risk and symptom severity, and psychiatric comorbidity (Zisook et al., 2007b, 2004) when compared with late-onset MDD individuals. Similar additional characteristics may also help distinguish between different subgroups of bipolar patients. BD type I (BD-I) patients may be distinguished from MDD and BD type II (BD-II) by having an earlier age at onset and first hospitalization, more lifetime episodes, higher number of hospitalizations, more severe psychiatric comorbidities, more frequent marital difficulties and divorces, more frequent episodes of unemployment, and poorer socio-economic status (Leverich and Post, 1996, 1998). Moreover, some researchers also demonstrated the existence of less severe symptoms together with more chronic course and more frequent episodes, a higher number of comorbidities (Baek et al., 2011; Fornaro et al., 2010), and more severe interpersonal impairments and altered social adjustment (Akiskal et al., 2006) in BD-II compared to BD-I patients (Judd et al., 2003; Vieta et al., 1997).

Further clinical features have been proposed to substantially characterize differential subgroups of patients with major affective disorders in the recent years and have gained increasing prominence. These concepts are mainly focused on duration of untreated illness, and illness duration based on their close relationship with recurrence rate, likelihood of hospitalization, poor prognosis, and bipolarity (Park et al., 2014; Drancourt et al., 2013; Benazzi, 2009).

Indeed, most studies that investigated age-related characteristics of depressed patients mainly focused on MDD without systematically addressing BD (Husain et al., 2005) even if published data suggest that older MDD and BD patients present with different clinical characteristics compared to younger individuals (Baek et al., 2011; Fornaro et al., 2010; Akiskal et al., 2006; Judd et al., 2003; Vieta et al., 1997; Leverich and Post, 1998, 1996).

However, whether and to what extent these specific characteristics may help to identify subgroups of patients with a more negative prognosis and differential illness trajectories in the clinical practice is a matter of debate. Given this contradictory context, it is generally very important to explore the potential of specific clinical features to differentiate patients' subgroups as well as its possible predictive value accounting for the duration of current illness and age of illness onset.

The main objective of our study was to compare socio-demographic and clinical characteristics of younger adults and older unipolar/bipolar patients in a sample of 675 outpatients. Furthermore, we also compared socio-demographic and clinical characteristics of a smaller subgroup of patients with a longer (> 2 years) duration of untreated illness and residual inter-episodic symptoms which are generally considered as significant predictors of illness severity. Finally, we also explored what are the most relevant predictors accounting for the duration of current illness and age of illness onset in the mentioned sample.

2. Methods

2.1. Participants

The sample of this naturalistic cohort study included 675 currently euthymic patients with major affective disorders of which 428 (63.4%)

were diagnosed with unipolar and 247 (36.6%) with bipolar disorders; participants had an age ranging from 18 to 85 years (mean = 54.9 ± 15.9). They were currently euthymic patients with the following latest psychiatric diagnoses when admitted: 34.8% of subjects were diagnosed with unipolar MDD, single episode; 26.7% with unipolar MDD, recurrent episode; 1.9% with dysthymia; 5.5% with BD-I, most recent depressive episode; 3.7% with BD-I, more recent manic episode; 6.2% with BD-I, more recent mixed episode; 2.7% with BD-II, more recent hypomanic episode; 13% with BD-II more recent depressive episode, and 5.5% with cyclothymia. When later recruited, they were all consecutive outpatients receiving only maintenance treatment that have been followed by our university outpatient service for at least 12 months. Specifically, their psychoactive medication regimens and their psychopathological conditions were stable for at least 6 months.

2.2. Procedure and measures

All participants were admitted to the Department of Neuroscience (DINOGMI), University of Genoa, outpatient service, between July 2014 and January 2017. The inclusion criteria were a diagnosis of major affective disorders such as MDD, dysthymia, BD-I, BD-II, and cyclothymia as specified, and a current age > 18 years. Mood symptoms (at the time of assessment) were rated and classified according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV, TR) (even regarding melancholic, and psychotic depressive symptoms) (American Psychiatric Association, 2001). Exclusion criteria were any conditions affecting the ability to fill out the assessment including delirium, Alzheimer's disease or any severe neurological diseases including mental retardation, and denial of the informed consent. Mental retardation has been assessed initially with a comprehensive physical examination and a complete medical, family, social, and educational history which is carried out from existing medical and school records as well as interviews with parents. If mental retardation was suspected, the Wechsler Adult Intelligence Scale was administered. Subjects with a current known or suspected history of drug/alcohol dependence and abuse during the past 6 months were excluded from the present study while lifetime substance use had been investigated first by clinicians performing the mental examination and then confirmed using the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). The most frequently reported lifetime substance abuse types were: alcohol (6.2%), cannabis/marijuana (4.3%), stimulants/cocaine (1.5%), heroin (0.9%), major sedatives (1.3%).

Psychiatric histories and lifetime assessment of mood episodes and affective symptoms were extracted from clinical records systematically collected and verified using the MINI. Affective symptoms and episodes before patients' recruitment in our Institute were based on the evaluation of previous medical records together with direct interviews with both the patient and family members.

Concerning specific clinical variables such as prior psychoactive treatments, age at onset, previous hospitalizations, medical comorbidities, a careful and detailed data collection was carried out: means of structured interviews were used to confirm clinical information, and specific rating scales/comprehensive interviews were used to assess clinical characteristics, and administered by both psychiatrists and psychologists which were appropriately trained to improve the inter-rater reliability. The illness histories were retraced thorough by clinical files, and lifetime computerized medical records. All available information have been cross-referred. Predominant polarity was calculated only for bipolar patients and defined as 2/3 of the total number of depressive, mixed, manic, or hypomanic episodes of the same polarity according to Colom et al. (2006). All patients accepted voluntarily to participate in the study and gave their informed consent. The study design was approved by the local Ethical Review Board.