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Research report

Mania and depression. Mixed, not stirred

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ABSTRACT

Objective: Current criteria for mixed bipolar episode do not allow an adequate understanding of a vast majority of bipolar patients with mixed (hypo) manic-depressive features, keeping the qualification of "mixed episodes" for bipolar type I only. This study was aimed to test the existence of a bipolar-mixed continuum by comparing the characteristics of three groups classified according to patterns of past and current manic or mixed episodes.

Method: 134 bipolar I inpatients were divided according to their pattern of excitatory "mixed-like" episodes in three groups: 1) lifetime history of purely manic episodes without mixed features (PMA); 2) lifetime history of both manic and mixed episodes (MIX) and 3) lifetime history exclusively of mixed, but not manic, episodes (PMIX). Differences in clinical and demographic characteristics were analyzed by using chi-square head-to-head for categorical data, one-way ANOVA for continuous variables and Tukey's post-hoc comparison. Logistic regression was used to control for data validity.

Results: PMIX had higher rates of depressive predominant polarity and less lifetime history of psychotic symptoms, and had received more antidepressants both lifetime and during 6 months prior to index episode. PMIX had more suicide attempts and Axis I comorbidity than PMA.

Discussion: PMIX is likely to have a higher risk for suicide and higher rates of comorbidities; current DSM-IV-TR criteria are not fit for correctly classifying these patients and this may affect treatment appropriateness. The concept of "mixicity" should be extended beyond bipolar I disorder to other bipolar disorder subtypes.

1. Introduction

Mixed states are broadly defined as the coexistence of both manic and depressive features within the same mood episode. Mixed states were first described by Emil Kraepelin (1899) and Wilhelm Weygandt (1899). These authors pointed at these episodes as the cornerstone of manic-depressive insanity. Since then, the definition of mixed states by the nosology has suffered from several changes: in the first edition of the DSM (American Psychiatric Association, 2000), for instance, the term "manic depressive reaction, mixed type" was used rather loosely, while the second edition (1968) required that "manic and depressive symptoms appeared almost simultaneously" in order to diagnose "mixed" manic-depressive. In the DSM-III (1980) and DSM-III-R (1987), the diagnosis of bipolar disorder, mixed, required the "full symptomatic picture of both manic and major depressive episodes, intermixed or rapidly alternating every few days", whereas in the DSM-IV (1994) and the DSM-IV-TR

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(2000), the term "mixed episode" was introduced and required that criteria were met for both manic and depressive episodes each day for at least 1 week, that either socio-professional and/or everyday life impairment or psychosis be present, and that medical conditions and drugs do not account for symptoms.

However, these narrow criteria fail to include many presentations seen in everyday practice (Perugi et al., 1997; Perugi et al., 2001; Suppes et al., 2005; Benazzi, 2007; Vieta and Suppes, 2008). Thankfully, the Task Force for the DSM-5 (First, 2011) is oriented towards abolishing the mixed episode and shifting it to "mixed features specifier". This would allow clinicians to consider mixed states in a less restrictive way, and extend them beyond the bipolar I subtype.

Limiting mixed states to bipolar I disorder disregards the clinical relevance of subthreshold mixed symptoms occurring in the context of a broader bipolar spectrum, with relevant clinical and treatment implications (Vieta, 2005; Swann et al., 2009; Goldberg et al., 2009; Dodd et al., 2010).

Recent efforts focused on establishing operational definitions of mixed states, especially according to prevalent polarity (depressive or manic); this enhances sensitivity in their detection (McElroy et al., 1992; Koukopoulos and Koukopoulos, 1999; Akiskal and Benazzi, 2004; Vieta, 2005; Henry et al., 2007; Swann et al., 2009). Despite this, the definition and operationalization of mixed states remain still unsolved, leading to important limitations in the management of bipolar patients (Vieta, 2005).

The prevalence of mixed states ranges from 9% to 23%, depending on the diagnostic criteria applied to a cohort; more restrictive criteria, like those of DSM-IV (American Psychiatric Association, 2000) and ICD-10 (WHO, 1992), yield lower figures, while the broader Cincinnati criteria (McElroy et al., 1992), based on clinical judgment, yield higher figures. However, higher concordance was found between the Cincinnati and ICD-10 criteria, which had moderate concordance with DSM-IV-TR criteria (Vieta and Morralla, 2010).

Mixed states are associated with earlier age at first hospitalization and longer duration of illness (Cassidy and Carroll, 2001; Valentí et al., 2011), with an increased relapse risk (Kessing, 2008; Baldessarini et al., 2010), a higher prevalence of substance use (González-Pinto et al., 2007) and other comorbidities (Goldberg and McElroy, 2007), a higher risk of suicide (Henry et al., 2007; Goldberg et al., 2009; Swann et al., 2009; González-Pinto et al., 2007, 2010; Valentí et al., 2011), lower recovery rates in the long-term (Azorin et al., 2009), and lower response to antidepressant drugs (ADs) (Goldberg et al., 2007; Frye et al., 2009; Valentí et al., 2011).

Baldessarini et al., (2010) found that bipolar I patients followed-up for 24 months after hospitalization for their first manic episode differed from those hospitalized for their first mixed episode in morbidity. Overall morbidity was 1.6-times higher in bipolar patients with an initial mixed state than in bipolar patients with a first purely manic episode; the former subsequently developed mixed states 12 times more than the latter, they were affected from major depression 6.5 times more often than the latter and had 69% more dysthymia during follow-up than patients presenting with an initial manic episode. These investigators concluded that their results do not support the equivalence of mania and mixed states, pointing to the existence of distinct clinical subtypes (Baldessarini et al., 2010).

The hypothesis of the present study is that bipolar I patients, regardless of the occurrence of purely depressive and hypomanic episodes, may differ on the grounds of whether their history includes past or current manic episodes only (purely manic, PMA), past or current manic *and* mixed episodes (MIX), or past or current mixed episodes only (purely mixed, PMIX). We expect these three groups to differ regarding their clinical course and characteristics.

2. Methods

One hundred and thirty four (N = 134) consecutive bipolar type I inpatients were included in the present study. All patients were admitted between January and June 2009 at the psychiatric Unit of Sant'Andrea Hospital (Rome, Italy) for a major affective acute episode (depressive, manic or mixed index episode). Diagnoses were made according to the DSM-IV criteria and confirmed through the Structured Clinical Interview (SCID-I and SCID-II) for DSM-IV-TR (First et al., 1996, 1997).

All patients provided written informed consent for the collection of their data for research, participation in the study and subsequent publication. The study protocol was approved by the Sant'Andrea Hospital Ethical Committee.

Assessments included the 21-item Hamilton Depression Rating Scale (HDRS-21, Hamilton, 1960) and the Young Mania Rating Scale (YMRS, Young et al., 1978), which were administered at admission and discharge from the hospital by trained raters to assess depressive (HDRS scores>20), manic (YMRS>20) or mixed (YMRS and $HDRS_{17}$ scores>14) symptoms.

The number and the type of affective episodes were retrospectively assessed at admission using the DSM-IV check-list for mania, hypomania, mixed episode and depression. This information was checked with the hospital medical records if these were available.

Several clinical variables were obtained from the structured interviews with patients and their relatives, including demographic data, number and polarity of episodes, number and duration of hospitalizations, age at onset, polarity of first episode, lifetime history of psychosis, suicidal behavior, Axis I and Axis II comorbidities, substance abuse, and psychiatric histories of first degree relatives past treatment with antidepressants, antipsychotic, anticonvulsant, and lithium treatment as well as information about social and occupational functioning.

Predominant polarity was defined according to Colom et al. (2006) operationalization, i.e., at least two thirds of a patient's past episodes belonging to one subtype. Mixed episodes were not considered as a part of any polarity.

Suicidality was measured through the number of attempts since the beginning of the illness and based on the presence or absence of suicidal ideation (through the suicide item of the HDRS or specific questions during interview).

2.1. Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS v.16 for Windows) for statistical analysis. Groups (PMA, MIX and PMIX) were compared for all measures shown in Tables 1 and 2.