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Research report

Mixed-state bipolar I and II depression: Time to remission and clinical characteristics

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ABSTRACT

Background: We compared the time to achieve remission and the clinical characteristics of patients with bipolar depressive mixed state and those with bipolar depressive non-mixed state.
Methods: The subjects ($N=131$) were inpatients diagnosed between 2006 and 2012 with bipolar I or II disorder, depression and were classified into the following three groups: "pure depressive state" (PD, $n=70$), "sub-threshold mixed state" (SMX, $n=38$), and "depressive mixed state" (DMX, $n=23$). Diagnosis of a DMX was in accordance with Benazzi's definition: three or more manic symptoms in a depressive episode. The subjects' charts were retrospectively reviewed to ascertain the time to achieve remission from the index episode and to identify other factors, such as demographic and clinical characteristics, specific manic symptoms, and pharmacological treatment, that may have contributed to remission.
Results: The time to achieve remission was significantly longer in the DMX ($p=0.022$) and SMX ($p=0.035$) groups than in the PD group. Adjustment for covariates using a Cox proportional hazards model did not change these results. Clinically, subjects with a DMX were more likely to have manic symptoms in the index episode, especially inflated self-esteem and psychomotor agitation than those in the PD.
Limitations: We investigated only inpatients and therefore could not comment on outpatients.
Conclusions: These findings showed that sub-syndromal manic symptoms in bipolar depression had different clinical characteristics and a more severe illness course, including a longer time to achieve remission, than did a pure depressive state.

1. Introduction

The coexistence of depressive and manic symptoms or the rapid alternation between these symptoms during the same time period has been considered a more severe form of mood episode than either one of these states alone. Mixed states are often protracted beyond acute episodes, psychotic symptoms are common, and suicide is a major risk (Freeman and McElroy, 1999). González-Pinto et al. (2011) indicated that patients with mixed episodes have a younger age at onset and a poorer long-term prognosis than do patients with non-mixed episodes. Most of those who attempt suicide suffer from a depressive mixed state with a predominantly bipolar II base, including strong predictors such as irritability and psychomotor agitation (Balázs et al., 2006). Not surprisingly, there are no clear recommendations for the treatment of patients with depressive mixed states (Ho et al., 2011; Muralidharan et al., 2013). Currently, the best treatment for bipolar mixed state is a three-pronged regimen including increasing/adding mood stabilizers and/or increasing/adding antipsychotics, as well as decreasing antidepressants (Ho et al., 2011). The mixed state, especially in patients with depressive episodes, has been considered to be an important diagnostic and treatment challenge.

In clinical situations, the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association, 2000) definition of a mixed state as the simultaneous presence of full manic and full depressive syndromes for at least 1 week is applied only to patients with bipolar I disorder. The International Statistical Classification of Diseases and Related Health Problems-10 (ICD-10) (World Health Organization, 1993) requires the coexistence or rapid alternation of prominent depressive symptoms and manic/hypomanic symptoms for at least 2 weeks. However, these criteria are too restrictive and are rarely satisfied in clinical situations, resulting in the exclusion of many patients who may be clinically considered as experiencing such a state.

To define and characterize these mixed states more accurately, many studies have compared the epidemiological and clinical characteristics and outcomes of bipolar depression using various criteria for the depressive mixed state. Benazzi and Akiskal (2001) have argued that the presence of two or three manic symptoms in a major depressive episode is associated with the occurrence of a mixed state. Syndromes such as "mixed depression" or "depressive mixed states," defined by the presence of three or more manic symptoms during bipolar II depressive episodes, have also been proposed (Benazzi and Akiskal, 2006). Perugi et al. (2001) described a depressive mixed state using Pisa criteria as a mixed state occurring

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during an episode of bipolar I depression. A depressive or manic episode with three or more symptoms of the opposite polarity has been suggested as a parsimonious definition of a mixed state (Swann et al., 2009).

However, both the clinical course, including the time to achieve remission, and the clinical characteristics of a depressive episode that is accompanied by sub-syndromal manic symptoms in patients with bipolar I or II disorder remain to be clarified.

In the present study, we compared the time to achieve remission of subjects with a bipolar depressive mixed state with that of subjects with a bipolar depressive non-mixed state. We also compared the demographics, clinical characteristics, specific manic symptoms, and pharmacological treatment, that may have contributed to remission between the groups. We used Benazzi's (Benazzi and Akiskal, 2006) definition (three or more manic symptoms within a depressive episode) as the criterion to determine which patients with a depressive mixed state who were originally diagnosed with bipolar I or II disorder and were hospitalized for depression should be included in the present study. Subjects were categorized into three groups: pure depressive state (no manic symptoms), sub-threshold mixed state (one or two manic symptoms), and depressive mixed state (more than three manic symptoms).

2. Methods

2.1. Patients

Medical charts were retrospectively reviewed at Yeouido St. Mary's Hospital, College of Medicine at The Catholic University of Korea in Seoul, Korea. All patients hospitalized at this institution had been diagnosed in clinical interviews with an Axis I disorder by a board-certified psychiatrist in accordance with the DSM-IV-TR (American Psychiatric Association, 2000). All subjects in this study met the DSM-IV-TR criteria (American Psychiatric Association, 2000) for bipolar I or II disorder, depression during the period from 2006 to 2012. The inclusion criteria included diagnosis of bipolar disorder according to the DSM-IV-TR (American Psychiatric Association, 2000); current depressive episode, non-mixed; and age 15–75 years. Exclusion criteria consisted of insufficient data, a severe comorbid medical or neurological condition that could contribute to mood symptoms; an organic brain lesion that may influence mood symptoms; a thought disorder, such as schizophrenia; a diagnosis of schizoaffective disorder; or a cognitive disorder, such as dementia, that can confound the phenomenology of a mood episode.

The charts of 185 subjects diagnosed with bipolar I and II disorder, depression were analyzed at baseline, and 54 cases were excluded based on the aforementioned criteria. Thus, 131 inpatients diagnosed with bipolar I or II disorder, depression were enrolled in the study and categorized into three groups: pure depressive state, sub-threshold mixed state, and depressive mixed state. The classification was performed in accordance with Benazzi (Benazzi and Akiskal, 2006)'s definition of a depressive mixed state, which included the DSM-IV-TR criteria (American Psychiatric Association, 2000) for manic symptoms: elevated/irritable mood, inflated self-esteem, decreased need for sleep, more talkative than usual, flight of ideas/racing thoughts, distractibility, psychomotor agitation, and high-risk behaviors, such as unrestrained buying sprees, sexual indiscretions, or foolish business investments.

2.2. Assessments

The patients' charts were reviewed to examine demographic and clinical characteristics, including age at onset, age at first treatment, age at admission, sex, marital status, education, employment, family history of mood disorder (especially family history of bipolar and depressive disorders), number of mood episodes (total number of mood episodes, number of depressive episodes, number of manic episodes, number of hypomanic episodes, and number of mixed episodes), number of hospitalizations for mood episodes (total number of hospitalizations for mood episodes, number of hospitalizations for depressive episodes, number of hospitalizations for manic episodes, and number of hospitalizations for mixed episodes), comorbid disorders (especially personality and substance use disorders), and suicidality (defined as any suicide attempts during the subject's lifetime).

The index episode was the depressive episode that led to the hospitalization between 2006 and 2012 selected for analysis in this study. If a patient experienced more than one hospitalization during the study period, only the data from the last admission were analyzed. To identify mixed features, patients were monitored for opposite-polarity symptoms, such as manic symptoms (according to the DSM-IV-TR criteria (American Psychiatric Association, 2000) for a manic episode). Two independent physicians (W.Y.S. and T.Y.J.) who were not informed about the purpose of the study independently evaluated the medical records for opposite-polarity symptoms.

Clinical data for the index episode included information about specific clinical subtypes such as melancholic features, atypical features, psychotic features, and chronicity. Index major depressive episodes that lasted for at least 2 years were considered to reflect chronicity (American Psychiatric Association, 2000). Symptom severity was measured with the global assessment of functioning (GAF) at admission and the clinical global impression-severity (CGI-S) at both admission and discharge. Moreover, the groups were also compared in terms of their pharmacological treatments, such as mood stabilizers (lithium and other anticonvulsants), antipsychotics, and antidepressants, at discharge.

We compared the groups with respect to the time to achieve remission from the index episode. In the present study, remission was defined as clinical improvement such that the patient was almost asymptomatic (i.e., showed minimal or no symptoms) and was able to engage in functional activities during 2 consecutive months (American Psychiatric Association, 2000; Zajecka, 2003).

2.3. Statistical analysis

Statistical analyses were performed using SAS for Windows (version 9.2). Statistical methods consisted of *chi*-square tests or Fisher's exact test with Bonferroni's correction for comparisons of categorical variables and analysis of variance (ANOVA) or the Welch–Satterthwaite method (when equal variances were not assumed) for continuous variables. *Post hoc* analysis using Tukey's procedure or Dunnett's T3 (equal variances were not assumed) was used to calculate mean differences and to determine significant differences among means. To identify the factors associated with mixed states, a multinomial logistic regression analysis was conducted. Independent variables included demographic information, clinical characteristics prior to the index episode, and clinical data from the index episode, including manic symptoms (according to the DSM-IV-TR criteria for a manic episode). The dependent variable was group assignment: pure depressive state (patients not meeting criteria for manic symptoms), sub-threshold mixed state (patients with one or two of these criteria), and depressive mixed state (patients with three or more of these criteria). A p-value of 0.05 was considered statistically significant; when Bonferroni's correction for comparisons of categorical variables was used, p-values of 0.017 were considered statistically significant. A p-value between 0.05 and 0.10 was considered to indicate a trend toward significance; when Bonferroni's correction for comparisons of categorical variables was used, p-values between 0.17 and 0.33 were considered to indicate a trend toward significance.