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Research report

A diagnosis of bipolar spectrum disorder predicts diagnostic conversion from unipolar depression to bipolar disorder: A 5-year retrospective study

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ABSTRACT

Background: The major aims of this study were to identify factors that may predict the diagnostic conversion from major depressive disorder (MDD) to bipolar disorder (BP) and to evaluate the predictive performance of the bipolar spectrum disorder (BPSD) diagnostic criteria.
Methods: The medical records of 250 patients with a diagnosis of MDD for at least 5 years were retrospectively reviewed for this study.
Results: The diagnostic conversion from MDD to BP was observed in 18.4% of 250 MDD patients, and the diagnostic criteria for BPSD predicted this conversion with high sensitivity (0.870) and specificity (0.917). A family history of BP, antidepressant-induced mania/hypomania, brief major depressive episodes, early age of onset, antidepressant wear-off, and antidepressant resistance were also independent predictors of this conversion.
Limitations: This study was conducted using a retrospective design and did not include structured diagnostic interviews.
Conclusions: The diagnostic criteria for BPSD were highly predictive of the conversion from MDD to BP, and conversion was associated with several clinical features of BPSD. Thus, the BPSD diagnostic criteria may be useful for the prediction of bipolar diathesis in MDD patients.

1. Introduction

The under-diagnosis of bipolar disorder (BP) is common, and in fact, BP is often either not diagnosed at all or falsely diagnosed as major depressive disorder (MDD; (De Fruyt and Demyttenaere, 2007). The rate of misdiagnosis or under-diagnosis was approximately 80% in a community sample (Hirschfeld et al., 2003) and 40% in a hospitalized sample (Ghaemi et al., 1999). This may be partly due to the diagnostic criteria for BP because the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), and DSM-5 criteria require the occurrence of a manic or hypomanic episode for a diagnosis of BP. It has been suggested that BP patients presenting with an episode of depression without a distinct history of mania/hypomania are practically impossible to diagnose correctly (Grotegerd et al., 2013), and approximately half of BP patients present with a major depressive episode as their first mood episode (Tondo et al., 2010; Etain et al., 2012). BP patients are three times more likely to suffer from depressive symptoms than from manic or hypomanic symptoms (Judd et al., 2002, 2003), and many BP-II patients seek help when in the depressed phase (Akiskal et al., 2000). Patients who begin BP with depressive episodes appear to be at increased risk for long-term morbidity, disability, and suicide (Baldessarini et al., 2010, 2012).

The misdiagnosis and under-diagnosis of BP are due in part to the 'soft' symptoms of bipolarity that characterize patients with non-classical BP (Katzow et al., 2003). Consequently, the search for bipolar signatures in the symptoms and course of MDD has intensified. Several clinical markers of soft bipolarity have been suggested, including mixed anxiety/depressive symptoms (Katzow et al., 2003), conditions associated with impulsivity such as substance abuse, borderline personality, bulimia, and attention deficit disorder (Regier et al., 1990; Katzow et al., 2003), atypical depressive features (Perugi et al., 1998; Mitchell et al., 2001), early age of onset (Neuman et al., 1997; Benazzi, 2009), recurrent depressive episodes (Benazzi, 2009), a family history of BP in first-degree relatives (Benazzi, 2009), brief major depressive episodes (De Fruyt and Demyttenaere, 2007), antidepressant-induced mania/hypomania (Hirschfeld et al., 2003),

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post-partum depression (Judd et al., 2002), treatment resistance (Woo et al., 2008), and specific affective temperament types. i.e., depressive, cyclothymic, hyperthymic, irritable, and anxious (Rihmer et al., 2010).

The concept of 'bipolar spectrum' arose from the work of Dunner et al. (1970), whose definition of bipolarity included varying degrees of mania and hypomania. This concept was developed by Klerman (1981) and later by Akiskal (1996) to include the continuum from psychotic mania through other expressions of bipolar I disorder and bipolar II disorder, to soft subsyndromal manifestations of bipolarity, i.e., soft or subthreshold bipolarity (Nusslock and Frank, 2011).

Later, Ghaemi et al. (2001, 2002) proposed an approach to the spectrum concept that focuses on how to distinguish BP from unipolar depression. He suggested that the following 11 features may predict the diagnosis of BP in patients with depressive symptoms and proposed that the definition of bipolar spectrum disorder (BPSD) is a potential sign of bipolarity: family history of BP in first-degree relatives; antidepressant-induced mania or hypomania; hyperthymic personality; recurrent major depressive episodes (>3); brief major depressive episodes (lasting an average of less than 3 months); atypical depressive symptoms; psychotic major depressive episodes; early age of onset of major depressive episodes (<25 years of age); postpartum depression; antidepressant "wear-off;" and treatment resistance (lack of response to ≥ 3 antidepressant treatment trials). Ghaemi et al. (2004) demonstrated that the proposed criteria can distinguish patients with bipolar depression from those with unipolar depression, but the proposed diagnostic criteria were not tested regarding their ability to predict the conversion from unipolar depression to BP.

A large proportion of patients suffering from MDD exhibit underlying soft bipolarity, and the identification of antecedents that predict the conversion from unipolar depression to BP would be highly beneficial for these patients. Thus, a set of patients diagnosed with MDD were retrospectively investigated in an attempt to identify the features and diagnostic criteria proposed for BPSD by Ghaemi et al. (2002) to analyze the predictive performance of the diagnostic criteria overall and of each clinical feature.

2. Methods

2.1. Patients and assessments

This study was a retrospective investigation that reviewed the medical records of patients who were hospitalized in the psychiatric ward of Yeouido St. Mary's Hospital, College of Medicine at The Catholic University of Korea in Seoul, Korea, between January 1, 2005 and December 31, 2008, with a diagnosis of MDD without prior history of mania or hypomania. The patients were clinically diagnosed with MDD according to the DSM-IV criteria at the index hospitalization. Those who were admitted for an adverse event or other non-psychiatric diagnostic or environmental etiology were excluded from the analyses. To be eligible for inclusion in this study, the patients were required to have had at least 5 years of follow-up care and to have been diagnosed with MDD or BP at the 5-year follow-up. Patients with insufficient data and those who had a severe comorbid medical or neurological condition that could contribute to depressive symptoms, a diagnosis of a mood disorder due to a general medical condition, or a diagnosis that converted from MDD to another diagnosis other than BP were excluded from the analyses.

A diagnosis of BPSD was made based on the proposed diagnostic criteria of Ghaemi et al. (2001), with the exception that postpartum depression was excluded from the criteria to avoid a gender bias that may affect the predictive ability of the criteria. The diagnoses of BPSD at index hospitalization and/or an Axis I disorder during the follow-up period were independently made by two physicians (IHS and HRW) who were blind to the purpose of the study and who separately evaluated the medical records. Based on the DSM-IV which noted that "manic-like episodes that are clearly caused by somatic antidepressant treatment (e.g., medication, electroconvulsive therapy, and light therapy) should not count toward a diagnosis of bipolar I disorder", patients who exhibited mania/hypomania only during periods of treatment with causative medications, such as antidepressants, were regarded as patients with MDD when we made the DSM-IV diagnosis. However, those subjects with sufficient manic/hypomanic symptoms to be diagnosed as bipolar disorder during the follow-up period were categorized in the conversion group irrespective of a history of antidepressant-induced mania/hypomania at the index hospitalization or during the follow-up period.

Clinical data from the index hospitalization included each item of the diagnostic criteria for BPSD as well as age at index hospitalization and sex. A history of the clinical characteristics, such as age at first psychiatric treatment, age at onset, and number of past major depressive episodes before the subjects visited our hospital, which were investigated at the time of the index hospitalization retrospectively, was also included in the analysis. As this was a retrospective study, all data were obtained during routine psychiatric examinations and treatment.

2.2. Statistical analysis

The clinical and demographic variables of patients with a diagnosis of MDD at index hospitalization and the 5-year follow-up (unipolar group) were compared with the variables of patients whose diagnosis changed from MDD at index hospitalization to BP during the follow-up period (conversion group). A Chi-squared test or Fisher's exact test was used to analyze categorical variables and an independent *t*-test or Mann–Whitney *U*-test was used to test continuous variables. To identify the independent predictors of the conversion from MDD to BP, a multinomial logistic regression analysis was conducted for which the independent variables were sex, age, psychiatric comorbidity, and the clinical features of BPSD. Statistical analyses were performed using SAS for Windows (ver. 9.2), and two-tailed *p*-Values with an alpha level of 0.05 were considered significant, except that a Bonferroni-corrected significance level of $p<0.0045$ (0.05/11 tests) was applied to the univariate analysis that compared the groups in terms of the proportion of subjects with each of the 10 proposed bipolar features in the modified BPSD diagnostic criteria who met the modified BPSD criteria.

2.3. Ethics

This study was approved by the institutional review board of Yeouido St. Mary's Hospital in Seoul, Korea, and was conducted according to the Declaration of Helsinki. The institutional review board approved the exemption for informed consent because this was a retrospective chart review study.

3. Results

During the study period, 448 patients were discharged with a diagnosis of MDD. Of these patients, 250 (55.8%) fulfilled the eligibility criteria for the study.

3.1. Diagnostic conversion from MDD to BP

Of the original 250 patients initially diagnosed with MDD, the conversion rate to BP was 18.4%. The demographic and clinical characteristics of these patients at the index hospitalization are