



Research report

Prevalence and predictors of bipolar disorders in patients with a major depressive episode: The Japanese epidemiological trial with latest measure of bipolar disorder (JET-LMBP)



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ARTICLE INFO

Article history:

Received 31 October 2014

Received in revised form

21 November 2014

Accepted 4 December 2014

Available online 15 December 2014

Keywords:

Bipolar disorder

Major depressive disorder

Prevalence

Differential diagnosis

DSM-IV-TR

ABSTRACT

Background: For patients with a major depressive episode, early differential diagnosis of bipolar disorder and subsequent appropriate treatment are critical. This study, conducted in clinical settings in Japan, examined patients with a major depressive episode to investigate the prevalence and predictors of bipolar disorders.

Methods: A total of 448 patients with a major depressive episode were interviewed using the Mini-International Neuropsychiatric Interview to determine the presence of mood episodes and psychiatric comorbidities. The diagnosis of bipolar disorder was based on the collected information according to the DSM-IV-TR.

Results: Of the 448 patients with a major depressive episode, 114 patients (25.4%) were diagnosed with bipolar disorder. Multivariate logistic regression identified five predictors that were significantly correlated with bipolar disorder: antidepressant-related switch to mania/hypomania, mixed depression, two or more previous mood episodes within the past year, early age at the onset of a major depressive episode (< 25 years), and a history of suicide attempts. The area under the curve of receiver operating characteristic analysis based on the multivariate logistic regression of the five predictors was 0.849.

Limitations: The diagnosis of bipolar disorder in patients was already conclusively confirmed by long illness observations but was not confirmed by a prospective study.

Conclusions: In patients with a major depressive episode, the differential diagnosis of bipolar disorder and major depressive disorder, which exhibit similar depressive symptoms, is essential. Several predictors identified in the present study may be useful in supporting a differential diagnosis of these disorders in routine clinical practice.

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1. Introduction

Bipolar disorder (BD) is a chronic disease characterized by repeated manic and depressive episodes alternating over a long period of time after disease onset with an extremely high risk of relapse and recurrence (Kanba et al., 2013; Keller et al., 1993). It is further known that many patients with BD have more prolonged depressive episodes than manic episodes during the illness (Judd et al., 2002; Judd et al., 2003). In an approximate 13-year prospective follow-up of patients with BD, the depressive episode duration was approximately 3 times (bipolar I disorder (BD-I)) to 40 times (bipolar II disorder (BD-II)) longer than the manic

episode duration (Judd et al., 2002; Judd et al., 2003). The majority of patients with BD visit psychiatrists during depressive episodes, which may reflect their greater self-awareness of depression compared with their awareness of experiencing mania/hypomania (Dell'Osso et al., 2002).

Differentiating in the clinical setting between bipolar depression and major depressive disorder (MDD) in patients with a major depressive episode (MDE) is critical because patients with BD who present with an MDE are likely to be diagnosed with MDD. This occurs because depressive episodes exist with both disorders (BD and MDD), and patients and physicians may not be aware of prior or future episodes of mania/hypomania (Hirschfeld et al., 2003). In a previous study, 20.8% of patients being treated for MDD were diagnosed with BD after administering the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Xiang et al., 2013). The onset episode in two-thirds of the patients with BD is a depressive episode (Daban et al., 2006), and unipolar-to-bipolar conversion in

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most BD patients with depressive onset occurs within 5–9 years (Akiskal et al., 1995) or on the average 6.4 years after onset of first depression (Akiskal et al., 1983). For these reasons, more than half of the patients with BD are initially diagnosed with MDD until a mania/hypomania episode, which can occur several years after onset. Hence, patients with an MDE being treated for MDD can actually suffer from BD, but they are not clinically diagnosed as such.

Diagnosing a patient with unrecognized BD as MDD is detrimental to the subsequent course and outcome of the disease, and therefore, it is an issue that must be addressed in the treatment of BD. Patients with BD who are diagnosed as having a MDD will be treated primarily with antidepressants. However, major treatment guidelines for mood disorders recommend mood stabilizers and antipsychotics as first-line drugs for the treatment of depression due to BD, rather than antidepressant monotherapy (Kanba et al., 2013; Yatham et al., 2013). Accordingly, no appropriate treatment is provided for unrecognized bipolar depression during this interim period, and the delay of appropriate treatment may result in prolongation of the disease or a significant increase in the incidence of suicide attempts (Altamura et al., 2010). For patients with an MDE, early diagnosis and appropriate treatment of BD are critical to improve the course and prognosis of BD.

For early diagnosis and appropriate treatment of BD in patients with an MDE, it may be beneficial to identify predictive factors of BD at the initial visit, even if information regarding previous manic/hypomanic episodes is not clear or is absent. The presence of such predictors specific to BD facilitates a further intensive medical interview for the discovery of BD in future years and for an accurate diagnosis. Specific predictors correlated with BD have been reported by multivariate logistic regression analyses (Angst et al., 2011; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013). The common predictors correlated with BD are family history of BD (Angst et al., 2011; Perlis et al., 2006; Takeshima and Oka, 2013), early onset of an MDE (Angst et al., 2011; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013), and history of multiple MDEs (Angst et al., 2011; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013). Generally, the candidate predictors in these studies are listed as predictors reported in earlier literatures (Angst et al., 2011; Takeshima and Oka, 2013). To our knowledge, there has been no study that performed multivariate logistic regression analyses of candidate predictors selected from a comprehensive record of several demographic and clinical features that are not limited to commonly accepted theories. In addition, previous studies (Angst et al., 2011; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013) did not examine quality of life (QOL) or child abuse, both of which have been recently identified as factors associated with the onset or clinical course of BD (Daruy-Filho et al., 2011; Etain et al., 2008).

The present study was conducted in a variety of medical facilities among patients with an MDE. This study aimed to determine the prevalence of BD in patients with an MDE and to identify predictors to support the diagnosis of BD using a comprehensive record of 74 demographic and clinical features that are not limited to commonly accepted theories. To identify patients with a high probability of BD among patients with an MDE, the predictive performance of combinations of these factors that are assessable at the initial visit was evaluated.

2. Subjects and methods

2.1. Study design and subjects

The Japanese epidemiological trial with the latest measure of bipolar disorder (JET-LMBP) was a multicenter, cross-sectional, epidemiological study conducted from April to June 2013 at 23 psychiatric facilities in Japan: 2 university hospitals, 3 general hospitals,

3 psychiatric hospitals, and 15 psychiatric clinics. Outpatients aged 20 to 65 years who presented with an MDE according to the DSM-IV-TR were included in the study (American Psychiatric Association, 2000). The following patients were excluded: those diagnosed with “schizophrenia and other psychotic disorders”, “mood disorder due to a general medical condition”, and “substance-induced mood disorder” according to the DSM-IV-TR; those at a high risk of an imminent suicide attempt (in the judgment of the investigator); and those who were determined to be unsuited to participate in the study by the investigator.

2.2. Study procedures

Written informed consent was obtained from patients who met all of the inclusion criteria and none of the exclusion criteria. After informed consent was obtained, eligible patients were interviewed using the M.I.N.I. to determine the presence of mood episodes and psychiatric comorbidities such as anxiety disorder and substance-related disorder (Otsubo et al., 2005; Sheehan et al., 1998). Mixed depression was defined as three or more positive items of D1b, D2b and D3a–g with respect to the present MDE in the D module (manic/hypomanic symptoms) of the M.I.N.I. according to Benazzi's definition (Benazzi, 2007). The method of the M.I.N.I. was modified in this study, D3a–g were asked regardless of the presence or absence of D1 and D2. In addition, various demographic and clinical characteristics were assessed using a patient background sheet. The patient background sheet consisted of 52 questions that included basic patient information such as age, sex, family history, features such as age of onset and number of episodes, and current symptoms such as mood reactivity, hypersomnia and excessive eating.

In addition, the patients were asked to complete three self-reported questionnaires: the 16-item Japanese version of the Quick Inventory of Depressive Symptomatology-Self Report (QIDS-SR-J), which is designed to assess the severity of depression (Fujisawa et al., 2010); the Japanese version of the 36-item Short-Form Health Survey (SF-36), which is designed to assess the health-related QOL (Fukuhara et al., 1998); and the Japanese version of the 38-item Child Abuse and Trauma Scale (CATS) (ver. 5.0.J.), which is designed to assess how frequently a particular abusive experience occurred during the subject's childhood and adolescence (Nakai et al., 2014; Sanders and Becker-Lausen, 1995; Tanabe et al., 2010). Based on the collected information and routine clinical interviews, the investigator made a principal diagnosis according to the DSM-IV-TR.

2.3. Statistical analysis

The SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was used for the analyses. In all statistical analyses, a two-sided significance level of 5% was used. The Fisher's exact test or Wilcoxon test was used to compare demographic characteristics between patients with BD and those with MDD.

To identify predictors correlated with BD, univariate logistic regression analyses were first performed for the demographic and clinical features of patients diagnosed with BD and those diagnosed with MDD. For the features with a *p* value of less than 0.001 and an odd ratio of 2 or more in the univariate logistic regression analyses, a multivariate logistic regression analysis was performed. The predictors with a *p* value of 0.05 or less in the multivariate analysis were identified to be significantly correlated with BD.

Finally, the predictive performance of the logistic regression equation and the combinations of the factors correlated with BD obtained by a multivariate logistic regression analysis was evaluated by a receiver-operating characteristic (ROC) curve analysis based on the logistic regression equation or the number of the predictors. In addition, the predictive performance of the logistic

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