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Original Article

Sociodemographic and clinical features of bipolar disorder patients misdiagnosed with major depressive disorder in China

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Objectives: Bipolar disorder (BD) is frequently misdiagnosed as major depressive disorder (MDD), which may lead to inappropriate treatment and poor outcomes. This study aimed to compare demographic and clinical features between patients with MDD and those with BD, but being misdiagnosed as MDD, in China.

Methods: A total of 1487 patients diagnosed with MDD were consecutively evaluated in 13 psychiatric hospitals or psychiatric units of general hospitals nationwide in China. The patients' sociodemographic and clinical characteristics were recorded using a standardized protocol and data collection procedure. The Mini-International Neuropsychiatric Interview (MINI) was used to establish DSM-IV diagnoses, and identify patients with MDD and those with BD, but being misdiagnosed with MDD.

Results: The proportions of BD (all types), bipolar I disorder (BD-I), and bipolar II disorder (BD-II) misdiagnosed as MDD in clinical practice were 20.8%, 7.9%, and 12.8%, respectively. Multiple logistic regression analyses revealed that compared to MDD patients, BD-I was characterized by more atypical depressive features (increased appetite, increased sleep, and weight gain) [odds ratio (OR) = 2.0, 95% confidence interval (CI): 1.2–3.2], more psychotic symptoms (OR = 2.1, 95% CI: 1.3–3.5), more lifetime depressive episodes (OR = 1.1, 95% CI: 1.1–1.2), and earlier age of onset (OR = 0.97, 95% CI: 0.9–0.99); BD-II was characterized by more psychotic symptoms (OR = 2.1, 95% CI: 1.4–3.1) and earlier age of onset (OR = 0.96, 95% CI: 0.9–0.97). In addition, compared to BD-II patients, BD-I patients were characterized by more frequent depressive episodes per year (OR = 3.1, 95% CI: 1.5–6.6).

Conclusions: Depressive episodes in the context of BD-I and BD-II, among those who were misclassified as MDD, present some different clinical features compared to MDD. This finding should be taken into account in guiding diagnostic practices in China.

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In clinical practice, diagnostic criteria for bipolar I disorder (BD-I) and bipolar II disorder (BD-II) depend on the presence or absence of manic or hypomanic episodes. A depressive episode is usually the first mood syndrome at the onset of bipolar disorder (BD), and depressive episodes are

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more frequent than manic or hypomanic episodes (1). Hypomania is often viewed as a normal experience by patients and therefore can be underreported (2). Also, clinicians do not always ask depressed patients about hypomania (3), and some depressed patients have not yet experienced a manic or hypomanic episode (4). As a result, patients with BD, particularly BD-II, are frequently misdiagnosed with major depressive disorder (MDD) and may receive inadequate or inappropriate treatment (2, 5). Thus, early identification of BD is of crucial importance.

Given the important implications for treatment and prognosis of BD, in the past few decades a number of studies have consistently identified sociodemographic, clinical-phenomenological, and biological differences between bipolar depression and MDD. Compared to MDD, commonly reported features of bipolar depression included younger age of onset, shorter duration of episodes, more prior episodes, social withdrawal, hypersomnia, hyperphagia, lability of mood, psychotic features, psychomotor retardation, and family history of BD (6). These findings were almost entirely based on studies of Western populations. Evidence suggests that features of mood disorders are not independent of the complex interplay of the biopsychosocial environment (7). It has been pointed out that Western psychiatric textbooks, diagnostic systems, and research findings do not cover the full range of mood symptoms experienced by Chinese patients (8, 9). Therefore, it is necessary to examine the demographic and clinical-phenomenological differences between bipolar depression and MDD in China.

This study examined whether BD patients misdiagnosed with MDD differ from those with MDD in terms of demographic and clinical features in Chinese clinical settings.

Methods

Study participants and settings

This study was part of the Diagnostic Assessment Service for People with Bipolar Disorders in China (DASP), which is an ongoing nationwide study initiated by the Chinese Society of Psychiatry (CSP), and aims to develop and test the usefulness of screening tools for BD in patients treated for MDD. Participants in the project were recruited in 13 major psychiatric hospitals/units [Beijing Anding Hospital (n = 177), Peking University Institute of Mental Health (n = 41), Beijing Huilongguan Hospital (n = 60), Shanghai Mental Health Center (n = 216), Shanghai Tongji Hospital (n = 39), Shenzhen Mental Health Centre (n = 140), the First Hospital of Harbin Medical University (n = 123), Hangzhou Seventh People's Hospital (n = 87), West China Hospital (n = 73), the Affiliated Brain Hospital of Nanjing Medical University (n = 166), Mental Health Institute of the Second Xiangya Hospital (n = 102), the Second Affiliated Hospital of Zhejiang University (n = 153), and the Third Affiliated Hospital of Sun Yat-Sen University (n = 110)] located in north, south, east, west, and central parts of China, and representing a range of clinical settings. The study period lasted from September 1, 2010 to February 28, 2011. Patients were enrolled if they were between 16 and 65 years old, were inpatients or outpatients, had a diagnosis of DSM-IV or ICD-10 MDD based on a review of medical records, understood the aims of the study, and provided informed consent. Exclusion criteria included: (i) a past diagnosis of BD; (ii) a history of or ongoing significant medical or neurological condition(s); (iii) depressive disorders secondary to a general medical or neurological condition; and (iv) having received electroconvulsive therapy (ECT) in the past month. The study protocol was approved by the Clinical Research Ethics Committees of the respective study centers.

Instrument and assessment procedure

Patients with MDD who were receiving treatment in the participating hospitals/units were consecutively referred by their treating psychiatrists to the research team during the study period to be screened for eligibility. Patients fulfilling the study entry criteria were invited to participate in the study.

Patients' basic sociodemographic and clinical data were collected in a clinical interview with a questionnaire designed for the study and were supplemented by a review of their medical records (Table 1). The diagnostic assessment of BD was conducted with the Chinese version of the Mini-International Neuropsychiatric Interview (MINI), Version 5.0, to establish DSM-IV BD-I/BD-II diagnoses (10, 11). High recurrence was defined as more than four major depressive episodes per year. The number of major depressive episodes was counted based on a review of medical records; to be considered as separate episodes, there had to be an interval of at least two consecutive months between episodes during which criteria were not met for an MDD. Age at onset was defined as onset of the first major depressive or manic episode (12).

Prior to the study, all 13 raters were trained in the use of MINI in diagnosing BD in 20 patients

treated for MDD. In this reliability exercise, their judgments of BD were compared to those of the best estimate clinical diagnoses (15 of the 20 patients were BD patients); the kappa values were >0.85. Whenever possible, the same raters evaluated the same group of patients throughout the study. After providing written consent following a full explanation about the study, patients met a rater for a confirmatory diagnostic interview based on DSM-IV criteria using the MINI supplemented by a review of medical records and, whenever possible, an interview of relatives.

Statistical analysis

Data were analyzed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to characterize the patients' sociodemographic and clinical features. Comparisons of the sociodemographic and clinical characteristics of patients with BD-I, BD-II, and MDD were performed by one-way analysis of variance (ANOVA) or the chi-square test, as appropriate. If these tests were significant, *post-hoc* tests were carried out. Stepwise multiple logistic regression analyses were used to compare demographic and clinical variables between MDD and BD-I, between MDD and BD-II, and between BD-I and BD-II. In the regression analyses, the diagnosis based on the MINI (MDD/BD-I, MDD/BD-II, and BD-I/BD-II) was entered as the dependent variable separately and all variables that showed a significant difference between the three groups in the aforementioned univariate analyses (age, gender, marital status, frequent depressive episodes, atypical depressive features, depressive episodes with suicidal ideation and/or attempts, psychotic symptoms, lifetime depressive episodes, seasonal depressive episodes, family history of psychiatric disorders, and age of onset) were entered as independent variables after study site was controlled for. The level of significance was set at 0.05 (two-tailed).

Results

In total, 1757 patients were screened and invited to participate in this study; 270 (15.4%) refused to participate or failed to complete the interview. There was no significant difference between the study patients and those who refused to participate or failed to complete the assessment in terms of age and gender. A total of 1487 patients were included in the analysis.

Of the 1487 patients, 309 (20.8%) satisfied DSM-IV criteria for BD; 118 (7.9%) for BD-I and 191 (12.8%) for BD-II. Table 1 displays the sociodemographic and clinical characteristics of the whole sample as well as separately for patients by diagnosis. Compared to MDD patients, BD-I patients were more likely to be male, had more frequent depressive episodes (more than four episodes/year), more atypical depressive features (increased appetite, increased sleep, and weight gain), suicide ideation and attempts, psychotic symptoms, more seasonal depressive episodes, a stronger family history of psychiatric disorders, more lifetime depressive episodes, younger age, and earlier age at onset. Compared to MDD patients, BD-II patients were more likely to be male and married, had more atypical depressive features (increased appetite, increased sleep, and weight gain), suicide ideation and attempts, psychotic symptoms, more seasonal depressive episodes, a stronger family history of psychiatric disorders, more lifetime depressive episodes, younger age, and earlier age at onset.

In multiple logistic regression analyses, compared to MDD, BD-I was characterized by more atypical depressive features (increased appetite, increased sleep, and weight gain), more psychotic symptoms, higher number of lifetime depressive episodes, and earlier age at onset; BD-II was characterized by more psychotic symptoms and earlier age at onset (Table 2). Compared to BD-II, BD-I was characterized by more frequent depressive episodes per year [odds ratio (OR) = 3.1, 95% confidence interval (CI): 1.5–6.6; p = 0.002].

Discussion

To the best of our knowledge, this is the first study systematically to compare the sociodemographic and clinical features between patients with MDD and those with BD-I or BD–II who have been misdiagnosed with MDD in China. We also have found no previous studies that have identified undiagnosed BD patients using the MINI and then compared their demographic and clinical features to those with MDD in other settings. Earlier studies have found that accurate diagnosis of BD usually takes eight to ten years (13) and BD, particularly BD-II, is frequently misdiagnosed as MDD, resulting in inadequate or inappropriate treatment (2, 5). The failure to treat with mood stabilizers in BD may lead to more frequent mood episodes, precipitation of a mixed state, increased risk of suicidal behaviors, and poorer outcome in general (14, 15). Therefore, correctly diagnosing BD in depressed patients has vitally important clinical implications. Similar to the findings of previous studies (16–21), the clinical presentation of depression in both BD-I and BD-II patients in the

Table 1. Basic demographic and clinical characteristics of patients treated for major depressive disorder (MDD)

	Entire sample (N = 1487)	BD-I (n = 118)	BD-II (n = 191)	MDD (n = 1178)	Statistics			*Post-hoc* analyses (p-values)[a]		
					χ^2	df	p-value	A	B	C
Gender, male	533 (35.8)	51 (43.2)	97 (50.8)	385 (32.7)	26.5	2	<0.001	0.20	0.02	<0.001
Married/cohabiting	1016 (68.3)	76 (64.4)	116 (60.7)	824 (69.9)	7.4	2	0.03	0.50	0.20	0.01
Employed	1024 (68.9)	76 (64.4)	136 (71.2)	812 (68.9)	1.6	2	0.50	—	—	—
Education					5.5	6	0.50	—	—	—
Primary and junior secondary school	439 (29.5)	31 (26.3)	52 (27.2)	356 (30.2)						
Senior secondary school	388 (26.1)	32 (27.1)	44 (23.0)	312 (26.5)						
College and university	597 (40.1)	47 (39.8)	85 (44.5)	465 (39.5)						
Postgraduate	63 (4.2)	8 (6.8)	10 (5.2)	45 (3.8)						
Frequent depressive episodes (>4 episodes/year)	142 (9.5)	35 (29.7)	17 (8.9)	90 (7.6)	60.3	2	<0.001	<0.001	<0.001	0.50
Depressive episodes with:										
Increased appetite, increased sleep, and weight gain	271 (18.2)	47 (39.8)	45 (23.6)	179 (15.2)	47.9	2	<0.001	0.002	<0.001	0.004
Suicidal ideation and/or attempts	871 (58.6)	82 (69.5)	124 (64.9)	665 (56.5)	11.2	2	0.004	0.40	0.006	0.03
Psychotic symptoms	258 (17.4)	45 (38.1)	55 (28.8)	158 (13.4)	65.7	2	<0.001	0.10	<0.001	<0.001
Panic symptoms	1162 (78.1)	99 (83.9)	148 (77.5)	915 (77.7)	2.5	2	0.30	—	—	—
Major depressive episodes following obvious causes, such as postpartum	735 (49.4)	59 (50.0)	98 (51.3)	578 (49.1)	0.3	2	0.80	—	—	—
Seasonal depressive episodes	201 (13.5)	33 (28.0)	34 (17.8)	134 (11.4)	28.7	2	<0.001	0.04	<0.001	0.01
Family history of psychiatric disorders	283 (19.0)	33 (28.0)	47 (24.6)	203 (17.2)	12.4	2	0.002	0.50	0.004	0.01
Age, years, mean (SD)	39.5 (12.8)	35.5 (11.1)	35.5 (12.7)	40.5 (12.8)	19.1[b]	21484	<0.001	0.90	<0.001	<0.001
Age at onset, years, mean (SD)	33.4 (12.4)	28.0 (10.5)	28.8 (10.9)	34.6 (12.5)	31.4[b]	21484	<0.001	0.60	<0.001	<0.001
No. of lifetime depressive episodes, mean (SD)	2.1 (2.8)	3.9 (4.1)	2.5 (3.0)	1.9 (2.6)	31.2[b]	21484	<0.001	<0.001	<0.001	0.006

Values are presented as n (%) unless otherwise specified. BD-I = bipolar I disorder; BD-II = bipolar II disorder; df = degrees of freedom; SD = standard deviation.
[a]A = BD-I versus BD-II; B = BD-I versus MDD; C = BD-II versus MDD.
[b]*F* statistic.

Table 2. Demographic and clinical characteristics independently associated with misdiagnosed bipolar disorders[a]

	B	p-value	OR	95% CI
BD-I and MDD (n = 1296)[b]				
Depressive episodes with increased appetite, increased sleep, and weight gain	0.7	0.006	2.0	1.2–3.2
Depressive episodes with psychotic symptoms	0.7	0.003	2.1	1.3–3.5
Lifetime depressive episodes	0.1	<0.001	1.1	1.1–1.2
Age at onset	−0.03	0.002	0.97	0.9–0.99
BD-II and MDD (n = 1369)[b]				
Depressive episodes with psychotic symptoms	0.8	<0.001	2.1	1.4–3.1
Age at onset	−0.04	<0.001	0.96	0.9–0.97

B = the coefficient for the constant in the model; BD-I = bipolar I disorder; BD-II = bipolar II disorder; CI = confidence interval; MDD = major depressive disorder; OR = odds ratio.
[a]Multiple logistic regression analysis with the MDD cohort as the reference group.
[b]Study site has been controlled.

present study were different from that of MDD patients, particularly in terms of atypical depressive features and psychotic symptoms, which were twice as frequent during depressive episodes in BD than in MDD.

Western studies have found that patients with BD-I or BD-II may have a ten-year earlier age at onset than those with MDD (21–23), and the gap between the age at onset of BD and of MDD probably has a strong genetic basis (24). In the present study, BD-I and BD-II patients had a younger age at onset than MDD patients (28.0 versus 28.8 versus 34.6 years, respectively). In addition, the age at onset of BD patients was considerably older than those in most [21.2 years (15); 22.7 years (25)], but not all [29.0 years (21)] Western studies. The possible biological or methodological reasons for the differences in results concerning age at onset need to be explored in future studies.

Cardiovascular mortality in BD patients is higher than that in MDD patients (26, 27). In the present study, in contrast to MDD, BD-I was more frequently characterized by atypical depressive features (increased appetite, increased sleep, and weight gain) that are risk factors for metabolic syndrome and are associated with cardiovascular diseases (28).

It was reported that younger age of onset, high recurrence of depressive episodes, atypical depressive features, psychotic symptoms, and a positive family history are classic validators of BD in Western settings (6, 12, 24). Most of these validators are also applicable to the Chinese patients involved in the present multicenter study. However, it is noteworthy that in Chinese patients BD-I and BD-II have different clinical presentations; BD-I was characterized by more frequent depressive episodes relative to BD-II after controlling for other variables.

The major merits of the present study were its large, multicenter sample and the standardized diagnostic assessment of BD. The results should be interpreted with caution because of some methodological limitations. First, as the survey only comprised consecutively recruited inpatients and outpatients receiving treatment for MDD in 13 major psychiatric hospitals/units, the results cannot be applied to all clinical settings in China. In addition, because of the cross-sectional nature of the study, the switching process from MDD to BD could not be observed. Prospective studies are warranted to address the switching process. Second, no standardized instruments were used to measure the severity of depressive symptoms. However, an earlier study using the Montgomery–Åsberg Depression Rating Scale (MADRS) found that no individual depressive symptoms discriminated between BD and MDD (15). Third, although inpatients and outpatients were both included in this study, their status (inpatient versus outpatient) at study entry was not recorded, so the influence of the treatment setting on the misdiagnosis of BD could not be explored. Fourth, some important clinical and psychosocial factors were not measured, such as the duration of contact with clinical services, particularly psychiatric services, and the estimated duration for which the patient remained misdiagnosed despite the first occurrence of a hypomanic or manic episode.

In conclusion, although there are currently no widely accepted diagnostic dividing lines between BD depression and MDD in clinical practice, our results indicate that there are subtle differences between the forms of depressive episodes occurring in the context of BD and MDD, the clinical use of which might be helpful in distinguishing BD from MDD in Chinese patients.

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Disclosures

The authors of this paper do not have any potential conflicts of interest in connection with this manuscript.

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