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SHORT COMMUNICATION

Prescribing patterns of antidepressants, antipsychotics and mood stabilizers in bipolar patients misdiagnosed with major depressive disorder in China

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Objective Bipolar disorder (BD) is frequently misdiagnosed as major depressive disorder (MDD), which may lead to inappropriate treatment and poor outcomes. This study aimed to examine prescribing patterns of antidepressants, antipsychotics and mood stabilizers in BD patients misdiagnosed with MDD in China.
Methods A total of 1487 patients originally diagnosed with MDD were consecutively screened for diagnostic revision in 13 psychiatric hospitals or psychiatric units of general hospitals in China nationwide. 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. Data on psychotropic prescriptions were collected by a review of medical records.
Results Three hundred and nine of the 1487 patients (20.8%) fulfilled DSM-IV criteria for BD; 118 (7.9%) for BD-I and 191 (12.8%) for BD-II on the MINI. Of the BD patients ($n = 309$), 227 (73.5%) received any use of antidepressants, 73 (23.6%) antipsychotics and 33 (10.7%) mood stabilizers. In multiple logistic regression analyses, compared with those with MDD, patients with BD-I were more likely to receive antidepressants (OR 1.7, 95% CI 1.1–2.8, $p = 0.02$), antipsychotics (OR 1.6, 95% CI 1.04–2.5, $p = 0.04$) and mood stabilizers (OR 3.9, 95% CI 2.1–7.2, $p < 0.001$), whereas patients with BD-II were more likely to receive mood stabilizers (OR 2.4, 95% CI 1.3–4.4, $p = 0.003$). There was no difference in the use of antidepressants (OR 1.1, 95% CI 0.8–1.5, $p = 0.7$) and antipsychotics (OR 1.3, 95% CI 0.9–1.9, $p = 0.2$) between BD-II and MDD. In addition, there was no difference between BD-I and BD-II in any use of antidepressants, antipsychotics and mood stabilizers.
Conclusions The prescription of antidepressants for BD patients misdiagnosed with MDD is very common, and only a very small proportion of patients received guideline-concordant treatment. Considering the potentially hazardous effects of inappropriate pharmacotherapy in

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this population, continuing education and training addressing the correct diagnosis of BD and rational use of psychotropic medications are needed in China. Copyright © 2012 John Wiley & Sons, Ltd.

KEY WORDS—bipolar disorder; major depressive disorder; prescription patterns

INTRODUCTION

Bipolar disorder (BD) is associated with significant role impairment, high mortality and massive economic burden. Although attention has focused more on mania and hypomania in the past, recent studies suggest that bipolar depression is closely associated with occupational impairment and risk of suicide, which leads to severe morbidity (Valtonen *et al*., 2008; Rosa *et al*., 2010). In addition, BD patients experience longer time in the depressive phase compared with their manic phase (Kupka *et al*., 2007). Therefore, it is vitally important to optimize the treatment for bipolar depression (Kilbourne *et al*., 2005).

A depressive episode is often the first mood syndrome at the onset of BD (APA, 2002; Solomon *et al*., 2006; Angst *et al*., 2011), and depressive episodes occur more frequently than hypomanic or manic phases (APA, 2002; Solomon *et al*., 2006). Patients with BD, particularly BD-II, are frequently misdiagnosed with major depressive disorder (MDD) and may receive inadequate or inappropriate treatment (APA, 2002; Hirschfeld *et al*., 2003). Notably, antidepressant monotherapy is not recommended for patients with bipolar I disorder as it can induce rapid cycling (Nivoli *et al*., 2011). As a consequence, such patients may have poorer outcome and a course of illness characterized by chronic and recurrent mood episodes, more severe symptoms and more impaired psychosocial functioning than those optimally treated (Solomon *et al*., 2006).

Identifying the treatment patterns for this patient population could facilitate early recognition of bipolar depression and correction of the inappropriate treatment. Yet, we could locate only one large-scale study that described the prescribing patterns of psychotropic medications in patients with bipolar depression misdiagnosed as MDD (Matza *et al*., 2005). Matza *et al*. (2005) retrospectively compared BD patients misdiagnosed with MDD with recognized BD, MDD and healthy controls. The misdiagnosed group had higher rates of psychotic disorders than the MDD group, whereas the prescription of antidepressants was similar between these two groups.

The aim of this study was to examine prescribing patterns of psychotropic medications including antidepressants, antipsychotics and mood stabilizers in BD patients misdiagnosed with MDD in Chinese clinical settings.

METHODS

Study participants and settings

This study is part of the Diagnostic Assessment Service for People with Bipolar Disorders in China (DASP), an ongoing nationwide study initiated by the Chinese Society of Psychiatry that aims to develop and test the usefulness of screening tools for BD in patients misdiagnosed with MDD. The first survey of the DASP project was carried out in 13 major psychiatric hospitals/units located in the north, south, east, west and central parts of China representing a range of clinical settings. The study lasted from 1 September 2010 to 28 February 2011. Both inpatients and outpatients were enrolled if they were aged between 16 and 65 years, 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 (1) past diagnosis of BD; (2) history or ongoing significant medical or neurological condition(s); (3) depressive disorders secondary to a general medical or neurological condition; and (4) electroconvulsive therapy in the past month.

The study protocol was approved by the clinical research ethics committees of the respective study centers. Written consent was obtained from patients or their guardians for those who were younger than 18 years of age as long as they verbally agreed to participate.

Instrument and assessment procedures

Patients with MDD who were receiving treatment in the participating hospitals/units were consecutively referred by their treating psychiatrists to the research team. Patients fulfilling study entry criteria and providing written informed consent were invited to complete a clinical assessment. Demographics and clinical information and prescription of antidepressants, antipsychotics and mood stabilizers were collected by a review of medical records. In this study, psychotropic drugs were categorized according to the World Health Organization Anatomic Therapeutic Chemical system (WHO Collaborating Centre for Drug Statistic Methodology, 2002; Chong *et al*., 2010), and mood stabilizers include valproate, lithium, carbamazepine, phenobarbital, phenytoin, lamotrigine, topiramate and zonisamide. In addition, polypharmacy was defined as the concurrent use of two or more psychotropic drugs, including antidepressant, antipsychotic or mood stabilizer.

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The diagnostic assessment of BD was conducted with the validated Chinese version of the Mini International Neuropsychiatric Interview (MINI), version 5.0, to establish DSM-IV BD-I/BD-II diagnoses (Sheehan *et al*., 1998; Si *et al*., 2009). Prior to the study, all 13 raters were trained in the use of MINI, diagnosing BD in 20 patients with MDD. In this reliability exercise, their judgments of BD were compared with the best estimate diagnoses (Leckman *et al*., 1982); the kappa values for each rater were more than 0.85.

Statistical analysis

Data were analyzed with the SPSS 13.0 (SPSS Inc, Chicago, IL, USA). Descriptive statistics were used to characterize the patients' sociodemographic and clinical features. Comparisons of the demographic and clinical characteristics and use of psychotropic drugs of patients with BD-I, BD-II and those with MDD were performed by one-way ANOVA or chi-square test, as appropriate. If these tests were significant, *post hoc* tests were carried out. Multiple logistic regression analyses with the "Enter" method were used to identify independent associations of diagnoses with prescribing patterns. In the stepwise regression analyses, any use of antidepressants, antipsychotics, mood stabilizers and polypharmacy were entered as the dependent variable separately, and diagnoses (BD-I, BD-II and MDD) based on the MINI and demographic variables that showed significant difference between the three groups in univariate analyses (age, sex and marital status) were entered as independent variables. The level of significance was set at 0.05 (two-tailed).

RESULTS

Altogether, 1757 patients were invited to participate in this study; 270 (15.4%) refused. There was no significant difference between the enrolled patients and patients who did not participate in terms of age or sex. Eventually, 1487 patients were included in the analyses.

Of the 1487 patients, 309 (20.8%) fulfilled DSM-IV criteria for BD; 118 (7.9%) for BD-I and 191 (12.8%) for BD-II on the basis of the MINI. Table 1 shows the basic demographic and clinical characteristics and the use of psychotropic drugs for the whole sample and separately by diagnoses.

In multiple logistic regression analyses, compared with those with MDD, patients with BD-I were more likely to receive antidepressants (OR 1.7, 95% CI 1.1–2.8, $p = 0.02$), antipsychotics (OR 1.6, 95% CI 1.04–2.5, $p = 0.04$) and mood stabilizers (OR 3.9, 95% CI 2.1–7.2, $p < 0.001$), whereas patients with BD-II were more likely to receive mood stabilizers (OR 2.4, 95% CI 1.3–4.4, $p = 0.003$). There was no difference in the use of polypharmacy between BD-I and MDD (OR 0.98, 95% CI 0.7–1.4, $p = 0.9$), and no difference in the use of antidepressants (OR 1.1, 95% CI 0.8–1.5, $p = 0.7$), antipsychotics (OR 1.3, 95% CI 0.9–1.9, $p = 0.2$) and polypharmacy (OR 1.1, 95% CI 0.8–1.5, $p = 0.7$) between BD-II and MDD.

We also conducted secondary analyses comparing prescribing patterns between BD-I and BD-II after controlling for age, sex and marital status by multiple logistic regression analyses. Finally, there was no significant difference in the use of antidepressants (OR 1.7, 95% CI 0.97–2.9, $p = 0.06$), antipsychotics (OR 1.2, 95% CI 0.7–2.1, $p = 0.5$), mood stabilizers (OR 1.6, 95% CI 0.8–3.4, $p = 0.2$) and polypharmacy (OR 0.9, 95% CI 0.6–1.4, $p = 0.6$) between the two groups.

DISCUSSION

To the best of our knowledge, this was the first nationwide study in China that examined the prescription patterns of psychotropic medications in BD patients misdiagnosed with MDD. The major finding of this study was that antidepressants were the most commonly used psychotropic drugs in this population (78.8% in BD-I and 70.2% in BD-II) followed by antipsychotics (26.3% in BD-I and 22.0% in BD-ii), whereas mood stabilizers were less likely to be used (13.6% in BD-I and 8.9% in BD-II).

Antidepressants have been the mainstay of treatment for depressive episodes of any kind. Approximately half of patients with bipolar depression are on antidepressants in daily clinical practice in the USA (Baldessarini *et al*., 2007). The frequency of antidepressants used in BD patients in this study (73.5%) was considerably higher than the previous reported figure (50%; Baldessarini *et al*., 2007), which could be explained by the misdiagnosed BD as MDD. Our figure is also higher than an earlier one (38.7%; Matza *et al*., 2005), which is perhaps due to the difference in the method of the surveys (cross-sectional versus retrospective). Multivariate analyses revealed that BD-I patients were even more likely to receive antidepressants than those with verified MDD. Earlier studies (Kemp *et al*., 2008; Tafalla *et al*., 2009) suggested that the clinical presentations of depression in BD were different from that of MDD probably because of a higher degree of brain disturbances existing in BD than in unipolar depression (Rybakowski and Twardowska, 1999; Borkowska and Rybakowski, 2001), which could account for the frequent lifetime depressive episodes and the more frequent use of antidepressants in BD than in MDD in this study.

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

	The whole sample ($n = 1487$)		BD-I ($n = 118$)		BD-II ($n = 191$)		MDD group ($n = 1178$)		Statistics			*Post hoc* analyses		
												A	B	C
	N	%	*N*	%	*N*	%	*N*	%	X^2	*df*	*p*	*p*	*p*	*p*
Male	533	35.8	51	43.2	97	50.8	385	32.7	26.5	2	<0.001	0.2	0.02	<0.001
Married/cohabitating	1016	68.3	76	64.4	116	60.7	824	69.9	7.4	3	0.03	0.5	0.2	0.01
Education									5.5	6	0.5	—	—	—
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						
Depressive episodes with psychotic symptoms	258	17.4	45	38.1	55	28.8	158	13.4	65.7	2	<0.001	0.1	<0.001	<0.001
Any use of antidepressants	1047	70.4	93	78.8	134	70.2	820	69.6	4.4	2	0.1	—	—	—
Paroxetine	245	16.5	25	21.2	26	13.6	194	16.5						
Venlafaxine	238	16.0	18	15.3	26	13.6	194	16.5						
Fluoxetine	147	9.9	14	11.9	20	10.5	113	9.6						
Any use of antipsychotics	299	20.1	31	26.3	42	22.0	226	19.2	3.8	2	0.1	—	—	—
Quetiapine	151	10.2	17	14.4	15	7.9	119	10.1						
Olanzapine	102	6.9	10	8.5	19	9.9	73	6.2						
Risperidone	16	1.1	2	1.7	1	0.5	13	1.1						
Any use of mood stabilizers	77	5.2	16	13.6	17	8.9	44	3.7	27.3	2	<0.001	0.2	<0.001	0.001
Valproate	48	3.2	14	11.9	8	4.2	26	2.2						
Lithium	26	1.7	2	1.7	6	3.1	18	1.5						
Mood stabilizer–antidepressant combination	62	4.2	12	10.2	12	6.3	38	3.2	15.4	2	<0.001	0.2	<0.001	0.04
Polypharmacy[a]	709	47.7	56	47.5	94	49.2	559	47.5	0.2	2	0.9	—	—	—
Antidepressants only	735	49.4	56	47.5	87	45.5	592	50.3	1.7	2	0.4	—	—	—
Antipsychotics only	33	2.2	4	3.4	5	2.6	24	2.0	1.1	2	0.6	—	—	—
Mood stabilizers only [b]	10	0.7	2	1.7	5	2.6	3	0.3	—	—	—	—	—	—
FDA-approved drugs for bipolar depression														
OFC	26	1.7	3	2.5	5	2.6	18	1.5						
Quetiapine only	14	0.9	2	1.7	3	1.6	9	0.8						
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*F*	*df*	*p*	*p*	*p*	*p*
Age (years)	39.5	12.8	35.5	11.1	35.5	12.7	40.5	12.8	19.1	2, 1484	<0.001	0.9	<0.001	<0.001
Age at onset (years)	33.4	12.4	28.0	10.5	28.8	10.9	34.6	12.5	31.4	2, 1484	<0.001	0.6	<0.001	<0.001
Lifetime depressive episodes	2.1	2.8	3.9	4.1	2.5	3.0	1.9	2.6	31.2	2, 1484	<0.001	<0.001	<0.001	0.006

A = BD-I versus BD-II; B = BD-I versus MDD; C = BD-II versus MDD; OFC = olanzapine–fluoxetine combination.
[a]Polypharmacy was defined as the concurrent use of two or more psychotropic drugs, including antidepressant, antipsychotic or mood stabilizer.
[b]Use of mood stabilizers between the three groups was not compared because of the low frequency.

We found that 47.5% of the BD-I patients and 45.5% of the BD-II patients received antidepressant monotherapy—a prescription that is not recommended by treatment guidelines (Nivoli *et al*., 2011), as it can induce either mood instability or even rapid cycling. It is noteworthy that although some studies have found that certain antidepressants, particularly SSRIs, are effective and safe as a concurrent treatment for bipolar depression (Gijsman *et al*., 2004), this issue remains controversial. For example, recent studies (Baldassano *et al*., 2011; Amit and Weizman, 2012) reported that antidepressants do not have a robust effect in bipolar depression regardless of the class of the drug or bipolar types. In addition, some studies found that antidepressants may not significantly increase the risk of switch to manic or hypomanic episodes, particularly with concurrent use of mood stabilizers (Baldassano *et al*., 2011; Amit and Weizman, 2012). Other reports, however, suggest that the likelihood of polarity changes, mixed symptoms and shorter euthymic periods increase if patients are exposed to antidepressants for longer than a year (Strejilevich *et al*., 2011). Given the limited advantage and the risk of switch to mania, it seems that antidepressants may not be useful as the first line treatment for bipolar depression (Baldassano *et al*., 2011).

Multiple logistical regression analysis revealed that BD-I patients were more likely to receive antipsychotic treatment than those with verified MDD, which could be explained by the more frequent psychotic symptoms associated with BD-I than MDD in this study. Earlier studies found that the frequency of BD patients on antipsychotic medications range between 55% and 100%, with the pooled estimate of 68% (Tohen and Zarate, 1998). In this study, only a small proportion of BD patients (23.6%) received

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antipsychotic drugs, which is probably due to the misdiagnosis of BD as MDD. Although more frequent prescription of antipsychotics is closely associated with manic presentation (Soares *et al*., 1999; Levine *et al*., 2001), the unrecognized mania in the present sample could decrease antipsychotic prescription.

In the past decades, the US Food and Drug Administration (FDA) approved only two drugs for the treatment of bipolar depression: the olanzapine–fluoxetine combination (OFC) and quetiapine (Baldassano *et al*., 2011). Contrary to the FDA's recommendation, in this study only 2.5% of BD-I patients and 2.6% BD-II patients were on OFC, whereas the corresponding figures for quetiapine were 14.4% and 7.9%, respectively.

Most current guidelines and expert consensus statements recommend mood stabilizers in the acute and maintenance phase of BD (Goodwin, 2003). However, only 13.6% of BD-I patients and 8.9% of BD-II patients received them in this study although they are both higher than the figure in MDD (3.7%). The misdiagnosis of BD is likely to be responsible for the low rate of mood stabilizer prescriptions. On the other hand, 10.2% and 6.3% of BD-I and BD-II patients, respectively, received a combination of mood stabilizers and antidepressants. It should be kept in mind that mood stabilizer–antidepressant combinations are not proven to be superior to mood stabilizers as sole treatment for bipolar depression (Nemeroff *et al*., 2001).

A host of studies (Bowden, 2001; Mitchell *et al*., 2001; Benazzi, 2003; Rybakowski *et al*., 2005; Kemp *et al*., 2008; Tafalla *et al*., 2009) suggested that there was a difference in the clinical presentations of depression between BD-I and BD-II. Therefore, it was expected that the prescription patterns of polypharmacy, antidepressants, antipsychotics and mood stabilizers between the two groups would be different. In this study, however, the results did not support this assumption.

The major merits of this study are its large sample and the multicentre assessment of bipolar depression in Chinese patients treated for MDD. Limitations of this study include, first, some important factors likely to influence psychotropic drug prescriptions, such as treatment settings (inpatient or outpatient), number of episodes in the past year, prior use of medications, response to treatment, contraindications to certain psychotropic drugs and reimbursement policies, that were not evaluated or recorded. Second, because of the cross-sectional nature of the study, the causality of the relationship between sociodemographic and clinical factors and prescription patterns could not be determined. Third, no standardized instruments were used to measure the severity of depressive symptoms. Finally, the sampling was not random, which is likely to have an effect on the generalization of the findings.

In conclusion, the results indicate that the prescription of antidepressants for BD misdiagnosed as MDD is very common. Only a very small proportion of patients received FDA-approved treatment. Considering the potentially hazardous effects of inappropriate treatment in this patient population, continuing education and training addressing the correct diagnosis of BD and rational use of psychotropic medications are needed in China.

CONFLICT OF INTEREST

There is no conflict of interest concerning the authors in conducting this study and preparing the manuscript.

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