

Risk factors for suicide attempts in patients with bipolar disorder misdiagnosed with major depressive disorder: results from a national survey in China

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Abstract

Background: Bipolar disorder (BD) is a kind of mental disorder with the greatest risk of suicide, but it is often misdiagnosed as major depressive disorder (MDD) clinically. This study aimed to analyze the sociodemographic factors and clinical characteristics associated with suicide attempts (SA) in patients with BD misdiagnosed with MDD in China.

Methods: A total of 1487 MDD patients were consecutively enrolled in 13 mental health centers in China. Data on patients' sociodemographic and clinical characteristics were collected using a standardized protocol. Of these, 306 BD patients were misdiagnosed with MDD according to the Mini International Neuropsychiatric Interview (MINI). Suicide attempters and non-attempters were classified by the suicidality module of the MINI. Multiple logistic regression analyses were performed to assess the association between the independent variables of interest and SA in BD patients misdiagnosed with MDD.

Results: Of the 306 BD patients misdiagnosed with MDD, 225 (73.5%) were non-attempters and 81 (26.5%) were attempters. Compared to non-attempters, attempters were older ($Z = 2.2$, $p = 0.03$) and had more admissions ($\chi^2 = 6.1$, $p = 0.013$), more frequent depressive episodes, more atypical characteristics (e.g. increased appetite, weight gain, and more sleep time) ($\chi^2 = 5.8$, $p = 0.016$), more suicidal ideation ($\chi^2 = 27.3$, $p < 0.001$), more psychotic symptoms ($\chi^2 = 7.4$, $p = 0.006$) and more seasonal depressive episodes ($\chi^2 = 5.6$, $p = 0.018$). Multiple logistic regression analyses revealed that attempters were characterized by more suicidal ideation (OR = 5.7, 95% CI: 2.6–12.5) and frequent depressive episodes (OR = 2.4, 95% CI: 1.3–4.6). The limitations of this study include its cross-sectional design and data collection by suicide attempters' retrospective recall.

Conclusions: The findings of this study suggest that BD patients misdiagnosed with MDD are at a higher risk of suicide, and more frequent depressive episodes and suicidal ideation are risk factors for attempted suicide. Early identification of and interventions for these risk factors might reduce the risk of suicide in BD patients misdiagnosed with MDD.

Background

Suicide is a major public health problem throughout the world (Nordentoft 2011). Although China's suicide rate dropped significantly from 2002 to 2015, the rate of decline has slowed or even reversed in certain groups, underscoring the urgent need for targeted suicide prevention programs (Jiang et al. 2018). Suicidal behavior is becoming a great challenge for psychiatry, other fields of medicine, and society as a whole, owing to the difficulty in predicting suicidal behavior. Thus, suicide prediction and prevention are receiving increasing attention (Gonda et al. 2012).

There are many reasons for suicide, but suicide is almost always associated with potential mental disorders (Wasserman et al. 2012), about 50–90% of suicide deaths can establish a diagnosis of mental

illness, with mood disorders being the most common (Cavanagh et al. 2003; Hawton and van Heeringen K 2009; Gonda et al. 2012).

Patients with major affective disorder (MAD), that is, major depressive disorder (MDD), bipolar disorder (BD), are highly vulnerable to suicidal behavior (Pompili et al. 2008). Furthermore, patients with BD are at a higher risk of suicidal behavior than those with other mental disorders (Chen and Dilsaver 1996; Kessler et al. 1999; Szádóczy et al. 2000; Mitchell et al. 2004; Valtonen et al. 2005, 2008; Abreu et al. 2009; Elizabeth et al. 2009; Cassidy 2011; Hales et al. 2011).

However, the first episode of BD is usually a depressive episode, manic or hypomanic episode often occurs after the depressive episode which is more frequent than manic or hypomanic episode (Solomon et al. 2006; Judd et al. 2003). Moreover, manic or hypomanic episode is usually retrospectively established, and there will be memory bias (Perlis 2005; Yen et al. 2007). Therefore, BD patients are often misdiagnosed as major depressive disorder (MDD) and may not receive adequate or appropriate treatment (Hirschfeld et al. 2003). It is possible that only receiving a single antidepressant treatment will lead to emotional instability, induce manic episode, and even increase the risk of suicide (Birnbaum et al. 2003; Shi et al. 2004; Matza et al. 2005; Berk and Dodd 2005). Compared with BD patients, BD patients misdiagnosed as MDD have higher suicide risk, higher nursing requirements for inpatients with mental illness, and higher total medical costs (Birnbaum et al. 2003; Shi et al. 2004; Matza et al. 2005; Nasrallah 2015). A recent systematic review and meta-analysis still found that 17% of BD patients were misdiagnosed and treated with MDD in primary care (Daveney et al. 2019). Therefore, the suicide-related problems in BD patients misdiagnosed with MDD need more attention.

Currently, suicide risk factors are often studied in relation to attempted suicide rather than committed suicide (Holma et al. 2010).

A previous suicide attempt is a strong predictor of a completed suicide (Bega et al. 2012). Thus, studying SA is pivotal to identifying those at risk of future completion (Suominen et al. 2004). SA is an important proxy outcome when investigating the risk factors for suicide (Holma et al. 2010).

To date, no systematic studies have examined the risk factors for future SA in BD patients misdiagnosed with MDD in China or other countries. This study analyzed data from the Diagnostic Assessment Service for People with Bipolar Disorders (DASP) database (Holma et al. 2010; Hu et al. 2012; Chen et al. 2014; Xin et al. 2018), which aimed to test the usefulness of screening tools for BD in patients initially diagnosed as MDD.

Patients who met the study criteria were invited to participate in the study. The general socio-demographic and clinical data of patients were collected through questionnaires designed in clinical interviews, supplemented by a review of their medical records. In order to establish DSM-IV BD diagnosis, Mini International Neuropsychological interview (MINI) Version 5.0 was used for the diagnosis evaluation of BD (Sheehan et al. 1998; Si et al. 2009).

Methods

Subjects

The DASP is a national study that was initiated by the Chinese Society of Psychiatry (CSP), which aimed to develop and test the usefulness of screening tools for patients with BD treated for MDD (Hu et al. 2012; Chen et al. 2014; Xin et al. 2018). The study was conducted in 13 major psychiatric hospitals or psychiatric units of general hospitals from September 1, 2010 to February 28, 2011. In-patients and out-patients who met the following criteria were enrolled: (i) aged between 16 and 65 years, (ii) diagnosed with DSM-IV or ICD-10 MDD based on a review of medical records, (iii) satisfied the major depressive episode criteria, and (iv) understood the aims of the study and were able to provide informed consent. The exclusion criteria were as follows: (i) a past diagnosis of BD, (ii) in remission state, (iii) in a manic (or hypomanic) episode, (iv) a history of or ongoing significant medical or neurological condition(s), (v) depressive disorders secondary to a general medical or neurological condition, or (vi) had received electroconvulsive therapy (ECT) 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.

Instruments and assessment procedure

Patients who fulfilled the study criteria were invited to participate in the study. Patients' general sociodemographic and clinical data were collected using a questionnaire designed for the study in a clinical interview, supplemented by a review of their medical records. The diagnostic assessment of BD was performed using the validated Chinese version of the Mini International Neuropsychiatric Interview (MINI), Version 5.0, to establish DSM-IV BD diagnoses (Sheehan et al. 1998; Si et al. 2009).

The suicidality module of MINI includes the following specific questions that assess SA: C1-5 "Did you attempt suicide within the past month?"; C1-6 "In your lifetime, did you ever make a suicide attempt?". Patients who responded "yes" to both or one of the items were classified as the suicide-attempted group; those who answered "no" to both questions, they were classified as the non-suicide-attempted group.

Prior to the study, all thirteen raters were trained in the use of the BD diagnostic instrument on 20 patients with MDD. The kappa values of all instruments were above 0.85 for each rater. Wherever possible, the same raters evaluated the same group of patients throughout the study.

Statistical procedures

Statistical analyses were performed using SAS 9.13 (SAS Institute Inc., Cary, North Carolina). Mann-Whitney U tests were used for continuous variables non-normally distributed. Continuous variables were

presented as mean \pm standard deviation (SD). Categorical variables, such as sex, marital status, were expressed as percentages (%) and compared using the Chi-square. For potential risk factors, variables with a P-value of less than 0.1 in a univariate analysis were selected and included in a multivariate logistic regression model. Odds ratio (OR) and 95% CI were evaluated to assess associations between risk factors and SA for the BD patients misdiagnosed with MDD. All tests were two-tailed and P-value less than 0.05 was considered as statistically significant.

Results

Description of samples

A total of 1,487 patients diagnosed with MDD from 13 study sites were enrolled based on the diagnostic criteria. Of them, 309 patients were re-diagnosed to BD according to the MINI V5.0. After excluding three patients due to lack of information on the suicidal module of MINI, 306 patients were included in analyses. The incidence of SA was 15.6% (183/1178) in MDD patients. Of the BD patients, 26.5% (81/306) were suicide attempters and 73.5% (225/306) were not.

Basic Sociodemographic and Clinical Features

With regards to the basic sociodemographic and clinical characteristics, the SA group were older ($Z = 2.2$, $p = 0.03$) and experienced more frequent depressive episodes (> 4 in the past year) ($\chi^2 = 15.0$, $p < 0.001$), more depressive episodes with increased appetite, weight gain, and more sleep time ($\chi^2 = 5.8$, $p = 0.016$), more depressive episodes with suicidal ideation ($\chi^2 = 27.3$, $p < 0.001$), more depressive episodes with psychotic symptoms ($\chi^2 = 7.4$, $p = 0.006$), more seasonal depressive episodes ($\chi^2 = 5.6$, $p = 0.018$), more number of admissions ($\chi^2 = 6.1$, $p = 0.013$) than did non-attempters (Table 1–2).

Table 1

Basic socio-demographic factors of non-suicide attempters versus suicide attempters in BD patients misdiagnosed with MDD

Item	Total (n = 306)		Non-suicide attempters (n = 225)		Suicide attempters (n = 81)		Statistics		
	N	%	N	%	N	%	χ^2	df	P
Female	159	52.0	113	50.2	46	56.8	1.0	1	0.310
Married	189	61.8	134	59.6	55	67.9	1.8	1	0.185
Unemployed	97	31.7	75	33.3	22	27.2	1.4	1	0.306
Education(senior secondary school and below)	157	51.3	116	51.6	41	50.6	0.02	1	0.885
	Mean	SD	Mean	SD	Mean	SD	Z		
Age(years)	35.3	12.0	34.6	12.3	37.4	11.1	2.2		0.030

Table 2

Clinical factors of non-suicide attempters versus suicide attempters in BD patients misdiagnosed with MDD

Item	Total (n = 306)		Non-suicide attempters (n = 225)		Suicide attempters (n = 81)		Statistics		
	N	%	N	%	N	%	χ^2	df	P
Number of admissions (> 1)	34	11.1	19	8.4	15	18.5	6.1	1	0.013
Frequent depressive episodes (> 4 in the past year)	52	17.0	27	12.0	25	30.9	15.0	1	< 0.001
Depressive episodes with atypical features	89	29.1	57	25.3	32	39.5	5.8	1	0.016
Depressive episodes with suicidal ideation	204	66.7	131	58.2	73	90.1	27.3	1	< 0.001
Depressive episodes with psychotic symptoms	99	32.4	63	28.0	36	44.4	7.4	1	0.006
Depressive episodes with anxiety symptoms or disorder	1155	78.1	185	82.2	60	74.1	2.5	1	0.115
Depressive episodes with precipitating factor	156	51.0	110	48.9	46	56.8	1.5	1	0.223
Seasonal depressive episodes	65	21.2	41	18.2	25	30.9	5.6	1	0.018
Family history of psychiatric disorders	79	25.8	52	23.1	27	33.3	3.3	1	0.071
On antidepressant	254	83.0	183	81.3	71	87.7	1.7	1	0.194
	Mean	SD	Mean	SD	Mean	SD	Z		
Age at onset (years)	28.4	10.7	28.6	11.1	27.7	9.6	-0.2		0.841

Correlates of SA

A multiple logistic regression analysis demonstrated that more depressive episodes with suicide ideation ($\beta = 1.7$, OR = 5.7, $p < 0.001$) and more frequent depressive episode (> 4 in past year) ($\beta = 0.9$, OR = 2.4, $p = 0.007$) were associated with SA in BD patients misdiagnosed with MDD (Table 3).

Table 3

Multivariate logistic regression analysis of socio-demographic and clinical factors associated with SA in total BD patients misdiagnosed with MDD (n = 306)

Risk factor	β	Wald χ^2	OR	95%CI	p-value
Depressive episodes with suicidal ideation	1.7	18.8	5.7	2.6–12.5	< 0.001
Frequent depressive episodes (> 4 in the past year)	0.9	7.3	2.4	1.3–4.6	0.007

Discussion

Misdiagnosis of BD has an important clinical impact and might imply a variety of negative outcomes. The National Depressive and Manic Depressive Association Survey (Hirschfeld et al. 2003) revealed that as many as 69% of the patients with BD had received an inaccurate diagnosis, with MDD being the most frequent one. The proportion of patients with BD misdiagnosed with MDD was 20.8% in our DASP study (Hu et al. 2012). Among patients with mood disorders, the prevalence of suicidal behavior was as high as 15–20% (Bostwick and Pankratz 2000). SA are also prevalent in this population, with studies showing that up to 50% of patients with BD and 30–40% of patients with MDD have a lifetime history of SA (Malone et al. 1995; Sokero et al. 2003; Valtonen et al. 2005; Schaffer et al. 2015; Dong et al. 2019). However, other studies have reported that the lifetime incidence of SA in MDD patients was only 15.9% (Chen and Dilsaver 1996), and a study with a follow-up of 34–38 years found that the suicide rate of BD patients was only 7% (Angst et al. 2002). Reports of suicide or attempted suicide rates vary widely from study to study. In this sample of patients recruited from the DASP study, SA was reported by 26.5% of BD patients misdiagnosed with MDD. People with BD who were misdiagnosed as MDD were usually treated only with antidepressants, which could have a number of adverse consequences, including an increased risk of mania or hypomania and suicide (Ghaemi et al. 2000; Birnbaum et al. 2003; Shi et al. 2004; Das et al. 2005; Gao et al. 2008; Pacchiarotti et al. 2011; Viktorin et al. 2014). As a result, making a correct diagnosis and providing appropriate treatment to such patients are crucial, which should be given more attention by clinicians.

The suicide-attempted-group with BD who were misdiagnosed with MDD differed significantly from non-suicide-attempted group in terms of higher ages, higher frequency of depressive episodes (> 4 in the past year), depressive episodes with more atypical characteristics (e.g. increased appetite, weight gain, and more sleep time), suicidal ideation, psychotic symptoms, seasonal depressive episodes, and number of hospital admissions (Table 1–2). Regarding the relationship between depressive episodes and SA, a retrospective study reported that the experience of a depressive first episode significantly differed between attempters and non-attempters, and depressive first episodes and bipolar II disorder were significantly associated with SA in those patients (Ryu et al. 2010). Meanwhile, a previous study reported that nearly all depressive symptoms were commonly reported by the bipolar I disorder group, which was demonstrated by a comparison of the frequencies of depressive symptoms reported by the patients (Bega et al. 2012). Patients with BD were more likely to endorse atypical symptoms such as weight gain

and hypersomnia(Bega et al. 2012).Therefore, clinicians should consider the polarity of the first mood episode and the characteristics of the depressive episode when evaluating suicide risk in BD patients. Likewise, many studies of suicide in BD patients have suggested that various sociodemographic and clinical factors increase the risk for SA in BD, such as suicide ideation(Eikelenboom et al. 2012), psychotic symptom(s)(Wang et al. 2015), multiple hospitalizations(Oquendo et al. 2000; Azorin et al. 2009), which are identical to the findings of our study. Regarding ages and the presence of psychotic symptoms, contrary to our findings, a prospective study found that BD patients with SA are younger(Galfalvy et al. 2006; Ruengorn et al. 2012), and a Thai cohort study showed that psychotic symptoms are negatively correlated with SA, which might be due to these patients' lack of ability to plan a SA(Ruengorn et al. 2012).

In this study, the logistic model identified depressive episodes with suicidal ideation and frequent depressive episodes (> 4 in the past year) as the risk factors for SA in BD patients misdiagnosed with MDD. Suicidal ideation are closely related to suicidal behavior and are often considered as the first step before suicidal death or SA(Eikelenboom et al. 2012). The first SA usually occurs in the first year of suicidal ideation(Kessler et al. 1999). But not all suicide patients develop SA. In a prospective study, 61% of patients with BD had suicidal thoughts during onset, while only 20% of patients with suicidal thoughts had suicidal behaviors during the same period(Valtonen et al. 2005). Suicidal ideation as a state (elevated in the depression or mixed phase) or specific dependence (associated with broader negative factors, including the subjective severity of despair and depression) is a significant risk factor for SA(Oquendo et al. 2004; Valtonen et al. 2006). In clinical practice, timely identification of initial suicidal thoughts is very important for developing strategies to prevent suicidal behavior(Keilp et al. 2012). For frequent episodes of bipolar disorder (> 4 in the past year), it is also clinically known as rapid circulation. Most studies consider rapid circulation as a risk factor for SA in BD patients(Leverich et al. 2003; MacKinnon et al. 2005; McIntyre et al. 2008; Parmentier et al. 2012). In a study involving 387 patients with BD rapid circulation type, more than 41% patients had SA at least once(Gao et al. 2009). Hawton et al. systematic review found that BD patients with rapid circulation and mixed type had a higher risk of suicide, while SA patients with rapid circulation had a 54% higher risk than the latter (Hawton et al. 2005). As the present study was aimed at investigating BD patients misdiagnosed with MDD, the risk factors for SA are most likely related to depressive episodes. The depressive symptoms were more severe for these patients. Moreover, previous studies have reported more frequent SA during the depression phase of BD patients(Oquendo et al. 2000; Hawton et al. 2005; Valtonen et al. 2006; Azorin et al. 2009; Ryu et al. 2010). However, this study found that the risk factors of SA in the special group of BD patients misdiagnosed with MDD were not specific. Suicidal ideation and frequent depressive episodes (> 4 in the past year) were also risk factors for SA in recognized BD patients(Leverich et al. 2003; MacKinnon et al. 2005; McIntyre et al. 2008; Parmentier et al. 2012) and MDD patients(Eikelenboom et al. 2019), although there were different results(Hawton et al. 2005; Kupka et al. 2005).

This study is the first large-scale, multicenter study to examine the risk factors of SA in BD patients misdiagnosed with MDD in China. However, there are several limitations that must be considered. First, given the cross-sectional design of the study, we could not establish a causal relationship between

patients' demographic and clinical characteristics and the risk of SA. Second, much of the data were retrospectively collected, and thus, recall bias might have affected the main findings. Third, the MINI was used as the reference diagnostic tool, not the structured clinical interview for DSM-IV Axis I Disorders (SCID-I) in our study, despite being good reliability and validity between them (Sheehan et al. 1998; Si et al. 2009). Fourth, the investigation of suicide variables was not the primary aim of the DASP project, therefore, no special suicide assessment tool was used to evaluate SA and other potential risk factors for SA were not identified. Fifth, since the objects of this study were not easily identified in clinical practice, the significance of this study was limited and we did not collect the number and onset time of manic episodes. Further, we were unable to demonstrate an association between several indicators reported in previous studies; for example, the associations of SA with gender, education level, occupation, comorbidity, and family history were not observed. Inconsistencies might result from differences in the study participants, methodology, measures, and statistical analysis. Thus, more studies of the risk factors for SA in BD patients misdiagnosed with MDD are needed to address these limitations.

Conclusion

In conclusion, this study found that among BD patients misdiagnosed as MDD, the prevalence rate of SA was 26.5%, which was associated with suicidal ideation and more frequent depressive episodes. Focusing on these two risk factors might help clinicians to identify patients at a high risk for SA and implement effective preventive interventions to prevent suicides.

Declarations

Acknowledgments

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Authors' Contributions

SI TM designed research. YANG FD, WANG G, FANG YR, LU Z, YANG HC, HU J, CHEN ZY, HUANG Y, SUN J, WANG XP, LI HC, WANG Y and ZHANG JB performed research and collected data. JI ZP, XIN LM, SU YA and CHEN L analyzed data. CHEN L, XU YY, WANG SL and DU JG wrote the manuscript.

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Availability of data and materials

The datasets generated and/or analyzed during the present study are not publicly available.

Ethics approval and consent to participate

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.

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no competing interest.

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