Current situation and influencing factors of acute treatment of bipolar disorder with mixed features in China

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January 30, 2024

Abstract

Background: DSM-5 proposes the concept of bipolar disorder with "mixed features ", which is of great benefit to clinical practice. However, the clinical management of BD with mixed features is more challenging.This investigation examined the prescribing patterns and factors influencing guidelines disconcordance for the acute treatment of bipolar disorder with mixed features in mainland China. Methods:This real-world study enrolled 688 patients with acute bipolar disorder through the National Bipolar Pathway Survey Replication (BIPAS-R). We used CUDOS-M and MINI-M scales based on DSM-5 criteria to improve the sensitivity of screening for bipolar disorder with mixed features. Guideline inconsistency judgments were determined by comparison with the Canadian Network for Mood and Anxiety Treatments(CANMAT) guidelines for treatment recommendations for bipolar disorder with mixed features. Logstic regression was used to analyze the influencing factors of guideline disconcordance. Results: Among 688 cases of acute bipolar disorder, 235 cases (34.2%) were (hypo) mania with mixed features and 213 cases (30.9%) were depression with mixed feature. Without considering the order of treatment, the inconsistency rates of (hypo) mania and depression with mixed features with the guidelines were 29.4% and 55.4%, respectively. (Hypo) mania with mixed features BD-II (OR=0.52; 95% CI 0.29-0.93), age at study entry $>$ 24 years (OR=2.4; 95% CI 1.3-4.3), and the number of episodes $>$ 4 in the past year in depression with mixed features (OR=1.9; 95% CI 1.08-3.6), which increased the risk of treatment disconcordance of guidelines. Conclusions:Our findings suggest that BD with mixed features is more common.

1. INTRODUCTION

Bipolar disorder (BD) is a chronic severe mental illness with early onset and recurrent episodes. With the increase and aging of the global population, the global burden of disability adjusted life years (DALYs) of BD is heavier (Ferrari, et al.,2016).As early as the 19th century, the German psychiatrist Kraepelin introduced the term "mixed state", after which the concept of mixed state in BD was gradually recognized(Rakesh, et al.,2017).With the gradual deepening of people's understanding of BD, the concept of mixed traits has changed amidst ongoing controversy. The U.S. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revised* (DSM-IV-TR) has a highly restrictive definition of mixed state, defining a mixed episode as a threshold manic episode occurring simultaneously with a threshold major depressive episode (MDE) and meeting the appropriate diagnostic criteria at the same time. However, this limitation makes the diagnostic sensitivity of mixed seizures insufficient and lacks scientific validity and clinical practicality (Swann, et al.,2013).Therefore, the concept of "mixed features" was introduced in the DSM-5, and the diagnosis of mixed episodes was removed, which applies to any kind of affective episode. If three or more anti-polar symptoms were met, the diagnosis of mixed features could be made(Rosenblat and McIntyre,2017).However,

three overlapping symptoms of irritability, inattention, and psychomotor agitation were excluded (Malhi, et al.,2019).

Evidence suggests that BD with mixed features is common in clinical practice (Malhi, et al.,2019).A recent systematic review based on DSM-5 criteria showed that in BD, the prevalence of depression with mixed features was 33.5% and the prevalence of (hypo) mania with mixed features was 30.0%(Vázquez, et al.,2018) . BD with mixed features is a complex overlapping state that combines the characteristics of depressive and manic episodes. It is characterized by an earlier age of onset, a higher risk of suicide and comorbidity, a worse response to treatment, and a worse prognosis, which makes great difficulties in diagnosis and treatment(Swann, et al.,2013). Nevertheless, the inadequate identification of BD with mixed features in clinical practice has to some extent adversely affected the treatment of patients, and there is an urgent need to address this issue (Malhi, et al.,2019).

Unfortunately, recent progress in the pharmacological treatment of patients with BD with mixed features remains rather limited, with most studies using mixed episodes in DSM-IV as the standard, and its treatment remains a major challenge (Chakrabarty, et al.,2020). In clinical practice, the recognition rate of BD with mixed features is low, and the choice of treatment plan is more subjective.The latest guidelines from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the International Society for Bipolar Disorder (ISBD) recommend mood stabilizers and second-generation antipsychotic drugs as the core treatment options for BD with mixed features, and do not recommend the use of antidepressants(Yatham, et al.,2021).So far, there are no studies on the prevalence of BD with mixed features and the consistency of treatment regimens with guidelines in China.The purpose of this study is to present national survey data on the prevalence and acute phase treatment of BD with mixed features in routine clinical practice in mainland China.

2. METHODS

2.1 Subject

This is a real-world study of the National Bipolar Pathway Survey Replication (BIPAS-R). From November 2021 to May 2022, a total of 1060 patients with BD, including 688 cases in acute phase and 372 cases in remission, were enrolled from 20 centers (13 psychiatric hospitals and 7 psychiatric departments of general hospitals) in mainland China. This research was approved by the Research Ethics Board of Hongkou Mental Health Center (2021-D01).All patients used a standardized electronic questionnaire of WeChat mini program to collect information.Written informed consent was obtained from each participant before any study-related procedures were performed.For participants with impaired capacity/capability to consent, written informed consent was obtained from the legal guardian. Inclusion criteria:(1) Age of 18-65 years old, both sexes, junior high school or above education level, able to read and complete the self-assessment questionnaire; (2) Current or most recent episode meets DSM-5 diagnostic criteria for a (hypo) manic or depressive episode of bipolar disorder. (3) treated or untreated patients; (4) cognitive level sufficient to understand informed consent and study content. Exclusion criteria:(1) substance or drug-induced bipolar disorder; (2) BD caused by other physical diseases; (3) mania or depression with other severe psychiatric symptoms and unable to cooperate with the questionnaire; (4) Other circumstances were not appropriate to participate in the study.

2.2 Clinical assessment

A standardized electronic questionnaire was used to collect information from each patient at enrollment, including general demographic information, clinical characteristics, comorbid physical or mental diseases, family history, diagnosis and drug treatment plan, and other clinical data of interest. All clinical data were collected and assessed by the physician in charge at the time of enrollment.The diagnosis of mixed features is based on the DSM-5, and BD with mixed features is divided into (hypo) mania with mixed features and depression with mixed features. In addition, the Chinese CUDOS-M (Clinically Useful Depression Outcome Scale Supplemented with Questions for the DSM-5 Mixed Features Specifier) and MINI-M[Mini International Neuropsychiatric Interview(Hypo)Manic Episode with Mixed Features- DSM-5 Module]scales were also used to screen out patients with mixed features in order to expand the sample size and screen out

more patients with potential mixed features. The study showed (Fei, et al.,2021) that the Chinese-CUDOS-M has an internal consistency Cronbach's alpha value of 0.86, a specificity of 0.87 and a sensitivity of 0.89 at a CUDOS [?]9 score, which has good reliability in Chinese practice and can effectively identify BD depression with mixd features. The sensitivity and specificity of Mini-M were 0.91 and 0.70, respectively. MINI-M has good reliability and validity, which can be used as a standardized tool for screening manic patients with mixed features(Hergueta and Weiller,2013).Therefore, we chose the Chinese version of the above two scales to assist in screening patients with mixed features for further study.

2.3 Definitions of guideline in consistencies

Recommendations for pharmacological treatment of acute BD with mixed features by CANMAT/ISBD guidelines (Yatham, et al.,2021) were used to determine the treatment(s) as guideline concordance or disconcordance. The use of these guidelines as "standard" was justified because there was no update on treatment-guidelines for bipolar disorder with mixed features in China since 2014 and the guidelines of CANMAT/ISBD for BD with mixed features were commonly recommended during continuing medical education and clinical practice in Mainland China. Treatment protocols for (hypo)mania with mixed features:Lithium, divalproex sodium, carbamazepine, aripiprazole, ziprasidone, olanzapine, quetiapine, risperidone, paliperidone, and in combination with other psychotropic drugs are in accordance with the guidelines. First-generation antipsychotics (especially haloperidol) and antidepressants are not recommended. Treatment protocols for depression with mixed features:Lithium, divalproex sodium, lamotrigine, carbamazepine, aripiprazole, lurasidone, ziprasidone, olanzapine, olanzapine and fluoxetine combination, quetiapine and in combination with other psychotropic drugs are in line with the guidelines.Antidepressant monotherapy or adjunctive therapy is not recommended. Therefore, protocols other than the above are not considered to meet the guideline recommendations.

2.4 Statistical analysis

Demographic data, clinical characteristics and treatment regimens were statistically described. Enumeration data were expressed as constituent ratio [n, %], and measurement data were expressed as MEDIAN. The treatment patterns of patients with mixed characteristics were analyzed by descriptive statistics, and compared with the guidelines to analyze whether they were consistent. Logistics regression analysis was used to analyze the included variables such as gender(male vs.female), hospital type(general vs. psychiatric), clinical classification(BD-Ivs.BD-II), comorbid mental disorders(yes vs. no), family history(yes vs. no), age at study entry([?]Median vs. ¿Median), year of first onset y([?]Median vs. ¿Median), number of episodes in past year ([?]Median vs. ¿Median),and exploratory analysis was used to analyze the factors affecting the inconsistency with the guidelines. Statistical significance was set at α=0.05, two tailed,in order to detect potentially clinically meaningful associations.

3.RESULTS

3.1 Demographic and clinical characteristics

A total of 688 patients with BD in the acute phase were enrolled in this study, and a total of 448 cases with mixed features. (Hypo)manic with mixed features 235 cases (34.15%),depression with mixed features 213 cases(30.9%). As shown in the table 1 below.

The proportion of females (65.5%) in the group of (hypo)mania with mixed features was higher than that of males (34.5%), the majority were Han Chinese (99.2%), most had high school or higher education (78.3%),mainly originated from specialized hospitals(60.4%),and were mainly hospitalized (68.5%),and most patients had no current psychiatric or somatic disease co-morbidity or family history of psychiatric disorders. BD-I (54.1%) was more common than BD-II(45.9%), and the first mood episode was mainly depressive episode (65.9%). The median age at study entry was 24 years, and the median age at first episode was 18 years. Median number of recurrent episodes in the past year was 4.

The proportion of females (65.3%) in the depression with mixed features group was higher than that of males (34.7%), the vast majority were Han Chinese (97.7%), most had high school or higher education

(83.6%), mainly originated from specialty hospitals (58.2%),were predominantly hospitalized (56.3%),and most patients had no current co-morbidities of psychiatric or somatic disorders, or a family history of psychiatric disorders. BD-II (60.1%) was more common than BD-I (39.9%), and the first mood episode was mainly depressive episode (86.8%). The median age at study entry was 21 years, and the median age at first episode was 17 years. Median number of recurrent episodes in the past year was 4.

TABLE1 General demographic and clinical characteristics of BD with mixed features

Characteristics [n,%]	(Hypo)manic with mixed features N=235	(Hypo)manic with mixed features N=235	(Hypo)manic with mixed features N=235	Depression with mixed features N=213
Gender	Gender			
Male	Male	81(34.5)	74(34.7)	74(34.7)
Female	Female	154(65.5)	139(65.3)	139(65.3)
Race	Race			
Han	Han	233(99.2)	208(97.7)	208(97.7)
Other	Other	2(0.8)	5(2.3)	5(2.3)
Education level	Education level			
High School and above	High School and above	184(78.3)	178(83.6)	178(83.6)
Other	Other	51(21.7)	35(16.4)	35(16.4)
Hospital category	Hospital category			
Psychiatric	Psychiatric	142(60.4)	124(58.2)	124(58.2)
General	General	93(39.6)	89(41.8)	89(41.8)
Treatment Place	Treatment Place			
Hospitalization	Hospitalization	161(68.5)	120(56.3)	120(56.3)
Outpatient	Outpatient	74(31.5)	93(43.7)	93(43.7)
Subtype	Subtype			
BD-I	BD-I	127(54.1)	85(39.9)	85(39.9)
BD-II	BD-II	108(45.9)	128(60.1)	128(60.1)
Mood state at first onset	Mood state at first onset			
Hypomanic/manic episode	Hypomanic/manic episode	50(21.3)	21(9.9)	21(9.9)
Depressive episode	Depressive episode	155(65.9)	185(86.8)	185(86.8)
Mixed episodes	Mixed episodes	30(12.8)	7(3.3)	7(3.3)
Family history of mental disorder	Family history of mental disorder	19(8.1)	10(4.7)	10(4.7)
Current co-morbidity	Current co-morbidity			
Mental disorder	Mental disorder	11(4.7)	7(3.3)	7(3.3)
Physical disorder	Physical disorder	20(8.5)	10(4.7)	10(4.7)
Age at study entry(years)	Age at study entry(years)	24*	21*	21*
Age at first-onset(years)	Age at first-onset(years)	18*	17*	17*
Number of episodes in past year	Number of episodes in past year	4*	4*	4*

* denotes the median MEDIAN

3.2 Pharmacological treatment strategies in the acute phase of (hypo) mania with mixed features

As shown in Table 2, among 235 patients with BD (hypo) mania with mixed features in the acute phase, 22 (9.4%) patients did not receive any medication and 51 (21.6%) patients received a single type of medication.The most commonly prescribed combination of two drugs (n=121,51.5%) included a mood stabilizer combined with an antipsychotic (n=98, 41.7%),a mood stabilizer combined with an antidepressant (n=8, 3.4%), an antipsychotic combined with an antidepressant (n=6, 2.6%), and two antipsychotics combined (n=8, 3.4%).Twenty-nine (12.4%) patients received three medications, including a mood stabilizer plus an antipsychotic with an antidepressant (n=13, 5.6%), and a mood stabilizer plus two antipsychotics (n=16, 6.8%).Twelve (5.1%) patients were treated with four or more medications. A total of 69 patients were not treated according to the guidelines, with an inconsistency rate of 29.4%. (No drug n=22, single antidepressant n=8, combined antidepressant n=39, total n=69)

TABLE 2 Patterns of pharmacological treatments in patients with acute bipolar(hypo)mania with mixed features

Treatment strategies [n,%]	(Hypo)manic with mixed features N=235
No agent	22(9.4%)
One agent	51(21.6%)
MS	27(11.4%)
RA	16(6.8%)
Antidepressant	8(3.4%)
Two agents	121(51.5%)
MS+ RA /NRA	98(41.7%)
MS+ antidepressant	8(3.4%)
RA + antidepressant	6(2.6%)
RA+RA /NRA	9(3.8%)
Three agents	29(12.4%)
MS+ RA /NRA + antidepressant	13(5.6%)
MS+ RA + RA /NRA	16(6.8%)
Four agents(contains antidepressants)	12(5.1%)

MS:Mood stabilizer, including lithium, divalproex sodium, carbamazepine.

RA:Recommended antipsychotics , second-generation antipsychotics recommended by CANMAT guidelines for (hypo) mania with mixed features.

NRA:Non-recommended antipsychotics, second-generation antipsychotics not recommended by CANMAT guidelines for (hypo) mania with mixed features.

3.3 Pharmacological treatment strategies in the acute phase of depression with mixed features

As shown in Table 3, among 213 BD depression with mixed features in the acute phase, 21 (9.9%) patients did not receive any medication and 38 (17.8%) patients received a single type of medication. The most commonly prescribed combination of two drugs (n=89,41.8%) included a mood stabilizer combined with an antipsychotic (n=47, 22.1%), a mood stabilizer combined with an antidepressant (n=21, 9.9%),an antipsychotic combined with an antidepressant (n=20, 9.4%), and two antipsychotics combined (n=1, 0.4%).Forty-seven (22.1%) patients received three medications, including a mood stabilizer plus an antipsychotic with an antidepressant (n=33, 15.5%), a mood stabilizer plus two antipsychotics (n=13,6.2%), and two antipsychotics combined with an antidepressant (n=1, 0.4%). Eighteen (8.4%) patients were treated with four or more medications. A total of 118 patients were not treated according to the guidelines, with an inconsistency rate of 55.4%. (No

drug n=21, single antidepressant n=3, single non-recommended antipsychotic n=1,combined antidepressant n=93, total n=118)

TABLE3 Patterns of pharmacological treatments in patients with acute bipolar depression with mixed features

Treatment strategies [n,%]	Depression with mixed features N=213
No agent	21(9.9%)
One agent	38(17.8%)
MS	23(10.8%)
RA	11(5.2%)
NRA	1(0.4%)
Antidepressant	3(1.4%)
Two agents	89(41.8%)
MS+RA/NRA	47(22.1%)
MS+ antidepressant	21(9.9%)
RA/NRA+ antidepressant	20(9.4%)
RA+NRA	1(0.4%)
Three agents	47(22.1%)
MS+RA/NRA+ antidepressant	33(15.5%)
MS+RA+RA/NRA	13(6.2%)
RA+NRA+ antidepressant	1(0.4%)
Four agents(contains antidepressants)	18(8.4%)

MS:Mood stabilizer, including lithium, divalproex sodium, lamotrigine ,carbamazepine.

RA:Recommended antipsychotics , second-generation antipsychotics recommended by CANMAT guidelines for depression with mixed features.

NRA:Non-recommended antipsychotics, second-generation antipsychotics not recommended by CANMAT guidelines for depression with mixed features.

3.4 Factors influencing treatment in consistency with guidelines in the acute phase of BD with mixed features

Applying logistic regression analysis models to the eight included variables gender, hospital type, clinical subtype, whether co-morbid psychiatric disorders, family history, age at entry, age at first episode, and number of episodes revealed that not all variables had an effect on guideline consistency. The results showed that in patients with bipolar (Hypo) mania with mixed features, BD-II increased the risk of treatment inconsistency with guidelines, OR=0.52 (95% CI 0.29-0.93), and older age at study entry (>24 years) significantly increased the risk of treatment inconsistency with guidelines, OR=2.4 (95% CI 1.3-4.3), while the remaining variables were not statistically significant. In patients with bipolar depression with mixed features, the number of episodes in the past year (>4 times) significantly increased the risk of treatment inconsistency with guidelines, OR=1.9 (95% CI 1.08 to 3.6), and the remaining variables were not statistically significant. As shown in Table 4 below.

TABLE4 Factors influencing the inconsistent treatment with guidelines in the acute phase of BD with mixed features

Risk factors
(Hypo) mania with mixed features N=235
Clinical subtype (BD-II)
Age at study entry(¿24years)

Risk factors
Depression with mixed features, N=213
the number of episodes(¿4 times)

4. DISCUSSION

To the best of our knowledge, this is the first multicenter study to compare the prevalence of BD with mixed features according to DSM-5 and the consistency of treatment regimens with the guidelines in mainland China. Our results showed that the prevalence of (hypo)mania with mixed features was 34.2%, and the depression with mixed features was 30.9%. According to CANMAT, the rate of inconsistency with the guidelines was 29.4% for bipolar mania with mixed features, and 55.4% for depression with mixed features, without considering the order of treatment. The main factors affecting the guideline inconsistency were clinical subtype (BD-II), age at study entry (> 24 years), and the number of episodes in the past year (> 4 times), while the other variables had no significant effect. Interestingly, we found that the prevalence of BD with mixed characteristics according to the criteria of ICD-10 and DSM-5 was 20.8% and 29.5%, while the detection rate of CUDOS-M and MINI-M scales based on DSM-5 was 65.1%, which was much higher than the above criteria.This may be due to the fact that mixed features is a dynamic process in itself, and the sensitivity of the scale is higher than that of the DSM-5, which is helpful for clinicians to detect potential patients with mixed features.

The updated DSM-5 in 2013 proposed mixed features, which was regarded as a concomitant feature and effectively improved the recognition rate of BD with mixed features (Perugi, et al.,2014). A cluster study based on DSM-5 diagnostic criteria to analyze the similarity between unipolar depression and BD suggests that unipolar depression with mixed features is more similar to BD, indirectly supporting that mood disorders are a continuous spectrum disorder (Ferentinos, et al.,2017).To date, there have been few systematic epidemiological investigations of BD with mixed features (Vieta, et al.,2014; McIntyre, et al.,2015).However, mixed features are characterized by high prevalence, recurrent mood episodes, severe disease symptoms, high comorbidity and suicide rates, and poor clinical outcomes, which seriously affect patients' social function and quality of life(Fagiolini, et al.,2015; Lee Mortensen, et al.,2015; McIntyre, et al.,2015).The results of this cross-sectional study showed that the incidence of depression with mixed features in BD (30.9%) was slightly lower than that of (hypo) mania with mixed features (34.2%). An international study showed that the prevalence of BD-I depression and mania with mixed features was 34% and 20.4%, respectively, and BD-II depression and (hypo) mania with mixed features was 33.8% and 5.1%(McIntyre, et al.,2015). Another recent systematic review analysis based on DSM-5 diagnostic criteria showed that the prevalence of bipolar depression with mixed features was 33.5%, and the prevalence of (hypo)mania with mixed features was 30.0%(Vázquez, et al.,2018). The prevalence of mixed features in this study was generally consistent with that in the above studies, but the incidence of (hypo) mania with mixed features was slightly higher than that of depression with mixed features. One study used different diagnostic criteria of ICD-10, DSM-IV and DSM-5 respectively, and the results showed that the prevalence of mixed features was about 7.0%, 28.0% and 66.0% respectively(Cassidy, et al.,2008). This further highlights clinical usefulness of DSM-5 in diagnosing BD with mixed features compared with ICD-10 and DSM-IV(Betzler, et al.,2017).

The results of this survey showed that more than half of the patients with bipolar mixed features were female (n=293,65.4%), the proportion of BD-I and BD-II was similar in patients with (hypo)mania mixed features, and the proportion of BD-II was significantly higher than that of BD-I in patients with depression mixed features.The first episode was mainly depression, and the median age of first onset was [?]18 years. Nevertheless, family history and co-morbid psychiatric or somatic disorders were not prominent, which is inconsistent with previous findings (Sole, et al.,2017). Although there are some differences with previous studies, the results of this survey also support the disease characteristics of women with double concomitant mixed features, which are more likely to be affected by the disease, at an earlier age of onset, most of the first episodes are depressive episodes, and the onset pattern is complex(Shim, et al.,2015; Sole, et al.,2017).

Based on the concept of evidence-based medicine, many international guidelines and management recommendations for BD with mixed features do not recommend the use of antidepressants in the acute treatment (Rakesh, et al.,2017; Heinz, et al.,2018; Chakrabarty, et al.,2020; Yatham, et al.,2021).In mainland China, the most common prescription for the treatment of BD with mixed features is a combination of two drugs, specifically a mood stabilizer plus a second-generation antipsychotic, which is in line with guidelines. Without considering the order of treatment, the discordance rate between the guidelines and mania with mixed features was 29.4%, and that of depression with mixed features was as high as 55.4%. The use of antidepressants alone or in combination was still the main factor inconsistent with the guidelines, which was more prominent in patients with depression and mixed features, followed by no drug treatment. A survey in China showed that the inconsistency rate of treatment with the guidelines in the acute phase of BD (hypo)manic and depression was 11.1% and 50.2% respectively(Wang, et al.,2014, 2014).The inconsistency rate of this study is higher than the above results. Up to now, there has been no study on the consistency of acute treatment with guidelines in mainland China. Further analysis of the possible reasons for the inconsistency is as follows. On the one hand, the clinical manifestations of patients with mixed features are complex and easy to be misdiagnosed and missed diagnosed(McIntyre, et al.,2015) ,and doctors have not yet fully identified patients with mixed features in clinical practice. On the other hand, there is insufficient attention to mixed features and understanding of guidelines in clinical practice, and excessive reliance on subjective clinical experience, which may lead to the treatment plan contrary to the guidelines. Inappropriate use of antidepressants in the treatment of BD can itself increase the risk of mixed episodes and rapid cycling, while the use of antidepressants in patients with mixed features can exacerbate agitation, irritability and worsen symptoms of opposite polarity (Takeshima,2017),thus making treatment more difficult. Although the research evidence on the treatment of BD with mixed features is not very strong, second-generation antipsychotics (recommended by CANMAT guidelines) and mood stabilizers (lithium, valproate, carbamazepine, etc.) alone or in combination remain the currently recommended pharmacological treatment options(Rosenblat and McIntyre,2017; Yatham, et al.,2021).The Systematic Treatment Enhancement Program for Bipolar Disorder(STEP-BD) found that intensive psychosocial treatments (cognitive behavior therapy, family-focused therapy, or interpersonal and social rhythm therapy) as adjuncts to pharmacotherapy were more beneficial than a brief psychoeducational treatment (collaborative care) in enhancing stabilization from bipolar depression(Bowden, et al.,2012).Furthermore,a recent Network meta-analysis (NMA) included 39 randomized controlled trials with a total of 3863 patients, and the results showed that medication combined with manualized psychotherapy could effectively reduce the recurrence rate of BD compared with conventional drug therapy(Miklowitz, et al.,2021). In addition, ECT may be considered in cases of significant safety concerns, such as acute suicidality or drug intolerance, or in refractory cases (Fagiolini, et al.,2015), but mood stabilizers and atypical antipsychotic medications should be the cornerstone of the management of BD with mixed features in the acute phase(Rosenblat and McIntyre,2017).

We also further analyzed the factors influencing the inconsistency of the guidelines and found some meaningful outcomes.We found that BD-II (OR=0.52, 95% CI 0.29-0.93) was a factor for inconsistent guidelines of (hypo)manic with mixed features and that older age at entry $>$ 24 years (OR=2.4, 95% CI 1.3-4.3) significantly increased the risk of inconsistency with guidelines. The risk factor of depression with mixed features was the number of episodes in the past year ($>$ 4 times), which significantly increased the risk of treatment inconsistency with guidelines (OR=1.9 95% CI 1.08-3.6). Gender (female) was not a factor affecting guideline inconsistency in this study, either in patients with (hypo)manic or depression with mixed features. BD-II usually presents as depressive episodes with longer and more frequent episodes, which increases the risk of antidepressant use (Tondo, et al.,2017). Yet studies show that even when antidepressants are used against guidelines, the duration of depressive episodes is not reduced (Frankle, et al.,2002). In this study, the age of onset of patients with mixed characteristics did not affect the treatment inconsistency, whereas older age at entry ($>$ 24 years) increased the risk of treatment inconsistency. The meta-analysis showed that patients with BD at an earlier age of onset had more severe depressive symptoms, comorbid anxiety and substance dependence, and needed longer treatment time, but there was no obvious resistance to treatment response (Joslyn, et al.,2016).Clinician-specific factors such as age, education level, and training experience have been reported to influence prescribing patterns and guideline consistency (Dennehy, et al.,2005; Perlis,2007; Xiang,

et al.,2013),and these factors could not be completely removed in this study.Moreover, a recent systematic review showed that the different use of terminology recommended in clinical practice guidelines (CPG) is also a complicating factor affecting the evidence-based treatment of BD (Gomes, et al.,2022).

4.1 Limitations

There are some limitations of this study. First, the study was conducted in 20 large psychiatric and general hospitals in mainland China. Most of them are located in provincial capitals or municipalities and are controlled by the central government. Current practice of treating patients with BD with mixed features in small and medium-sized cities, villages, or communities was not included in this study, so the sample size and representativeness are limited. Second, this study was a cross-sectional survey based on medical records and scales, and we were unable to examine the dynamics of treatment regimens in patients with dual concomitant mixed features.Some psychotropic medications may be a continuation of prior regimens for mood episodes, and certain medications may not be specifically prescribed for patients with mixed features. In addition, some other treatments such as physiotherapy and psychotherapy were not included. Finally,this study is a descriptive real-world study without assumptions and may not be representative of patients with BD with mixed features outside China.

5. CONCLUSIONS

The results of the study showed that BD with mixed features was more common, with 34.2% and 30.9% of (hypo) mania and depression with mixed features, respectively. CUDOS-M and MINI-M have high sensitivity to help screen patients with BD with mixed features, but lack specificity. Under natural conditions, there are obvious differences in the treatment inconsistency of guidelines in patients with acute BD mixed features. This inconsistency is very common (more than 50%) in patients with depression and mixed features, and antidepressant monotherapy or combination therapy is the main reason for such high inconsistency rates in this survey population. Factors associated with guideline inconsistencies included clinical type (BD-II) and patient-specific characteristics (older age at study entry and more episodes in the past year). In clinical practice, there is insufficient understanding of BD with mixed features and the potential harm of inappropriate drug treatment in this population. There is a need for continued education and training in China to avoid misdiagnosis and inappropriate psychotropic drug treatment of comorbid mixed features, and to bridge the gap between clinical practice treatment and guidelines.

AUTHOR CONTRIBUTIONS

Bo Fu and Miao Pan: conceptualization and writing – original draft.

Lin Tang and Sanqiang Zhang: formal analysis and editing.

Yiru Fang,Zuowei Wang ,Yuncheng Zhu: methodology and writing and original draft preparation.

Guiyun Xu, Zhiyu Chen, Xiaohong Li, Wenfei Li, Zhian Jiao, Mingli Li, Yong Zhang, Jingxu Chen, Xiuzhe Chen, Na Li, Jing Sun, Jian Zhang, Shaohua Hu, Haishan Wu, Zhaoyu Gan, Yan Qin, Yumei Wang, Yantao Ma, Xiaoping Wang: data curation and investigation and review.

All authors have read and agreed to the published version of the manuscript.

The authors declare no conflicts of interest.

FUNDING

This study was supported by an open project (Prospective cohort study of the first-treatment of bipolar disorder) of Henan Clinical Research Center for Mental Disorders, and Shanghai Clinical Research Center for Mental Health (SCRC-MH, 19MC1911100), Shanghai Key Medicine Specialties Program (ZK2019A06), Scientific Research Project of Shanghai Municipal Health Commission (202040318).

ACKNOWLEDGMENTS

The authors gratefully acknowledge the support and guidance from the Chinese Society of Neuroscience & Psychiatry and the Chinese Academy of Bipolar Disorders. The authors also gratefully acknowledge all physicians who contribute subjects essential for this survey in the following hospitals:The Affiliated Brain Hospital of Guangzhou Medical University, Hangzhou Seventh People's Hospital, Beijing Anding Hospital ,Capital Medical University, Anhui Mental Health Center, Shandong Provincial Hospital, Hongkou Menta Health Center of Shanghai, West China Hospital Sichuan University, Tianjin Anding Hospital, Beijing Huilongguan Hospital, Shandong Mental Health Center, The first Affiliated Hospital of Kunming Medical College, Nanjing Brain Hospital, Shenzhen Kang Ning Hospital, The First Affiliated Hospital Zhejiang University School of Medicine, The Second Xiangya Hospital of Central South University, No. 3 Hospital of Zhongshan University, Dalian Seventh People's Hospital, The First Hospital of Hebei Medical University, Peking University Institute of Mental Health.

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