

Clinical Features of Patients With Major Depressive Disorder and Bipolar Disorder Depressive Episodes With Mixed Features

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Primary research

Keywords: major depressive disorder, bipolar disorder depressive episode, mixed features

Posted Date: March 17th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-306630/v1>

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Abstract

Background: To investigate the clinical phenomenology and clinical features of the new concept of major depressive disorder and bipolar disorder depressive episodes with mixed features.

Methods: A total of 357 patients with major depressive disorder or bipolar disorder depressive episodes were assessed, we compared the differences of clinical features with or without mixed features.

Results: According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, the overall prevalence of mixed features was 9.52% (34/357) in major depressive disorder and bipolar disorder depressive episodes; specifically, the prevalence was 6.0% in major depressive disorder and 23.3% in bipolar disorder depressive episodes. Compared with the non-mixed features group, the mixed features group had more single individuals ($P=0.002$), earlier onset age ($P=0.003$), more patients with an onset age <25 years ($P=0.001$), and more previous incidences and prior hospitalizations ($P<0.001$, $P=0.004$, respectively), and fewer melancholic features ($P=0.013$). Logistic regression analysis showed that marital status (OR=0.237) and previous incidence (OR=1.478) was associated with mixed features.

Conclusion: It indicates that previous incidence may be a risk factor of in patients with major depressive disorder and bipolar disorder depressive episodes with mixed features, and marital status may be a protective factor.

Introduction

Affective disorders are one of the most common types of mental disorders, and the worldwide lifetime prevalence of affective disorders is 9.6%[1]. Evidence from clinical research and practice shows that mixed features are common in affective disorders[2, 3] and that mixed features seriously affect the patient's quality of life and social functioning as well as lead to more frequent recurrence, more severe symptoms, greater risk of suicide, higher rates of comorbidities, lower efficacy of medication, and a poorer prognosis of the disease. The financial burden of these disorders is substantial[4–10], and the awareness of both the prevalence and burden of affective disorders with mixed states is increasing; however, the misdiagnosis of mixed states and the subsequent lack of treatment are common in clinical settings [11].

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for mixed episodes are one of the most widely used sets of criteria. The DSM-IV-TR definition for mixed episodes is that almost every day for at least a week, manic and depressive symptoms are simultaneous, this diagnosis can only be applied to bipolar disorder type I, and the criteria are too strict. The DSM-5 [12] revised the criteria from DSM-IV. the DSM-5 included a "mixed features" specifier for manic episodes and major depressive episodes, and the mixed features conform to the requirements of clinical practice[13, 14]. At present, there is still a lack of systematic epidemiological investigations at home and abroad of major depressive disorder or bipolar disorder with mixed features as strictly defined by the DSM-5[15]. This study is the first to investigate the incidence, demographic characteristics, clinical

characteristics of major depressive disorder and bipolar disorder depressive episode with mixed features in using the new classification of diseases in China.

Methods

Study sample

The subjects were outpatients or inpatients from one of three largest psychiatric hospitals in China. The survey was conducted from August 2015 to September 2017.

The inclusion criteria were as follows: (1) met the diagnostic criteria of unipolar depressive episode or bipolar depressive episode set by DSM-IV; (2) Hamilton depression scale (HAMD-17) score ≥ 18 ; and (3) aged 18–65. The exclusion criteria were as follows: (1) persons currently suffering from severe and unstable physical diseases; (2) pregnant and lactating women; (3) organic mental disorder; and (4) comorbidities of substance abuse (excluding nicotine dependence) and personality disorders.

Measures and instruments

After consistency training (interrater reliability, Kappa value = 0.86), psychiatrists diagnosed patients through clinical interviews using the mini-international neuropsychiatric interview (MINI).

General demographic data were collected, including age, sex, nationality, marital status, occupational status, and years of education. Clinical data were collected as well, including age of onset, family history of mental disorders, previous incidence, previous hospitalizations, frequent attacks (frequency of attacks ≥ 4 times per year), suicidal ideation, suicide attempts, psychotic symptoms, inducement of the onset of the disease, early onset (age of first onset < 25), suicide risk (the presence and degree of suicide risk was assessed by the MINI scale), atypical features (such as marked hyperorexia, weight gain, or increased sleep), anxiety symptoms (nervousness, significant insecurity, fear of not being able to concentrate, fear of something bad happening, fear of losing control), somatic symptoms (appetite drops obviously, significantly reduced libido, weight loss), obsessive-compulsive symptoms, catatonia, and melancholic features.

The DSM-5 criteria for mixed features are as follows^[12]. At least three of the following manic/hypomanic symptoms are present nearly every day during the majority of the day of a major depressive episode: (1) elevated, expansive mood, (2) inflated self-esteem or grandiosity, (3) more talkative than usual or pressure to keep talking, (4) flight of ideas or subjective experience that thoughts are racing, (5) increased energy or goal-directed activity (either socially, at work or school, or sexually), (6) increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments), (7) decreased need for sleep (feeling rested despite sleeping less than usual, in contrast to insomnia).

HAMD-17^[16] was used to assess the degree of depression. The Young Mania Rating Scale (YMRS) assessed whether mania was present.

Statistical analysis

Data were analysed using SPSS 17 software (SPSS Inc., USA). Descriptive statistics were used to characterize the patients' sociodemographic factors. Comparisons of the sociodemographic and clinical characteristics of the patients with mixed features and those without mixed features were conducted using standard bivariate methods: the t-test (t) or Mann-Whitney U test (Z) were used to compare continuous measures, and the chi-squared test (χ^2) was used to compare categorical measures. Findings of interest that were preliminarily associated with mixed features at a significance level of $P \leq 0.2$ (to adjust for multiple comparisons) were also entered into a multivariable logistic regression with mixed features as the outcome. The level of significance was set at 0.05 (two-tailed).

Results

A total of 357 patients participated in the study. This study showed that the prevalence of mixed features across major depressive disorder and bipolar disorder depressive episodes was 9.52% (34/357), including prevalences of 6.0% among those with major depressive disorder and 23.3% among those with bipolar disorder depressive episodes. This study found that bipolar disorder depressive episodes were more often accompanied by mixed features, and this difference was statistically significant ($P < 0.05$).

Basic sociodemographic and clinical characteristics

Compared with those without mixed features, being single was more common among patients with mixed features (70.6% vs 42.1%, $P = 0.002$) (Table 1).

Additionally, in the patients with mixed features, the onset age was earlier [(25.97 \pm 13.29) vs (33.8 \pm 14.83), $P = 0.003$], more individuals had an onset age < 25 years (64.7% vs 33.1%, $P = 0.001$), previous incidences were more common [(3.71 \pm 2.25) vs (2.08 \pm 1.60), $P < 0.001$], previous hospitalizations were more common [(1.58 \pm 1.50) vs (0.95 \pm 1.04), $P = 0.004$], melancholic features were less common (42.4% vs 64.5%, $P = 0.013$), and the HAMD-17 score was lower [(24.03 \pm 3.55) vs (25.62 \pm 4.17), $P = 0.049$] (Table 2).

Table 1

General demographic data for patients with major depressive disorder and bipolar depressive episodes with and without mixed features

Factor	Mixed (n = 34) (n,%)	Non-mixed (n = 323) (n,%)	Total (n = 357) (n,%)	t/χ²	df	P
Female	22(64.7)	194(60.1)	216(60.5)	0.278	1	0.713
Single	24(70.6)	136(42.1)	160(44.8)	10.091	1	0.002
Unemployed	13(38.2)	144(44.6)	157(44.0)	0.503	1	0.587
Age (years) mean ± SD	35 ± 15.53	39.1 ± 14.58	38.70 ± 14.70	1.548	355	0.122
Education (years) mean ± SD	13.44 ± 4.10	12.87 ± 4.06	12.92 ± 4.06	-0.783	355	0.434

Table 2

Clinical characteristics of patients with major depressive disorder and bipolar depressive episodes with and without mixed features

Factor	Mixed (n = 34) (n,%)	Non-mixed (n = 323) (n,%)	Total (n = 357)(n,%)	t/Z/ χ^2	df	P
Diagnosis						
Bipolar disorder depressive episode	17(50.0)	56(17.3)	34(9.5)	20.175	1	< 0.001
major depressive disorder	17(50.0)	267(82.7)				
Family history of mental disorders	13(38.2)	89(27.6)	102(28.6)	1.959	2	0.376
Previous incidence (mean \pm SD)	3.71 \pm 2.25	2.08 \pm 1.60	2.24 \pm 1.73	-5.122	356	< 0.001
Prior hospitalizations (mean \pm SD)	1.58 \pm 1.50	0.95 \pm 1.04	1.01 \pm 1.11	-2.877	354	0.004
Frequent attacks (\geq 4 times/year)	2(5.9)	6(1.9)	8(2.2)	2.275	1	0.132
Atypical features	4(11.8)	18(5.6)	22(6.2)	2.022	1	0.155
Suicidal ideation	23(67.6)	210(65.0)	233(65.3)	0.094	1	0.759
Suicide attempts	9(26.5)	58(18.0)	67(18.8)	1.463	1	0.227
Psychotic symptoms	10(29.4)	84(26.0)	94(26.3)	0.184	1	0.668
Anxiety symptoms	26(76.5)	234(72.4)	260(72.8)	0.252	1	0.616
Melancholic features	14(42.4)	207(64.5)	221(61.9)	6.210	1	0.013
Obsessive compulsive symptoms	3(8.8)	14(4.3)	17(4.8)	1.355	1	0.244
Somatic symptoms	14(41.2)	187(57.9)	201(56.3)	3.495	1	0.062
Catatonia	1(2.9)	15(4.7)	16(4.5)	0.214	1	0.643
Onset of the incentive	9(26.5)	120(37.2)	129(36.1)	1.521	1	0.218
Onset age < 25 years	22(64.7)	107(33.1)	129(36.1)	13.293	1	0.001
Suicide risk	10(29.4)	109(33.9)	119(33.3)	0.272	1	0.602
Age of first onset (years) mean \pm SD	25.97 \pm 13.29	33.80 \pm 14.83	33.05 \pm 14.85	2.953	356	0.003

Factor	Mixed (n = 34) (n,%)	Non-mixed (n = 323) (n,%)	Total (n = 357)(n,%)	t/Z/χ ²	df	P
HAMD-17 score	24.03 ± 3.55	25.62 ± 4.17	25.41 ± 4.29	1.978	355	0.049

Multivariable logistic model of factors associated with mixed features

General demographic and clinical characteristics were included in the logistic regression analysis. The results showed that marital status and previous incidences were independently and significantly associated with mixed features (Table 3).

Table 3
Multivariable logistic model of factors associated with or without mixed features (n = 357)

Factor	B	SE	Waldχ ²	OR(95% CI)	df	P
Marital status	-1.438	0.436	10.887	0.237(0.101–0.558)	1	0.001
Previous incidence	0.391	0.087	19.974	1.478(1.245–1.755)	1	< 0.001

Discussion

Due to using different definitions of mixed states, the prevalence of patients meeting the criteria for mixed states varies. Previous studies have shown that approximately 30–40% of patients with bipolar disorder have experienced mixed-state emotional episodes[4]. The prevalence of mixed states in depression is between 20% and 80%[17, 18]. In this study, strictly according to the DSM-5 diagnostic criteria, the results show that the prevalence of mixed features with major depressive disorder and bipolar disorder depressive episodes was 9.52%, which is different from the findings of a previous large-sample study using DSM-5 criteria. A prospective study by Tondo L et al. found that the total prevalence of mixed features was 21.9%[19]. Vazquez GH et al. [18] found that the overall prevalence of mixed features was 27.8%, this finding may be related to the small sample size. In this study, 6.0% of patients had mixed features with major depressive disorder, which was lower than the prevalence reported in a large study conducted by Perugi G et al.[17], who found a prevalence of 7.5%, and significantly lower than the prevalences reported by Tondo L et al.[19] and Vazquez GH et al.[18] (16.8% and 23.8%, respectively). In this study, 23.3% of patients had bipolar disorder depressive episodes with mixed features; this prevalence was reported to be 19.6% [15](Shim IH et al.), 30.2%[20](Tondo L et al.), and 35%[19](Vazquez GH et al.) in other studies. In addition, this study found that patients with bipolar disorder depressive episodes were more likely to have mixed features (P < 0.05) than patients with major depressive disorder, which was similar to previous results[18].

In this study, in terms of general demographic and clinical characteristics, there was no significant difference in gender and occupational status between the mixed features and non-mixed features groups; this result is similar to Gonzalez-Pinto A et al.[7]. In this study, among people with mixed features, the prevalence of single people was higher (70.6%) than that of non-single people; similarly, Tondo L et al. [19] found among people with mixed features, the prevalence of unmarried people (57.7%) was higher than that of married people, and the divorce rate was higher (15.9%) among people with mixed features than among those without mixed features. These findings may be related to patients' emotional instability, recurrent episodes and difficulty maintaining stable relationships. This study found among those with mixed features, the average onset age was 25.97 years, and an onset age < 25 years was more common in this group than in the non-mixed features group. Tondo L et al.[19] found an average onset age of 29.5 years among those with mixed features, and Shim IH et al. [15] found a significantly lower average onset age (21.6 years when using the diagnostic criteria of DSM-5. The current findings suggest that the onset age of patients with mixed features is between 20 to 30 years old; further studies are needed to prove this, as the early onset age may be related to poor long-term prognosis, disease severity and genetic predisposition. In this study, we found that the patients with mixed features had more previous incidences and more previous hospitalizations, which was similar to findings from previous studies based on DSM-5 diagnostic criteria[7, 15].

In this study, there were no differences in suicidal ideation, suicide attempts, or suicide risk. These findings are similar to the results of Shim IH et al.[15], who suggested that while the suicide risk was higher among patients with mixed features than among those without mixed features, the difference was not statistically significant. However, previous studies have suggested that patients with bipolar disorder or major depressive disorder with mixed features have a higher suicide risk than those without mixed features. McIntyre RS et al. [20] found that major depressive disorder patients with mixed features may have higher suicide risk behaviour. Other studies using the DSM-5 criteria have even found that mixed features are the strongest risk factors for suicidal behaviour[8]. However, the relationship between mixed features and suicidal tendency as defined by the DSM-5 has not been well studied[8, 21].

In this study, there was no significant difference in the rate of attrition between the mixed and non-mixed groups after one year. Patients with mixed features had lower rates of compliance with medication, lower recovery rates, higher recurrence rates, and higher rates of switching to [hypo]mania. This is consistent with previous research results[20, 22]. At present, there are few studies on the therapeutic effects of affective disorders with mixed features as defined by DSM-5. Shim IH et al. [6] studied the remission time of 131 patients with bipolar disorder and major depressive disorder and found that the remission time of the group with mixed features was significantly longer than that of the group without mixed features. Mazarini L et al. [10] found that high rates of depressive episode recurrence were associated with mixed features. There were also different research results in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which found that the treatment remission rate is higher among patients with mixed features[23].

Limitations

There were limitations in this study. The limited sample size of this study inhibited us from distinguishing the clinical characteristics and disease progression of major depressive disorder and bipolar disorder depressive episode patients with mixed features.

Conclusion

In summary, despite the limitations of this study, The results showed that marital status and previous incidence may be independent risk factors for mixed features as defined by the DSM-5 criteria. Future research will focus on different aspects of affective disorders with mixed features, which will help to identify this population in clinical practice, further understand the clinical characteristics of patients with affective disorders with mixed features, and guide drug treatment.

Abbreviations

DSM-5

Statistical Manual of Mental Disorders, Fifth Edition

DSM-IV

Statistical Manual of Mental Disorders, Fourth Edition

MINI

the mini-international neuropsychiatric interview

HAMD-17

Hamilton depression scale

YMRS

The Young Mania Rating Scale

Declarations

Acknowledgements

The authors thank all clinicians who helped organize the study at each study site.

Authors' Contributions

Chen, Lin conceived the study, developed the study protocol. All authors contributed to writing and revising the manuscript. All authors read and approved the final manuscript.

Funding

This study was supported by the Beijing Municipal Science and Technology Project (Z151100004015087).

Availability of data and materials

Data could be obtained upon request to the corresponding author.

Ethics approval and consent to participate

This study was approved by the Ethics Committee and Institutional Review Board of Peking University HuiLongGuan Clinical Medical School. All patients have written informed consent prior to their enrollment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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