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·Original Article·

Atypical features and treatment choices in bipolar disorders: a result of the National Bipolar Mania Pathway Survey in China

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ABSTRACT

In this study, we examined the point prevalence rate of atypical features in bipolar disorder, and estimated the potential impact of these features on treatment practices in China. Using the atypical features criteria of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV), we documented the atypical symptoms in 3 906 consecutive participants with bipolar disorder enrolled at 26 psychiatric services across China. We further assessed the association between atypical features and the treatment approaches, including the prescription of antidepressants. The overall point prevalence rate of atypical features was 9.1% among patients with various bipolar disorder subtypes. When the definition was broadened to include atypical features B, the overall rate increased to 11.8%. Interestingly, among patients with the mixed state and remission subtypes, there was a significant difference in the rates of antidepressant medication usage between patients who met and those who did not meet the criteria for atypical features B. These findings indicate a trend of using antidepressants for these two types of patients with atypical features. Further, for both mixed state and remission patients, treatment approaches were related to atypical features B. Our findings provide evidence to assist clinicians to readily recognize atypical features in bipolar subtypes and can propose treatments based on these diagnoses.

Keywords: atypical features; bipolar; treatment; antidepressant

INTRODUCTION

Bipolar disorder (BP) is characterized by recurring periods of high or low mood, thinking and activity, associated with hypomanic, manic, depressed, and mixed states[1], making it difficult to diagnose. This complexity and diversity of symptoms has led to a number of different prevalence estimates. When taking into account type I (BP-I), type II (BP-II), and sub-threshold types, prevalence estimates have ranged from 1.5% to 6% in the USA[2-6]. In China, estimates are less specific, as up to 91.7% of patients with mood disorders never seek medical help[7], but the latest investigations conducted in four provinces place the prevalence rate somewhat lower than that in the USA, with 0.1% for BP-I and 0.3% for BP-II[7]. This discrepancy is unsurprising — diagnosing BP is still challenging for clinicians worldwide.

A particularly confounding factor in the difficulty faced by clinicians when making a diagnosis of BP, is

the largely unacknowledged atypical features (ATFs), such as mood reactivity, hyperphagia, hypersomnia or weight gain, interpersonal rejection sensitivity, and leaden paralysis[1] that can manifest alongside the better-known basic characteristics. While ATFs were introduced into the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV) after several studies on atypical depression[8-10] and other studies that have found overlaps between depressed patients with ATFs and BP-II[11-15], the atypical features of patients with BP have still not been well-studied. As a result, there is a lack of coherent findings related to ATFs in BP[13, 16, 17].

A further challenge faced by clinicians is how to best treat those patients they do diagnose with BP. Earlier studies reported that atypical depression symptoms may preferentially respond to antidepressants — for example monoamine oxidase inhibitors and tricyclic antidepressants[18-20] — and later a prominent meta-analysis indicated that antidepressants are effective in the short-term treatment of bipolar depression[21]. However, another study, the Systematic Treatment Enhancement Program for Bipolar Disorder, noted that the effects of maintained treatment showed no discernible difference between BP patients using antidepressants and those not using antidepressants[22]. At present, few treatment guidelines for BP recommend antidepressants as an adjunctive therapy to mood stabilizers, and no treatment guidelines recommend antidepressants as a monotherapy[23-26]. Despite these guidelines, a previous study reported that it is not uncommon to prescribe antidepressants for BP patients in China on a prolonged basis[27].

Given the relatively low diagnostic rates of BP and the reluctance of people in China to seek treatment for mood disorders as well as the lack of adherence to treatment guidelines, there is a pressing need to investigate the diagnosis and treatment of BP in China. The present report was designed to fill that gap by investigating the point prevalence of ATFs in BP and assessing their impact on treatment methods in China.

PARTICIPANTS AND METHODS

Study Design

To establish a database of BP clinical pathway in China, the National Bipolar Mania Pathway Survey (BIPAS) was carried out in 15 psychiatric hospitals and 11 psychiatry departments of general hospitals distributed throughout the mainland of China, between November 2012 and January 2013. A sample of 3 906 patients with a diagnosis of BP were recruited. Most of the patients were Han Chinese, their mean age was 34.75 ± 14.09 years, and 48.1% were female. Of these patients, 774 (19.8%) were in their first episode, 2109 (54%) were recurrent, and 1023 (26.2%) were at the stable/maintainance stage (see supplemental data for detailed information).

All inpatients and outpatients at the 26 services were consecutively screened and their medical records were reviewed. The patients were enrolled if they met the diagnostic criteria for BP as determined by the International Classification of Disease - 10 Edition (ICD-10). If patients met the criteria, socio-demographic and clinical features such as age at onset, first episode type, and psychiatric and medical histories were recorded. The current symptoms of participants were assessed by psychiatrists with at least six years of experience in both research and clinical practice, while medication data were independently reported by the patients, their family members, and their medical records when available. Both the research psychiatrists and assistants were trained before the study to ensure fidelity with protocols. Prior to inclusion in the study, all potential participants were informed of the parameters of this study, and provided written consent. All protocols and procedures were approved by the Ethics Committee of Shanghai Mental Health Center and the other participating institutions, and were conducted in accordance with the relevant national and international guidelines, as well as the Declaration of Helsinki.

Clinical Assessment

All patients enrolled in this study were diagnosed with subtypes of BP according to the ICD-10 criteria. Based on the DSM-IV definitions, ATFs were defined as mood reactivity plus two or more items of ATF B symptoms, which include hyperphagia, hypersomnia or weight gain, interpersonal rejection sensitivity, and leaden paralysis[1]. The researchers also examined the point prevalence by ATF B criteria, which refers to a patient having at least two of the four symptoms listed above[14].

Statistical Analysis

All socio-demographic and clinical features were gathered from surveys and observations and then summarized with descriptive statistics that allowed for further comparison between different BP subtypes using the χ^2 test. Statistical significance was set at $\alpha = 0.05$. To explore the relationship between ATFs and six subtypes of BP, multinomial logistic regression was used (see Table S1 for details). Because we focused on the point prevalence of the atypical depressive features in BP rather than the diagnosis of atypical depression according to DSM-IV, the variable ATF B was used for regression analysis. Several other confounding variables were included as well, to test if there was any significant difference or association: gender (male *versus* female), age at study entry, age at onset, current co-morbidity with mental disorders (no *vs* yes), current co-morbidity with physical disorders (no *vs* yes), mood state at onset (hypomanic/manic episode *vs* depressive episode), type of episode last time (mania, depression, mixed episode, rapid-cycling episode), and number of episodes in the past year. Using this information, the point prevalence of ATFs was individually computed among all of the subtypes present among the participants.

The χ^2 test was also used to explore the relationship between ATFs and the use of antidepressants (reported no or yes). The relationship between ATFs and different treatment approaches among all the subtypes of BP was also examined, to provide a clearer picture of treatments currently being used in China. In this study, ATF B was used as the main variable of ATFs, due to the possible impact of ATF B on treatment methods.

RESULTS

Demographic and Clinical Characteristics

Among the 3 906 patients with varying subtypes of BP, analysis showed no significant differences in terms of gender distribution, race, current comorbidity-mental disorders, or current comorbidity-physical disorders. However, some clinical characteristics showed significant differences (P <0.01) among the six subtypes of BP, notably mental health history and the number of episodes in the past year. Other variables, such as current state of episode, mood state at first episode, family history, age at entry, age at first episode, and episode type last time showed even higher significance (P <0.001; Table 1).

Distribution of Atypical Features in BP

We used multinomial logistic regression to explore the relationship between ATF B features and six subtypes of BP by comparing clinical variables among them. Using remission type as the internal reference index (P <0.05, see Table S1 for details), the results of these analyses showed that the ATF B features were significantly correlated with the subtypes of BP. First, we noted that the different subtypes exhibited different point prevalence rates of ATFs. The point prevalence rates of all atypical symptoms were relatively higher in patients exhibiting a mixed state (Table 2). Interestingly, rejection sensitivity was the most common symptom in all the BP subtypes (ranging from 42.5% in patients with recurrent mania to 64.3% in patients with mixed state). Second, based on the DSM-IV definition of ATFs, the overall rate of patients who met the criteria was 9.1%, with a specific breakdown as follows: 5.3% of manic patients without psychotic symptoms; 8.7% of those patients with psychotic symptoms; 7.4% of hypomanic patients; 11.3% of recurrent mania patients; 6.9% of remission patients; and most strikingly, 28.1% of mixed state patients. Finally, the overall rate of patients who met the ATF B symptom criteria was 11.8%. Specifically, this was less common in patients diagnosed with mania without psychotic symptoms (7.0%), but most common in mixed state patients (33.2%).

Association between Atypical Features B and Use of Antidepressants

The proportions of patients with and without ATF-B using antidepressant medication in each subgroup are shown in Table 3. Our analysis showed no significant differences between ATF B and non-ATF B patients in the hypomania, mania without psychotic symptoms, mania with psychotic symptoms, or recurrent mania subgroup in the use of antidepressants. In mixed state patients, those with ATF B symptoms were more likely to be using antidepressants (P <0.01) than those without ATF-B. A similar relationship was found in remission patients (P <0.001).

Impact of Atypical Features B Symptoms on Medication Approach

The current findings did not indicate any significant

Table 1. Demographic and clinical features

Characteristics		I	II	III	IV	V	VI	χ^2	*P*
Gender	Male	382	627	335	103	86	494	1.03	0.960
	Female	360	563	308	96	74	478		
Race	Han	733	1176	634	197	159	965	3.02	0.697
	Other	8	14	9	2	1	6		
Current state of episode	First	233	302	139	46	4	50	2652.39	<0.001
	Recurrent	460	842	479	112	147	69		
	Stable	49	46	25	41	9	853		
Mood state at first onset	Mania/Hypomania	466	673	397	89	111	553	31.13	<0.001
	Depression	296	517	246	110	49	419		
Co-morbidity, mental disorders (current)[a]	Yes	9	12	10	3	5	6	9.29	0.098
	No	733	1178	633	196	155	966		
Co-morbidity, physical disorders (current)	Yes	55	101	54	7	9	68	8.11	0.150
	No	678	1089	589	192	151	904		
Past history of mental health[b]	Yes	119	188	98	39	45	182	19.90	0.001
	No	623	1002	545	160	115	790		
Family history of mental health[c]	Yes	597	952	482	154	113	838	43.67	<0.001
	No	145	238	161	45	47	134		
Episode type (last time)	Mania/Hypomania	441	675	372	56	119	670	614.53	<0.001
	Depression	274	480	243	58	33	240		
	Mixed	22	28	18	78	3	51		
	Rapid-recycling	5	7	9	7	5	11		
Age at entry (years)		34.48 ±13.99	33.8 ±13.73	32.11 ±12.93	34.97 ±13.63	38.14 ±13.44	37.30 ±15.02	69.09	<0.001
Age at first episode (years)		27.64 ±12.0	26.85 ±11.21	25.55 ±10.86	28.69 ±11.7	27.99 ±9.94	28.48 ±11.9	35.76	<0.001
Episode number (past 12 months)		1.72 ±3.04	1.75 ±2.94	2.05 ±5.13	2.35 ±2.75	1.94 ±3.11	1.45 ±3.62	3.50	0.004

I, hypomania; II, mania without psychotic symptoms; III, mania with psychotic symptoms; IV, mixed state; V, recurrent mania; VI, remission. [a]Current psychiatric diseases other than BP; [b]Past psychiatric diseases other than BP; [c]Psychiatric diseases distributed in three generations of the family.

difference among most of the studied subtypes — hypomania, mania without psychotic symptoms, mania with psychotic symptoms, mixed state, and recurrent mania — in terms of medication used for treatment between patients that met the ATF B criteria and those who did not. However, in the remission subtype, the differences in treatment presented a significant correlation with the ATF B factor (*P* <0.001) (Table 4).

DISCUSSION

In the current study, a range of atypical symptoms was observed among all the currently known subtypes of BP. Using the DSM-IV criteria to define ATFs, the overall point prevalence was 9.1% across all patients. When the definition was broadened to include ATF B, the overall rate increased to 11.8%. We further examined the impact of ATF B symptoms on treatment practices for BP and its

Table 2. Percentage of atypical features in each subtype of bipolar disorder

	Mood reactivity[a]	Hyperphagia[b]	Hypersomnia[c]	Rejection sensitivity[d]	Leaden paralysis[e]	ATF B criteria[f]	DSM-IV atypical features[g]
I	42	7.7	5.3	48.9	6.7	10.1	7.4
II	39.9	7.7	2.2	45.9	1.4	7.0	5.3
III	45.3	10.3	5.4	49.9	4.0	10.6	8.7
IV	61.8	15.1	21.1	64.3	24.1	33.2	28.1
V	44.4	7.5	5.6	42.5	2.5	8.1	11.3
VI	43.8	7.3	7.1	49.3	13.5	15.8	6.9

I, hypomania; II, mania without psychotic symptoms; III, mania with psychotic symptoms; IV, mixed state; V, recurrent mania; VI, remission. [a]χ^2 = 121.57, P <0.0001; [b]χ^2 = 17.31, P <0.01; [c]χ^2 = 120.42, P <0.001; [d]χ^2 = 26.20, P <0.001; [e]χ^2 = 220.72, P <0.001; [f]χ^2 = 134.70, P <0.001; [g]χ^2 = 34.90, P <0.0001.

Table 3. Distribution of antidepressant use among each subtype of bipolar disorder

Subtypes		Using antidepressant (%)	Not using antidepressant (%)	χ^2	P
I	ATF-B met	9 (12)	66 (88)	2.66	0.10
	ATF-B not met	131 (19.8)	531 (80.2)		
II	ATF-B	11 (13.4)	71 (86.6)	0	0.99
	ATF-B not met	147 (13.4)	953 (86.6)		
III	ATF-B	14 (20.9)	53 (79.1)	2.46	0.12
	ATF-B not met	79 (13.8)	495 (86.2)		
IV	ATF-B met	22 (33.8)	43 (66.2)	6.52	0.01
	ATF-B not met	23 (17.9)	108 (82.1)		
V	ATF-B met	2 (15.4)	11 (84.6)	0.07	0.79
	ATF-B not met	13 (8.9)	133 (91.1)		
VI	ATF-B met	55 (36.4)	96 (63.6)	43.85	<0.001
	ATF-B not met	115 (14.1)	701 (85.9)		

I, hypomania; II, mania without psychotic symptoms; III, mania with psychotic symptoms; IV, mixed state; V, recurrent mania; VI, remission.

subtypes in China, and obtained two interesting findings: (1) among the mixed state and the remission patients, there were significant differences in the use of antidepressants between those who met and those who did not meet the criteria of ATF B; and (2) among remission patients, the medication type was associated with the presence of ATF B.

In this study, the point prevalence rate of ATFs was lower than that in previous reports. To date, only three comparable studies on BP have been conducted, and they reported prevalence rates using ATF B of 30%[17], 32.6%[13], and 38.8%[11], while we found the point prevalence rate to be 11.8%. However, when the investigation of bipolar depression used the DSM-IV criteria for ATFs, the prevalence rate increased to 44.2%[14]. To our knowledge, this is the first survey on atypical features in BP by a national database in China, so this may explain some of the discrepancies. Such differences may mainly result from the variations in the populations studied. For example, the three comparable studies enrolled all types of BP patients, but in this study, we, for the first time, investigated the point prevalence rate of ATFs in only six types of patients. This was to take into account the fact that atypical symptoms

Table 4. The comparison of treatment remedies among each subtype of bipolar disorders

Subtypes		A (%)	B (%)	C (%)	A+C (%)	A+B (%)	B+C (%)	A+B+C (%)	Others (%)	χ^2	*P*
I	ATF-B met	20	7	6	2	29	0	1	10	8.4	0.26
		(26.7)	(9.3)	(8.0)	(2.7)	(38.7)	(0)	(1.3)	(13.3)		
	ATF-B not met	142	41	79	18	203	19	15	145		
		(21.5)	(6.2)	(11.9)	(2.7)	(30.7)	(2.9)	(2.3)	(21.9)		
II	ATF-B met	10	7	4	2	37	1	4	17	3.2	0.85
		(12.2)	(8.5)	(4.9)	(2.4)	(45.1)	(1.2)	(4.9)	(20.7)		
	ATF-B not met	170	86	77	25	450	17	28	247		
		(15.5)	(7.8)	(7.0)	(2.3)	(40.9)	(1.5)	(2.5)	(22.5)		
III	ATF-B met	3	3	9	1	31	0	4	17	12.1	0.74
		(4.4)	(4.4)	(13.2)	(1.5)	(45.6)	(0)	(5.9)	(25)		
	ATF-B not met	78	45	31	8	242	12	28	129		
		(13.6)	(7.9)	(5.4)	(1.4)	(42.2)	(2.1)	(4.9)	(22.5)		
IV	ATF-B met	5	14	6	3	16	6	7	8	11.8	0.09
		(7.7)	(21.5)	(9.2)	(4.6)	(24.6)	(9.2)	(10.8)	(12.3)		
	ATF-B not met	14	26	12	3	41	2	6	27		
		(10.7)	(19.8)	(9.2)	(2.3)	(31.3)	(1.5)	(4.6)	(20.6)		
V	ATF-B met	3	1	0	0	3	0	2	4	12.3	0.51
		(23.1)	(7.7)	(0)	(0)	(23.1)	(0)	(15.4)	(30.8)		
	ATF-B not met	15	22	2	6	73	3	2	23		
		(10.3)	(15.1)	(1.4)	(4.1)	(50.0)	(2.1)	(1.4)	(15.8)		
VI	ATF-B	13	8	3	21	68	4	27	10	50.6	<0.001
		(8.4)	(5.2)	(1.9)	(13.6)	(44.2)	(2.6)	(17.5)	(6.5)		
	ATF-B not met	100	66	15	45	486	14	41	46		
		(12.3)	(8.1)	(1.8)	(5.5)	(59.8)	(1.7)	(5.0)	(5.7)		

I, hypomania; II, mania without psychotic symptoms; III, mania with psychotic symptoms; IV, mixed state; V, recurrent mania; VI, remission. A, mood stabilizer; B, antipsychotic drug; C, antidepressant; others, sedative and other anti-anxiety drugs.

make an important contribution to the recognition of BP: e.g., the characteristic of bipolarity predicted a higher likelihood of the diagnosis of BP in patients with major depressive disorder[28]. This decision was carefully thought out during the design of the study, as bipolarity is similar to the ATFs described in our study, and some evidence suggests that atypical symptoms are valuable in distinguishing BP-II disorder from depression[29, 30].

Among the atypical symptoms present in BP, the rate for those categorized as "rejection sensitivity" was the highest in our study. This finding is concordant with the basic clinical characteristics of BP, and underlies the relationship between rejection sensitivity and irritability and related symptoms[1, 28]. We also found that each of the atypical symptoms was most common among those patients exhibiting a mixed state; a not unexpected finding[31], since mixed state patients usually exhibit atypical depression symptoms, and atypical symptoms are among the core features of atypical depression in DSM-IV[1, 28]. Furthermore, some atypical symptoms such as hypersomnia have been assumed to indicate a balance of specificity and sensitivity for the diagnosis of BP-II disorder among depressed patients[30]. By extension, this suggests that we should focus on the ATFs during the diagnosis of

mixed states, as a failure to recognize BP in those treated for major depressive disorder is common in China[32].

In this study, we were also concerned about the impact of atypical symptoms on treatment approaches, such as the use of antidepressants. Several studies have highlighted the seriousness of the high prescription rate of antidepressants to treat bipolar disorder worldwide[33-35], and the mainland of China is no exception. In China, antidepressants are prescribed in many cases, even though their long-term use can have markedly negative outcomes, e.g., the risk of manic switch or suicide[34, 36]. If patients with BP have some non-specific symptoms, such as ATFs related to depression, treatment usually includes some clinical practices that are inconsistent with the guidelines. Our findings indicate that there is a tendency for the use of antidepressants among patients who meet the criteria of ATF B symptoms in the mixed state and the remission BP subtypes, both of which commonly have atypical symptoms. Earlier studies reported that atypical depression symptoms may respond to antidepressants, such as monoamine oxidase inhibitors and tricyclic antidepressants[18, 19], but more recent studies have suggested that there is a low rate of manic switch for serotonin reuptake inhibitors, and norepinephrine and dopamine reuptake inhibitors (bupropion). Both the previous and current clinical experience may contribute to the prescription of antidepressants, even if there is no consensus on their effects on BP during the acute[37] or maintenance periods[22].

Furthermore, we also examined the impact of atypical symptoms on treatment for BP. If compliance with the current treatment guidelines was usual in China, most clinicians would prefer a combination of drugs with different kinds of pharmacological action — atypical antipsychotics, mood stabilizers, and the like. The antidepressants should be carefully prescribed only for those patients with BP whose episodes are mainly in the depressive state. For example, for those patients with BP who are currently severely depressed for more than four weeks, bupropion may be the choice, when combined with a sufficient dose of mood stabilizer. However, our findings indicated that monotherapy is still unexpectedly common for all types of BP, although the presence of ATF B symptoms was associated with the treatment approach for remission BP patients. In addition, the antidepressants were still common for monotherapy or combination therapy. Unfortunately, we can draw few conclusions from this, as there is a lack of studies similar to ours.

Although this study offers several novel findings, there are limitations that should be considered. First, participating subjects were evaluated on a single appointment and most of the data were collected from their previous histories, which leaves room for errors in reporting or follow-up. Second, patients were recruited from specialized academic centers and may not be representative of the "real" situation of BP in mainland China. Third, BP was diagnosed according to ICD-10 but then DSM-IV ATFs were used. This was because ICD-10 is commonly used as the reference for diagnosis in China, and ATFs are only defined in DSM-IV criteria. Fourth, the treatment regimes prescribed to patients may be guided not only by disease-specific factors, but also clinician-specific factors. As we only focused on the ATFs without considering confounding factors such as age distribution, duration of disease, and co-morbidity of psychiatric diseases, there might be some potential confounding factors. We also did not assess the impact of different physicians on the treatment regimes. Despite these limitations, this study gives some guidance in refining further studies that can more effectively verify and expand the present results.

In conclusion, the current findings indicated that various atypical symptoms are commonly observed in all subtypes of BP (overall rate of 9.1% using the DSM-IV criteria for ATFs, 11.8% by the definition of ATF B). Of note, the ATFs were most common in mixed state patients. Likewise, among mixed state and remission patients, there was a higher frequency of antidepressant use when the patients met the criteria of ATF B; specifically, for remission patients, the treatment approaches were usually affected by whether or not ATF B symptoms were present. While this study reports on a survey built around information from a national database, it provides a framework of conclusions that are suggestive of larger issues with treating BP in the mainland of China. In particular, the findings highlight the need to strengthen the education of physicians on ATFs in BP, to help clinicians recognize different aspects of BP and depressive symptoms, and accordingly provide appropriate treatments.

SUPPLEMENTAL DATA

Supplemental data include detailed information of distribution of patients and one table, and can be found online at http://www.neurosci.cn/epData.asp?id=224.

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