The current state of benzodiazepines and Z-drugs use and their influences on bipolar disorder outcomes-A small sample analysis

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Research

Keywords: bipolar disorder, sleep disturbance, benzodiazepine, Z-drugs, mood stabilizer, suicide attempt, psychotic symptoms

Posted Date: April 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-394328/v1>

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Abstract

Background: Sleep disturbance and benzodiazepines (BZDs)/Z-drugs use are known to be common during affective episodes. Hence, we identified the probable outcomes of bipolar disorder that correlate with BZDs/Z-drugs use, aside from mood symptoms. We conducted an open-label, prospective study to describe the current use of BZDs and Z-drugs by patients with bipolar disorder during affective episodes. We evaluated the difference of characteristics between bipolar patients with sleep disturbance who chose BZDs/Z-drugs, and those who did not chose the drugs during and after affective disorder. The influences of BZDs/Z-drugs use on suicide attempt and psychotic symptoms during affective disorder were also investigated.

Results: Seventy patients with current affective episodes were studied. Among them, 61 had sleep disturbances. The amount of mood stabilizers use in the BZDs/Z-drugs group was significantly greater than that in the no BZDs/Z-drugs group ($p=0.038$) during affective episodes. After affective episode, sleep disturbances, especially midnight wakes, became more improved in BZDs/Z-drugs group compared to the no BZDs/Z-drugs group. By contrast, attention and decisiveness became more improved in the no BZDs/Z-drugs group than in the BZDs/Z-drugs group. Furthermore, we observed that BZDs/Z-drugs had an OR of 4.338 (95% CI 1.068-17.623, $p=0.040$), and other psychiatric drugs had an OR of 1.835 (95% CI 1.105-3.047, $p=0.019$) in relation to suicide attempt. After nine months, we found that BZDs/Z-drugs use was of no significant effect to depressive or manic severity, or to recurrence rate.

Conclusion: BZDs/Z-drugs use have no significant influence on variations in depressive or manic severity during the course of an affective episode. Nevertheless, BZDs/Z-drugs users took a greater amount of mood stabilizers than no BZDs/Z-drugs users. Finally, BZDs/Z-drugs or other psychiatric drugs polytherapy was regarded as a risk factor of suicide attempt during an affective episode.

Background

Bipolar disorder is a recurrent mood disorder with episodes of depression and mania. It is often associated with significant impairment in cognitive functioning, circadian rhythm abnormalities, decreased quality of life, and reduced life expectancy (la Cour Karottki et al. 2020). One of central features in bipolar disorder is sleep disturbance (Takaesu 2018), with anxiety disorder being among the most highly prevalent comorbidities. Unfortunately, comorbid anxiety disorders are linked to more affective relapses, increased suicidality, sleep disturbances, and increased barriers to effective treatment (Hawke et al. 2013). Benzodiazepines (BZDs) are taken by 25%-90% of patients with bipolar disorder (Chang et al. 2016) to manage anxiety and insomnia (Baldwin et al. 2013), despite their potential serious adverse effects, such as craving, withdrawal symptoms upon discontinuation, and increased falls, especially during long-term use (Janhsen et al. 2015). There is also evidence that BZDs have direct depressogenic effects, which may be particularly harmful to individuals with bipolar disorder (Michellini et al. 1996). These side effects may be the reason why patients with sleep disturbance are unwilling to administer with the drugs. On the other hand, because of proven efficacy, reduced side effects, and lesser

concerns about addiction, non-BZD receptor agonists (so-called Z-drugs) such as zaleplon, zolpidem, and zopiclone, have become the most commonly prescribed hypnotic agents approved to treat onset and maintenance insomnia (Schutte-Rodin et al. 2008). However, the spectrum of adverse effects is reportedly similar between Z-drugs and BZDs (Gunja 2013). Several studies have indicated that patients of bipolar disorder who used BZDs regularly showed higher levels of treatment resistance to mood stabilizers, and have a greater risk for both manic and depressive relapses independent of the effects of comorbid anxiety and insomnia (Bjorklund et al. 2016). Furthermore, BZDs use might be associated with greater risk for recurrence of an affective episode among patients with bipolar I and II disorders (Perlis et al. 2010). The other factors related to BZDs/Z-drugs use especially during affective episodes, such as suicidality and psychotic symptoms, are currently unknown.

The aim of this study was to investigate the factors associated with BZDs/Z-drugs use in patients with bipolar disorder and the influence of BZDs/Z-drugs on variations in (hypo)mania, depression, or mixed episode.

Materials And Methods

Recruitment of patients

Patients from the Shanghai Mental Health Center were consecutively recruited and interviewed from May 1, 2013 to May 1, 2014 in Shanghai Mental Health Centre.

Inclusion and exclusion criteria

All participants were over 18 years old, met the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, DSM-IV) (American Psychiatric Association. 1994) criteria for bipolar disorder, and sought medical help for current emotional episodes in the outpatient or inpatient psychiatric/psychological services of our institution. Only patients who were in a current affective episode, either (hypo)manic, depressive, or mixed episode, were included. The exclusion criteria were: (A) inability to complete the self-assessments, and (B) patients who had participated in any intervention study one or more years prior.

Database

All the patients received psychiatric screening interviews from trained psychiatrists. In the interview session, the clinicians interviewed the participants in an interview room using the doctor-rating assessment questionnaire. All clinicians were well-trained for this project to ensure assessment consistency. Participants completed the Mental Disorders Questionnaire (MDQ) and Quick Inventory of Depressive Symptoms (QIDS) as self-reporting questions in the same interview room with a clinician present, should any questions arise.

The doctor-rating assessment questionnaire also comprised the following data:

- identification number of the included person, including age and gender;

- dates of hospital visits, including the admission and discharge;
- onset and terminational dates of each affective episode;
- dates of initiation and cessation of all psychiatric drugs, and dosage of each drug during each affective episode; and
- other conditions presented during an affective episode, such as suicide attempt, and/or psychotic symptoms.

Study design

This was a prospective follow-up study that described the use of BZD/Z-drugs by patients with bipolar disorder during all affective episodes and their influences on outcomes. We also ascertained the overall influence of the use of hypnotics during (hypo)manic, depressive, or mixed episodes on the prognosis of the disease. During the course of the study, the included patients were followed-up regarding psychiatric drug prescription, including mood stabilizers, atypical antipsychotics, typical antipsychotics, antidepressants, BZDs/Z-drugs, and other anxiolytics. We tried to interview all the participants at the baseline, after their affective episode, and nine months after their stable emotional phase.

Statistical Analyses

Descriptive statistics were used to summarize patient characteristics, grouped into the cohort taking BZD/Z-drugs and those not taking BZD/Z-drugs. Changes in MDQ and QIDS score at baseline and after an affective attack were compared using the Mann-Whitney test. The associations between each predictor variable and the initiation of BZDs/Z-drugs were investigated using logistic regression modelling. Associations were estimated as odds ratios (ORs) with 95% confidence intervals (CIs). The effect of each variable was adjusted for the effects of all other variables in a full model, from which variables with a strong correlation to one or several other variables were removed. The robustness of this model was supported by results from an additional multivariable logistic regression analysis, wherein a stepwise selection of variables was performed. To study the long-term effect of BZD/Z-drugs, we modelled the MDQ score and QIDS score from questions 5 to 16 (QIDS'), which described receiving a prescription for BZD/Z-drugs during an affective episode, after an affective episode and after nine months, using a two-factorial design with interactions. All statistical analyses were performed in SPSS Version 22.0.

Results

Differences in demographic and clinical characteristics between BZDs/Z-drugs group and no BZDs/Z-drugs group

Seventy patients who met the inclusion and exclusion criteria were included in this study, with a median age of 30 years (interquartile range: 23.5–44.5 years). Approximately 81.4% (n = 57) were included in

inpatient care.

As QIDS reflected, the majority of patients (85.7%, $n = 61$) had sleep disturbances, such as difficulty falling asleep, midnight wakes, early-morning awakening, or hypersomnia. Patients with sleep disturbances were selected for analysis. Overall, 32 patients took one type of BZD or Z-drug, but some took two ($n = 8$) or even three ($n = 2$) BZDs/Z-drugs concomitantly. The median duration of BZD or Z-drugs use was 30 days (interquartile range: 22–55 days).

The clinical characteristics of the 61 patients with sleep disturbance are presented in Table 1. Anxiety disorder, substance abuse, and eating disorder were the most common psychiatric comorbidities, recorded for 2.86% [n (BZDs/Z-drugs group) = 1; n (no BZDs/Z-drugs group) = 1], 4.29% [n (BZDs/Z-drugs group) = 1; n (no BZDs/Z-drugs group) = 2], and 2.86% [n (BZDs/Z-drugs group) = 1; n (no BZDs/Z-drugs group) = 1] of patients in our bipolar disorder cohort, respectively. Furthermore, two patients were previously diagnosed with post-traumatic stress disorder (PTSD), one with dissociative disorder in the no BZDs/Z-drugs group and one with periodic psychosis in the BZDs/Z-drugs group. Overall, the two groups had no significant difference in age, gender, number of each type of emotional episode, duration of current episode, family history of mental illness, history of somatic diseases, combined mental illnesses, or previously diagnosed mental illnesses.

Table 1
Demographic and clinical characters in BZDs/Z-drugs group and no BZDs/Z-drugs group

	BZDs/Z-drugs group	No BZDs/Z-drugs group	Z/ χ^2	<i>p</i>
Sample size	28	33	/	/
Gender (Male)	19 (67.9%)	17 (51.5%)	0.062	0.506
Age (median, interquartile range)	32 (21.5–45.5)	31 (24–38.5)	-0.043	0.965
Occupational status (employed/temporarily employed/unemployed)	15 (45.5%)/2 (6.1%)/16 (48.5%)	11 (39.3%)/1 (3.6%)/16 (57.1%)	0.543	0.762
Years of schooling (median, interquartile range)	12 (9–15)	12 (9–15)	-0.415	0.678
Residence (solitary/cohabiting)	1 (3.6%)/27 (96.4%)	0 (0.0%)/33 (100.0%)	1.198	0.459
Number of (hypo)manic episodes (%)	15 (68.2%)	7 (31.8%)	2.748	0.116
Number of depressive episodes (%)	16 (50.0%)	16 (50.0%)	0.455	0.609
Number of mixed episodes (%)	2 (28.6%)	5 (71.4%)	2.075	0.231
Episode duration (days) (interquartile range)	71.5 (48.5–127.5)	120 (60–170)	-1.655	0.098
Having family history of mental illness	1 (3.57%)	1 (3.03%)	0.014	0.711
Having history of somatic diseases	2 (7.14%)	3 (9.09%)	0.436	0.421
Combined anxiety disorder (%)	1 (3.57%)	1 (3.03%)	0.014	0.711
Combined substance abuse (%)	1 (3.57%)	2 (6.06%)	0.201	0.562
Combined eating disorder (%)	1 (3.57%)	1 (3.03%)	0.014	0.711
Previously diagnosed with PTSD (%)	0	1 (3.03%)	2.437	0.207
Previously diagnosed with periodic psychosis (%)	1 (3.57%)	0	0.863	0.541
Previously diagnosed with dissociative disorder (%)	0	1 (3.03%)	1.198	0.459
Abbreviation: <i>PTSD</i> : post-traumatic stress disorder				

Types of BZD/Z-drugs

Based on their classification under the European Monitoring Centre for Drugs and Drug Addiction (Grimmsmann et al. 2018), we divided the BZDs into either short- or long-acting drugs. Of the patients who received a prescription for a BZD or Z-drug, 13 (28.3%) had received a long-acting substance,

whereas 30 (65.2%) had a short-acting substance, with the remaining 3 (6.5%) having had Z-drugs. The application of BZDs/Z-drugs in males and females is shown in Table 2. No significant differences were found between the male and female group.

Table 2
Treatment characteristics of BZD/Z-drugs

	BZD/Z-drugs	Number (%)	Male (%)	Female (%)	χ^2	<i>p</i>
Short-acting BZDs	Total number	13 (100.0%)	5 (38.5%)	8 (61.5%)	2.847	0.090
	Alprazolam	3 (23.1%)	0 (0.0%)	3 (23.1%)	4.810	0.057
	Lorazepam	9 (69.2%)	4 (30.8%)	5 (38.5%)	1.121	0.304
	Estazolam	1 (7.7%)	1 (7.7%)	0 (0.0%)	0.660	0.606
Long-acting BZDs	Clonazepam	30 (100.0%)	20 (66.7%)	10 (33.3%)	0.810	0.463
Z-drugs	Total number	3 (100.0%)	2 (66.7%)	1 (33.3%)	0.076	0.636
	Zolpidem	2 (66.7%)	1 (33.3%)	1 (33.3%)	0.096	0.637
	Zopiclone	1 (33.3%)	1 (33.3%)	0 (0.0%)	0.660	0.606
Abbreviation: <i>BZDs</i> : benzodiazepines						

Association between other psychotropic drugs and BZDs or Z-drugs use during affective episodes

All of the study participants took at least one type of psychotropic drug other than BZDs/Z-drugs during their (hypo)manic, depressive, or mixed episode, for a total of 316 psychotropic drug prescriptions. Most participants were on multiple drugs, with a median of four different drugs per patient (interquartile range: 3–6 drugs). Notably, 31 participants were on five or more regular psychotropic drugs. However, among the 61 participants with sleep disturbance, 33 did not choose BZDs/Z-drugs. Between the BZDs/Z-drugs group and no BZDs/Z-drugs group, we found a significant difference in the amount of mood stabilizers used during an affective episode ($p = 0.038$) but not after an affective episode ($p = 0.269$). The amounts of the other psychotropic drug types during and after an affective episode did not have significant differences. These results are presented in Table 3 and Table 4.

Table 3
Amounts of each psychotropic drug between two groups during affective episodes

	BZDs/Z-drugs group	No BZDs/Z-drugs group	Z	p
Number (%)	28 (45.9%)	33 (54.1%)	/	/
Mean rank of mood stabilizers	25.98	35.96	-2.070	0.038
Mean rank of atypical antipsychotics	29.16	33.87	-0.713	0.476
Mean rank of SSRIs	32.66	31.57	-0.177	0.859
Mean rank of SNRIs	30.72	32.84	-0.198	0.843
Mean rank of NaSSAs	31.28	32.47	-0.507	0.612
Mean rank of other antidepressants	31.26	32.49	-0.444	0.657
Mean rank of typical antipsychotics	30.74	32.83	-0.673	0.501
Mean rank of other anxiolytics	30.00	33.32	-1.890	0.059
Abbreviations: SSRIs: <i>selective serotonin reuptake inhibitors</i> ; SNRIs: <i>serotonin-norepinephrine reuptake inhibitors</i> ; NaSSAs: <i>noradrenergic and specific serotonergic antidepressants</i>				

Table 4
Amounts of each psychotropic drug between two groups after affective episodes

	BZDs/Z-drugs group	No BZDs/Z-drugs group	Z	p
Number (%)	27	34	/	/
Mean rank of mood stabilizers	33.05	28.59	-1.106	0.269
Mean rank of atypical antipsychotics	32.05	29.77	-0.625	0.532
Mean rank of SSRIs	29.47	32.80	-0.959	0.337
Mean rank of SNRIs	31.27	30.77	-0.210	0.833
Mean rank of NaSSAs	31.77	30.35	-0.655	0.513
Mean rank of other antidepressants	31.58	30.00	-1.314	0.189
Mean rank of typical antipsychotics	31.09	30.92	-0.117	0.907
Mean rank of other anxiolytics	32.27	29.50	-1.623	0.105

Variation of manic and depressive symptoms according to MDQ and QIDS scores

The change value and gradient of the total score for MDQ and QIDS were also compared. QIDS' are presented in Table 4, as we aimed to eliminate the sleep disturbance results. As presented in Table 5, the change value and gradient of the QIDS10 score were significantly different between the BZDs/Z-drugs group and the no BZDs/Z-drugs group. By contrast, we found no significant difference between these two groups in terms of change value and gradient of the MDQ, QIDS, and QIDS' scores. Furthermore, we observed no significant difference in the affective episode duration between the BZDs/Z-drugs group and no BZDs/Z-drugs group ($p = 0.098$).

Table 5
Score of MDQ and QIDS, and affective episode duration in two groups

	BZDs/Z-drugs group	No BZDs/Z-drugs group	Z	p
Change value of MDQ score	33.16	29.17	-0.889	0.374
Change value of QIDS1 score	34.20	27.23	-1.624	0.104
Change value of QIDS2 score	35.59	25.59	-2.329	0.020
Change value of QIDS3 score	33.92	27.55	-1.541	0.123
Change value of QIDS4 score	30.08	32.09	-0.482	0.630
Change value of QIDS1-4 score	35.33	25.89	-2.098	0.036
Change value of QIDS10 score	34.88	26.43	-1.971	0.049
Change value of QIDS15 score	32.35	29.41	-0.754	0.451
Change value of QIDS total score	28.27	33.32	-1.110	0.267
Change value of QIDS' score	29.89	31.94	-0.450	0.653
Gradient of MDQ score	33.13	29.20	-0.872	0.830
Gradient of QIDS1 score	27.39	34.06	-1.562	0.118
Gradient of QIDS2 score	35.39	25.82	-2.275	0.023
Gradient of QIDS3 score	34.14	27.30	-1.667	0.096
Gradient of QIDS4 score	29.82	32.39	-0.621	0.534
Gradient of QIDS1-4 score	35.20	26.05	-2.072	0.038
Gradient of QIDS10 score	35.00	26.29	-2.019	0.044
Gradient of QIDS15 score	31.70	30.18	-0.395	0.693
Gradient of QIDS total score	26.46	34.85	-1.846	0.065
Gradient of QIDS' score	28.45	33.17	-1.043	0.297
Mean rank of affective episode duration (days)	34.45	26.93	-1.655	0.098
Abbreviations: MDQ: <i>Mental Disorders Questionnaire</i> ; QIDS: <i>Quick Inventory of Depressive Symptoms</i> ; QIDS': <i>Quick Inventory of Depressive Symptoms, from questions 5 to question 16</i> .				

Association between suicide attempt and the amount of BZDs/Z-drugs and other psychiatric drugs

Among the variables considered for multiple logistic regression analysis, the amount of BZDs/Z-drugs and other psychiatric drugs remained in the model as independent risk factors of suicide attempt during an affective episode. Patients who took more than one type of BZDs/Z-drugs were more likely to have a suicide attempt than those who took only one type (OR = 4.338, 95% CI 1.068–17.623, $p = 0.040$) during an affective episode. Similarly, patients who took more than one type of other psychiatric drugs were more likely to have a suicide attempt than those who only took one type (OR = 1.835, 95% CI 1.105–3.047, $p = 0.019$) during an affective episode. However, with regards to the appearance of psychotic symptoms during an affective episode, the age, gender, hospitalization status, type of affective episode, and amount of psychiatric drugs did not have a significant effect.

Results after nine months

During the nine-month follow-up, recurrence was observed among 13 participants. Of them, five were in the BZDs/Z-drugs group and eight were in no BZDs/Z-drugs group. Depressive episode recurred among nine of them, whereas four had mixed episodes. However, the recurrence rate had no significant difference between the BZDs/Z-drugs group and no BZDs/Z-drugs group ($\chi^2 = 1.627$, $p = 0.227$). Because there were non-negligible interactions between the effect of time and BZDs/Z-drugs use, we performed stratified analyses by group to identify the effects of time. As shown in Fig. 1, the interaction effect of BZDs/Z-drugs use and time effect ($p = 0.566$) as well as BZDs/Z-drugs use effect ($p = 0.545$) had no significant impact on the improvement of manic symptoms, whereas time had a significant effect on it ($p < 0.05$) according to the MDQ score. Figure 2 shows that both the interaction effect ($p = 0.006$) and time effect ($p < 0.05$) significantly influenced depressive symptoms according to the QIDS score; however, BZDs/Z-drugs use effect had no significant impact on it ($p = 0.157$). After removing the score of sleep symptoms, similarly, both the interaction effect ($p = 0.037$) and time effect ($p < 0.05$) significantly influenced the QIDS' score, but BZDs/Z-drugs use effect had no significant impact on it ($p = 0.266$) (Fig. 3).

Discussion

In this study, we found that during an affective episode, approximately 81.7% bipolar disorder patients experience sleep disturbance. Among them, approximately 45.9% who initiated treatment with BZDs or Z-drugs continued such treatment for a maximum of seven months. Notably, polytherapy with BZDs/Z-drugs or other psychiatric drugs already exists, and turned out to be strong predictors for suicide attempt during an affective episode. Furthermore, a significant difference in the amount of mood stabilizers used was discovered between the two bipolar cohorts in our study, with or without BZDs/Z-drugs use.

One result of this study was that among the 33 patients who initiated BZDs or Z-drugs treatment, 90.9% used clonazepam, which is among the most commonly abused drugs worldwide (Shukla et al. 2017). Although warnings about the highly addictive properties of clonazepam have emerged in recent years (England et al. 2012), one explanation for the high rate of long-term use could be that the drug still plays a role in the management of acute anxiety attacks if the first-line treatment options, such as

antidepressants, have failed or cannot be used for some reason. Anxiety disorder often requires a long treatment duration, illustrated by a lower than expected proportion of patients with comorbid anxiety disorder in our study. Although Z-drugs were initially perceived as having little or no abuse potential, more recent data show that Z-drugs are associated with considerable psychological and physiological dependence and abuse (Victorri-Vigneau et al. 2014). Among these BZDs/Z-drugs users, only one male used clonazepam continuously for more than six months, representing a yearly incidence of long-term BZD use of 3.6% among BZDs/Z-drugs users with bipolar disorder. Hence, a certain level of vigilance is needed regardless of which BZD or Z-drug is prescribed.

On the other hand, while the BZD initiation rate was unaffected, the amount of mood stabilizers used was significantly higher among BZDs/Z-drugs users than among the no BZDs/Z-drugs group. This may seem somewhat difficult to explain, given that type of mood attack had been unrelated to BZDs/Z-drugs use. However, anxiety is a common symptom during depressive and mixed episodes, and can be seen as an integral part of bipolar illness. Anxiety symptoms may also persist between affective episodes along with subsyndromal affective symptoms (Judd et al. 2003). As anxiety is associated with a more severe illness course (Preti et al. 2016), these hard-to-treat symptoms might sometimes require choosing the lesser of two evils by, for instance, applying regimens of mood stabilizers and BZDs, despite their potentially harmful effects. Another explanation is the direct depressogenic effects of BZDs (Michellini et al. 1996), which may be one cause of emotional instability. Based on these, the use of more mood stabilizers and even more antidepressants could be feasible.

Furthermore, we found that polytherapy with BZDs/Z-drugs increased the risk of suicide attempt among patients with bipolar disorder. One previous study has presented a link between BZD treatment and past suicidal behavior in bipolar disorder (Bellivier et al. 2011), although no distinction was made between short-term and long-term use. In addition, anxiety is also associated with increased suicidality (Preti et al. 2016), as patients have anxious symptoms during an affective episode (such as depressive and mixed episodes) and experience a greater possibility of having these symptoms combined with suicidal ideation, which then leads to the treatment of anxiety by using BZDs. Another retrospective study, on the other hand, indicated that a history of self-harm also increased the risk for long-term BZDs/Z-drugs use (Wingård et al. 2018).

Unfortunately, our finding illustrating that BZDs/Z-drugs use was not a marker for a more severe course of illness is partly inconsistent with that of Perlis et al. (Perlis et al. 2010). This might be the cause that we could be explained by our inclusion of Z-drugs, which led to the sole effect of BZDs not being observed.

Despite our best efforts, we could not provide a conclusive finding on the influences of BZDs/Z-drugs use on all aspects of outcomes, as bipolar disorder is complex and changeable. Although we tried our best to cover every aspect of the clinical features of BZDs/Z-drugs use during an affective episode, the questionnaire did not provide a broad range of information in the strict sense. Another evident limitation of this study is that all of the questionnaires evaluating the aspects of depressive and manic severity

have been patient-reported. This may be short of the objective evaluations from clinicians, and thus led to some one-sided results. Moreover, due to their illness, some patients may not have answered the questions seriously, which may cause biases in our data. Fortunately, the clinicians who participated in this study were all well-trained to accurately record information to minimize the biases.

Conclusions

In this observational study, we observed the prominent use of clonazepam among our bipolar cohort with sleep disturbances. On the other hand, the use of BZDs/Z-drugs did not have any significant influence on depressive or manic severity. By contrast, polytherapy with BZDs/Z-drugs or other psychiatric drugs was predicted to increase suicide attempt during an affective episode. Furthermore, BZDs/D-drugs users appeared to take a higher amount of mood stabilizers than BZDs/D-drugs non-users. Ultimately, the influence of BZDs/D-drugs use need to be further explored among patients with bipolar disorder both during an affective episode and in the long term.

List Of Abbreviations

BZDs: benzodiazepines;

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;

MDQ: Mental Disorders Questionnaire;

QIDS: Quick Inventory of Depressive Symptoms;

ORs: odds ratios; **CI:** confidence intervals;

QIDS': QIDS score from questions 5 to 16;

T1: during an affective episode; **T2:** after an affective episode; **T3:** after nine months

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee at Shanghai Mental Health Center. And participants all provided written informed consent.

Consent for publication

The authors provide consent for publication.

Availability of data and material

The data will not be shared or made publicly available.

Competing interests

All authors have no conflict of interest to declare.

Funding

National Key Research and Development Program of China (2016YFC0906300 and 2016YFC1307100); National Natural Science Foundation of China (81701344 and 81771465); Program of Health Department of Shanghai Municipal Government (201740115); Science and technology innovation project of Shanghai Jiaotong University School of medicine (Humanities and Social Sciences) (WK2017).

Authors' contributions

LC, YF and WH contributed to the overall design of the study. All authors got involved sample collection. YC and WH undertook the statistical analysis and interpretation of data. YC completed the initial draft, which was reviewed by all authors. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank all patients and their families, and all investigators for their valuable contributions to this study.

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Figures

Figure 1

The interaction effect of BZDs/Z-drugs use and time effect ($p=0.566$) as well as BZDs/Z-drugs use effect ($p=0.545$) had no significant impact on the improvement of manic symptoms, whereas time had a significant effect on it ($p<0.05$) according to the MDQ score.

Figure 2

Both the interaction effect ($p=0.006$) and time effect ($p<0.05$) significantly influenced depressive symptoms according to the QIDS score

Figure 3

After removing the score of sleep symptoms, similarly, both the interaction effect ($p=0.037$) and time effect ($p<0.05$) significantly influenced the QIDS' score, but BZDs/Z-drugs use effect had no significant impact on it ($p=0.266$).