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Long-Term Benzodiazepine Use in Patients With Major Depressive Disorder in China

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PURPOSE: There have been no data about long-term benzodiazepine (BZD) use and its correlates in patients with major depressive disorder (MDD) in China. This study aimed to examine the prevalence of long-term BZD use (more than three months) and its demographic and clinical correlates in Chinese patients with MDD.
DESIGN AND METHODS: A total of 1,192 patients with MDD were examined in 10 mental health centers in China. Patients' socio-demographic and clinical characteristics and prescriptions for psychotropic drugs were recorded using a standardized form.
FINDINGS: A large portion of patients (36.2%) received long-term BZD treatment. Univariate analyses revealed that long-term BZD users were older, poorer, and had more impaired occupational functioning than patients not taking BZDs. Long-term BZD users had fewer psychotic symptoms and took less antipsychotic drugs. In multivariate analyses, long-term BZD use was independently associated with older age and more severe impaired occupational functioning; long-term BZD users were less likely to receive antipsychotic medications and traditional antidepressants (tricyclic antidepressants, tetracyclic antidepressant, and monoamine oxidase inhibitors).
PRACTICE IMPLICATIONS: Long-term BZD use was common in patients with MDD in China. A host of demographic and clinical factors were independently associated with long-term BZD use.

Introduction

Pharmaco-epidemiological studies have shown that benzodiazepines (BZDs) are among the most commonly prescribed psychotropic medications with the frequency ranging from 3.3% to 10.6% in the general population (Dag, 1997; Esposito, Barbui, & Patten, 2009; Sonnenberg et al., 2012). Several demographic and clinical correlates of BZD use have

been identified; for example, older age and female sex are among the most reported correlates (Cunningham, Hanley, & Morgan, 2010; Demyttenaere et al., 2008; Sonnenberg et al., 2012). Major depressive disorder (MDD) is also closely associated with use of BZDs (Demyttenaere et al., 2008; Lagnaoui et al., 2004; Sonnenberg et al., 2012).

BZDs are often prescribed for sleep disturbances and anxiety symptoms in MDD (Sanyal, Asbridge, Kisely, Sketris, & Andreou, 2011; Valenstein et al., 2004) and they may be superior to antidepressant (AD) monotherapy in the short term (Pfeiffer, Ganoczy, Zivin, & Valenstein, 2011). A systematic review of 10 randomized controlled studies found that adjunctive use of BZDs in MDD may increase the effectiveness of ADs and improve treatment adherence (Furukawa, Streiner, & Young, 2002). However, long-term use of BZDs may increase the risk of dependence (Griffiths & Weerts, 1997; Schweizer & Rickels, 1998), withdrawal syndrome (Lader & Petursson, 1981; Rickels, Case, Downing, & Winokur, 1983), cognitive impairment (Foy et al., 1995; Paterniti, Dufouil, & Alperovitch, 2002), and falls, particularly in the elderly (Bartlett, Abrahamowicz, Grad, Sylvestre, & Tamblyn, 2009; Pariente et al., 2008).

Considering the potential risks and side effects of long-term BZD use, it is important to investigate its prevalence and correlates in different patient populations. Western studies found that older age (Manthey et al., 2011; Veronese, Garatti, Cipriani, & Barbui, 2007), history of BZD use (Manthey et al., 2011), more severe anxiety symptoms (Manthey et al., 2011), and length of illness (Veronese et al., 2007) were associated with long-term BZD use in psychiatric patients. However, little information is available about the prescription patterns of long-term BZDs in MDD in Asian countries. This study examined the prevalence of long-term BZD use and its demographic and clinical correlates in patients with MDD in China.

Methods

Study Design and Participants

This study is part of an ongoing large-scale pharmacoepidemiological survey conducted in China. Ten major mental health centers located in 10 provinces and municipalities including Beijing, Guangdong, Hebei, Hubei, Jiangxi, Jiangsu, Jilin, Shaanxi, Shanxi, and Sichuan participated in the survey.

Inpatients and outpatients receiving treatment in the participating hospitals during the study period were consecutively referred by their treating psychiatrists to the research team to be screened for eligibility. All members of the research team were trained psychiatrists. Inclusion criteria included: (a) *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition diagnosis of MDD based on a review of medical records and a clinical interview, (b) age between 18 and 65 years, and (c) ability to understand the aims of the survey and willingness to provide written informed consent. Patients with a past diagnosis of bipolar disorder or suffering from major medical conditions were excluded. The study protocol was approved by the Ethics Committees of the participating centers.

Basic socio-demographic and clinical characteristics were collected using a form designed for the study. A lifetime suicide attempt was defined as "a self-destructive act carried out with at least some intent to end one's life" (Grunebaum et al., 2001). Following the ongoing Research on East Asia Psychotropic Prescription project (Chong et al., 2004; Shinfuku & Tan, 2008; Tor et al., 2011), positive (delusions, hallucinations or disorganized speech) and negative symptoms (affective flattening or avolition) and impairment of occupational functioning were evaluated in the diagnostic interview. Assessment of occupational functioning included performance on daily living skills, interpersonal relationships, and occupational skills.

Medications were recorded by referring to medical notes and were classified according to the anatomical–therapeutical–chemical coding (World Health Organization, 2011). BZDs were coded as N05BA, N05CD, and N03AE01 (WHO Collaborating Centre for Drug Statistics Methodology, 2012). Patients who reported current use of BZDs at the time of the survey were defined as BZD users, while those who had received BZDs for more than three months were defined as long-term BZD users (Manthey et al., 2010; Zandstra et al., 2002). Daily doses of BZDs were converted to approximate diazepam equivalents (Valenstein et al., 2004). When two or more types of BZDs were used concurrently, the duration of the longest use was counted, and a sum of equivalents for all BZDs was calculated.

In addition to BZDs, prescriptions of ADs, mood stabilizers, and antipsychotic drugs were also recorded. ADs were further classified into three types: (a) traditional ADs including tricyclic ADs (TCAs), tetracyclic antidepressants (TeCAs), and monoamine oxidase inhibitors (MAOIs); (b) any other ADs (novel ADs); and (c) combination of traditional and novel ADs.

Statistical Analyses

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS), version 13.0 (SPSS Inc., Chicago, IL, USA). Comparisons between long-term BZD users and non-long-term users in terms of demographic and clinical variables were conducted by chi-square tests, *t* tests, or Mann–Whitney *U* tests as appropriate. Multiple logistic regression analysis with the "Enter" method was used to examine if demographic and clinical characteristics were independently associated with long-term BZD use. Long-

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term BZD use was entered as the dependent variable, while after controlling for the study sites the independent variables included age, sex, employment, education, household income, length of illness, family history of MDD, number of depressive episodes, treatment setting, lifetime suicide attempts, psychotic symptoms and impairment in occupational functioning, antipsychotic drugs and mood stabilizers, and types of ADs. Significance level was set at .05 (two-sided).

Results

A total of 1,192 patients with MDD met the study criteria; of them 516 (43.3%) took BZDs, and 432 (36.2%) received long-term BZD treatment. Of the long-term BZD users ($n = 432$), 411 (95.1%) received one type of BZDs, and 21 (4.9%) two or more BZDs concurrently. The mean daily dose of BZDs in diazepam equivalents was 18.2 ± 33.2 mg and 18.5 ± 35.9 mg for the overall BZD users and the long-term BZD users, respectively. The most commonly BZDs prescribed in the long-term were alprazolam ($n = 202$; 44.4%), clonazepam ($n = 146$; 32.1%), and lorazepam ($n = 57$; 12.5%). As for the reason of taking BZDs, 64.8% of long-term BZD users ($n = 280$) reported to take BZDs because of sleep problems only, 19.7% ($n = 85$) because of anxiety only, and 9.3% ($n = 40$) because of both sleep and anxiety problems.

Table 1 presents the socio-demographic and clinical variables of long-term BZD users and the rest of the sample separately. Long-term BZD users were older, had lower household income, and reported impairment in occupational functioning more frequently compared with the non-long-term BZD users. Long-term BZD users had less psychotic symptoms and were less likely to receive antipsychotic drugs.

In multiple logistic regression analysis, older age (odds ratio [OR] 1.01, 95% confidence interval [CI] 1.01–1.03, $p < .001$) and more severe impairment of occupational functioning (OR 1.41, 95% CI 1.06–1.88, $p = .02$) were associated with long-term BZD use, while the concomitant use of antipsychotics (OR 0.59, 95% CI 0.4–0.86, $p = .006$) or traditional ADs (OR 0.43, 95% CI 0.21–0.9, $p = .02$) was negatively associated with it after adjusting for the study sites.

In order to identify the independent relationship of long-term BZD use with occupational functional impairment, we conducted a multiple logistic regression analysis with the "Enter" method; impairment in occupational functional was entered as the dependent variable, while long-term BZD use as the independent variable after adjusting for age, sex, length of illness, employment, and inpatient setting. Long-term

Table 1. Basic Demographic and Clinical Characteristics of Patients With Major Depressive Disorder

	Whole sample ($N = 1,192$)		Long-term BZD users ($n = 432$)		Non-long-term BZD users ($n = 760$)		Statistics	
	Mean	*SD*	Mean	*SD*	Mean	*SD*	T/Z	*p*
Age (year)	40.5	0.4	42.7	0.6	39.2	0.5	4.6	< .001
Household income (Yuan[a])	3,282	129	2663	110	3634	191	4.6	< .001
Number of episode	2.1	0.04	2.2	0.08	2.1	0.05	0.91	.37
Length of illness (month)	39.2	1.8	40.1	3.1	38.7	2.2	0.5	.65
	n	%	*n*	%	*n*	%	χ^2	*p*
Sex (female)	776	65.1	293	67.8	483	63.6	2.2	.15
Employment status (employed)	930	78.0	344	79.6	586	77.1	1.0	.344
Education level							5.6	.06
Primary or below	172	14.4	70	16.2	102	13.4		
Secondary school	716	60.1	268	62.0	448	59.0		
College or above	304	25.5	94	21.8	210	27.6		
Family history (positive)	183	15.4	63	14.6	120	15.8	0.3	.62
Treatment setting (inpatient)	369	31.0	138	31.9	231	30.4	0.3	.60
Suicide attempt	271	22.7	96	22.2	175	23.0	0.1	.75
Psychotic symptoms	76	6.4	19	4.4	57	7.5	4.4	.036
Impairment in occupational functioning	698	58.6	288	66.7	410	54.0	18.4	< .001
Antidepressant use							0.7	.88
None	53	4.5	19	4.4	34	4.5		
Traditional only	160	13.4	61	14.1	99	13.0		
Non-traditional only	937	78.6	335	77.6	602	79.2		
Combination	42	3.5	17	3.9	25	3.3		
Mood stabilizer use	78	6.5	21	4.9	57	7.5	3.1	.09
Antipsychotic drug use	237	19.9	65	15.1	172	22.6	10.0	.002

[a]1 USD = 6.1 Yuan; BZD, benzodiazepine; *SD*, standard deviation.

BZD use was independently associated with more severe occupational functional impairment (OR 1.7, 95% CI 1.3–2.2, $p < .001$).

Discussion

Long-term BZD use was common among patients with MDD in China, accounting for 36.2% of the study sample. The proportion of long-term BZD users was higher than the figures reported from Western countries. For example, a study in the Netherlands found that 12.4% of all patients with depression and anxiety were prescribed BZDs for at least three months (Manthey et al., 2011). More than one-quarter of depressed U.S. veterans (28.1%) received BZDs for 3 months or longer (Valenstein et al., 2004). However, there is little information with regard to the prevalence and risk factors associated with long-term BZD use in patients with MDD in Asian countries.

Long-term BZD use is associated with old age (Cunningham et al., 2010; Dag, 1997; Manthey et al., 2011; Veronese et al., 2007; Zandstra et al., 2002), female sex (Fortin et al., 2007; Jorm, Grayson, Creasey, Waite, & Broe, 2000), being divorced (Jorm et al., 2000) and in the lowest income quintile (Cunningham et al., 2010), history of BZD use (Dag, 1997; Manthey et al., 2011; Neutel, 2005), severe depressive (Cheng, Huang, Lin, & Shih, 2008; Luijendijk, Tiemeier, Hofman, Heeringa, & Stricker, 2008) and anxiety symptoms (Cheng et al., 2008; Manthey et al., 2011), length of illness (Veronese et al., 2007), psychiatric history (Zandstra et al., 2002), poor self-perceived life satisfaction (Fourrier, Letenneur, Dartigues, Moore, & Begaud, 2001; Zandstra et al., 2002), poor physical health (Cheng et al., 2008; Cunningham et al., 2010; Luijendijk et al., 2008; Zandstra et al., 2002), and frequent contact with medical services (Jorm et al., 2000). Our data suggest that long-term BZD use among patients with MDD is increased with age and is more frequent in patients who reported impairment in occupational functions.

In this study, patients taking combinations of BZDs and antipsychotics or BZDs and traditional ADs were less likely to be long-term users than those not taking them. This partly supports the finding that the absence of concomitant antipsychotics and mood stabilizers is a risk factor for long-term BZD use in MDD (Veronese et al., 2007). There is compelling evidence suggesting that BZDs should not be used as monotherapy in the treatment of MDD (Dunlop & Davis, 2008; Lai, Wang, Wu, Wu, & Lian, 2011) because they only have effects on insomnia and anxiety (Birkenhäger, Moleman, & Nolen, 1995; Johnson, 1985). Moreover, long-term use of BZDs may even worsen depressive symptoms in some patients (van Vliet, van der Mast, van den Broek, Westendorp, & de Craen, 2009).

The study has several limitations. First, long-term, sporadic use of BZDs in this study was not examined because it was not recorded in some study sites, which may lead to underestimating the frequency of long-term BZD use. Second, some additional variables that could have contributed to long-term BZD use or mediated the association between long-term use and occupational impairment, such as comorbid anxiety, insomnia, and other somatic symptoms, were not measured. Third, patients' psychiatric condition was not examined using standardized assessment tools. Finally, because of the cross-sectional design of the study, the causality between long-term BZD use and demographic and clinical characteristics could not be clarified.

In conclusion, long-term BZD use was common among patients with MDD in China and it was closely associated with severe occupational impairment. Considering the potential risks of dependence and other adverse effects, the rationale of long-term use of BZDs in MDD should be examined.

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