

Use of benzodiazepines in obsessive-compulsive disorder

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Abstract

Objectives: This study aimed to determine the frequency of benzodiazepine (BDZ) use in a large sample of patients with obsessive-compulsive disorder (OCD) and ascertain the type of BDZ used and the correlates and predictors of BDZ use in OCD.

Methods: The sample consisted of 955 patients with OCD from a comprehensive, cross-sectional, multicentre study conducted by the Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders between 2003 and 2009.

Results: The rate of BDZ use over time in this OCD sample was 38.4%. Of individuals taking BDZs, 96.7% used them in combination with other medications, usually serotonin reuptake inhibitors. The most commonly used BDZ was clonazepam. Current age, current level of anxiety and number of additional medications for OCD taken over time significantly predicted BDZ use.

Conclusions: This is the first study to comprehensively examine BDZ use in OCD subjects, demonstrating that it is relatively common, despite recommendations from treatment guidelines. Use of BDZs in combination with several other medications over time and in patients with marked anxiety suggests that OCD patients taking BDZs may be more complex and more difficult to manage. This calls for further research and clarification of the role of BDZs in the treatment of OCD.

Keywords: Anxiety; Benzodiazepines; Clonazepam; Obsessive-compulsive disorder; Treatment guidelines

Introduction

Despite the fact that obsessive-compulsive disorder (OCD) has been considered an anxiety disorder until the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), the usefulness of benzodiazepines (BDZs) in OCD has not been studied much. Most evidence regarding this issue comes from case reports and open-label studies with small numbers of participants. Thus, one open-label trial in 14 patients (Stein *et al.*, 1992) showed that alprazolam was not efficacious in the treatment of OCD. With regards to clonazepam, one randomised, double-blind, placebo-controlled trial conducted in 27 OCD patients (Hollander *et al.*, 2003) failed to demonstrate efficacy in OCD, but another study involving 28 patients and using a randomised, double-blind, multiple crossover design (Hewlett *et al.*, 1992) reported that clonazepam was as efficacious in OCD as clomipramine. Several case reports also suggested the effectiveness of clonazepam in OCD (Bodkin and White, 1989; Bacher, 1990; Hewlett *et al.*, 1990; Ross and Pigott, 1993). Following reports that BDZs might be useful to augment OCD treatment with serotonin reuptake inhibitors (SRIs) (e.g., Pigott *et al.*, 1992; Leonard *et al.*, 1994), one randomised controlled trial conducted in 37 patients (Crockett *et al.*, 2004) showed that a combination of sertraline and clonazepam did not lead to a better outcome in OCD than a combination of sertraline and placebo.

In view of these results, recent treatment guidelines either do not mention BDZs as a potential treatment for OCD (Baldwin *et al.*, 2014) or state that BDZs “have not demonstrated efficacy and are not recommended in the treatment of OCD” (Katzman *et al.*, 2014, p. 31). The latter applies to both BDZ monotherapy and their adjunctive use. However, most investigators commented that BDZs might still be useful in at least some cases of OCD. Thus, it has been suggested that BDZs might be useful for OCD patients with co-occurring anxiety disorders (Hollander *et al.*, 2003) or in those who

have not responded to SRIs, either as monotherapy (Hewlett *et al.*, 1992) or as augmentation treatment (Hewlett *et al.*, 1992; Hollander *et al.*, 2003; Crockett *et al.*, 2004).

Considering that the role of BDZs in the treatment of OCD has not been sufficiently investigated and the general popularity of BDZs in the treatment of anxiety disorders (Starcevic, 2014), it does not come as a surprise that, despite recommendations from treatment guidelines, BDZs seem to be relatively commonly prescribed for OCD. For example, a survey of the prescribing practices in nine international OCD centres has found that BDZs were used as augmenting (adjunctive) agents by 24.9% of patients (Van Ameringen *et al.*, 2014). Clonazepam was the most commonly prescribed BDZ in this survey, followed by bromazepam, alprazolam and lorazepam. A study of the characteristics of office-based visits by OCD patients in the United States between 2003 and 2010 reported that BDZs were prescribed in 29.0% of such visits (Patel *et al.*, 2014). An earlier survey from the United States revealed that 35.5% of OCD patients were treated with BDZs and that BDZ treatment was frequently associated with co-occurring mood and anxiety disorders (Blanco *et al.*, 2006). This study also reported that concurrent SRIs were administered in two-thirds of the cases in which BDZs were prescribed.

These data suggest that, despite not being officially considered a treatment for OCD, BDZs are still commonly administered to OCD patients. However, such practice has been understudied. There appears to be a tendency to prescribe BDZs in OCD to augment therapy with SRIs, but the reasons for this remain unclear. Therefore, the present study was undertaken with several goals. First, we aimed to determine the frequency of BDZ use in a large sample of OCD patients, both as monotherapy and in conjunction with other

medications. Second, we wanted to ascertain the type of BDZs used. Finally, the study aimed to investigate the correlates and predictors of BDZ use in OCD.

Consistent with the findings stated above, we hypothesised that between 25% and 35% of OCD patients were taking BDZs and that most of them were taking BDZs as augmentation therapy. We expected clonazepam to be used more often than other BDZs because of the aforementioned studies reporting some efficacy of this medication for OCD and the associated suggestion about certain serotonergic effects of clonazepam (Hewlett *et al.*, 1992). We also hypothesised that BDZ use was more likely in older and female patients with OCD, based on studies in various countries showing that BDZ use tends to be positively correlated with age and female gender (Lagnaoui *et al.*, 2004; Neutel, 2005; Petitjean *et al.*, 2007; Hollingworth and Siskind, 2010; Firmino *et al.*, 2011; Holm *et al.*, 2012; Sonnenberg *et al.*, 2012; Brunoni *et al.*, 2013; Cloos *et al.*, 2015; Olfson *et al.*, 2015).

In addition, we predicted that BDZ use in OCD reflected a more severe, more chronic and more complex illness, considering that BDZs are not the first-line treatment for OCD and that they would therefore be more likely to be prescribed to patients who failed to respond to standard monotherapy with SRIs or were otherwise treatment-resistant. In view of the well-documented anxiolytic effects of BDZs, we expected BDZs to be administered more often to individuals with higher levels of anxiety and more prominent co-occurring anxiety disorders and anxiety-inducing obsessions. The latter include aggressive, sexual, moral and religious obsessions (unacceptable/taboo thoughts), because they are usually experienced as particularly distressing, disturbing and anxiety-provoking (e.g., Brakoulias *et al.*, 2013). This last hypothesis is supported by one case series, which reported that aggressive obsessions

responded favourably to clonazepam treatment, either alone or in combination with clomipramine (Fontenelle et al., 2005).

Method

Subjects

The sample for this study was drawn from a cross-sectional research conducted by the Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders in seven specialised, university-affiliated sites in Brazil between 2003 and 2009. The design and characteristics of this project were described by Miguel *et al.* (2008). The present study included 955 patients who were at least 18 years of age.

The key inclusion criterion was the primary diagnosis of OCD. Only the presence of schizophrenia, dementia, mental retardation or any other condition that precluded understanding of the assessment procedure constituted grounds for exclusion. Participants were recruited from various mental health facilities and other referral sources and via advertisements, self-help groups and patient and professional organisations. The study was approved by the institutional review boards in all sites and all participants signed consent forms after the study had been explained to them.

Assessment instruments

The assessment procedures were described in detail by Miguel *et al.* (2008). The instruments that provided data for the purposes of the present study are listed below.

The Socio-Demographic and Clinical Questionnaire. This instrument was developed for the Brazilian Research Consortium on Obsessive-Compulsive Spectrum Disorders project. It

provided demographic information and data on the course and treatment of OCD. Some of its components are based on patient self-report, whereas others elicit information through a face-to-face clinical interview. Data on participants' use of BDZs and other medications, as well as data pertaining to the onset and duration of OCD, were obtained from this questionnaire.

The Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID-I; First et al., 1997). The SCID-I was used to establish that OCD was the primary diagnosis and to ascertain the presence of co-occurring mental disorders. The researchers were trained in the use of the SCID-I, as well as other clinician-administered measures listed below; inter-rater reliability figures for all these instruments were excellent (Miguel et al., 2008).

The Yale-Brown Obsessive-Compulsive Scale (Y-BOCS; Goodman et al., 1989). The Y-BOCS is a semi-structured, clinician-administered interview, widely used to measure the severity of OCD. It consists of a checklist of obsessions and compulsions and a 10-item severity scale. Up to 3 most prominent obsessions and compulsions are rated for severity, providing separate scores for the severity of obsessions and compulsions and a total Y-BOCS score, denoting the overall severity of OCD.

The Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS; Rosario-Campos et al., 2006). The DY-BOCS has both a self-report component and clinician-rated component. It was used to assess the severity of six symptom dimensions of OCD: (1) obsessions about harm due to aggression/injury/violence/natural disasters and related compulsions ("aggressive obsessions"); (2) sexual/moral/religious obsessions and related compulsions; (3) obsessions about symmetry/"just-right" perceptions and compulsions to count or order/arrange; (4) contamination obsessions and cleaning compulsions; (5) hoarding obsessions and

compulsions, and (6) miscellaneous obsessions and compulsions (e.g., relating to somatic concerns or superstitions).

The Beck Anxiety Inventory (BAI; Beck *et al.*, 1988) and *The Beck Depression Inventory* (BDI-II; Beck *et al.*, 1996) are widely used, psychometrically sound, self-report instruments that assess the severity of anxiety and depressive symptoms, respectively. Both instruments consist of 21 items, with each item being rated on a four-point scale and total scores on the BAI and BDI-II being obtained by summing the item scores.

Data analyses

Descriptive statistics and preliminary analyses were conducted in SPSS 22.0. Before conducting the analyses, missing values for the key variables were imputed using the expectation-maximization algorithm in SPSS. Thus, 41 of 21965 data points (0.19%) were imputed and Little's MCAR test indicated that data were missing completely at random: $\chi^2 = 33.31$, $df = 22$, $p = 0.058$.

Chi-square tests were used to compare categorical variables between the groups of BDZ users and non-users. Non-parametric Mann-Whitney U tests were used to compare the demographic and relevant clinical variables as the distributions for these variables were positively skewed (except for the Y-BOCS total score) and Kolmogorov-Smirnov tests indicated that the variables were not normally distributed.

Logistic regression analyses were conducted in MPlus where any BDZ use over time (present or absent) was regressed on current age, gender, Y-BOCS total score, duration of OCD, number of additional medications for OCD being taken over time, BDI-II score, BAI score,

DY-BOCS aggressive obsessions score and DY-BOCS sexual/moral/religious obsessions score. Site of recruitment was entered in the analysis as a level 2 between-subjects variable in order to account for between-site differences in the patterns of BDZ use. Given the possibility of collinearity between some of the variables in the analysis, Variance Inflation Factor (VIF) statistics were reviewed in SPSS. No VIF values were greater than 3.4 for the overall sample or 7.3 when examining collinearity within any given site.

Results

Of the 955 participants, 367 (38.4%) took BDZs at some point since the onset of their OCD, with 213 (58%) of BDZ users being female. Rates of BDZ use varied from 28.0% to 73.3% according to site of recruitment. Of those individuals taking BDZs, 12 (3.3%) used them as monotherapy, 342 (93.2%) took them with at least one SRI over time and 143 (39.0%) used BDZs with at least one antipsychotic medication since the onset of OCD. The most commonly used BDZ was clonazepam (278 patients or 75.7% of all BDZ users), followed by diazepam (122; 33.2%) and alprazolam (107; 29.2%). There were 250 (68.1%) participants who took only one type of BDZ, whereas 94 (25.6%) used two types of BDZs over time and 23 (6.3%) took three types of BDZs throughout the duration of their OCD.

Table 1 shows that BDZ users and BDZ non-users did not differ significantly with respect to the demographic characteristics, except for BDZ users' older mean current age. Table 2 compares BDZ users and BDZ non-users in terms of the relevant clinical variables. The duration of OCD was significantly longer among BDZ users and they also had significantly more prominent sexual/moral/religious obsessions and higher mean scores on both the BDI-II and BAI. The mean number of additional medications for OCD was significantly greater among BDZ users.

[Tables 1 and 2 about here]

Table 3 shows that, except for panic disorder with agoraphobia, BDZ users and BDZ non-users did not differ significantly with regards to the lifetime rates of co-occurring anxiety disorders. Results of the logistic regression analyses are summarised in Table 4, with current age, BAI score and number of additional medications for OCD emerging as significant predictors of BDZ use.

[Tables 3 and 4 about here]

Discussion

To the best of our knowledge, this is the first study focusing on the investigation of clinical predictors of BDZ use in OCD subjects. Well over one-third (38.4%) of individuals with OCD in this large Brazilian sample were treated with BDZs at some stage of their illness. This is higher than the previously reported rates of BDZ use in OCD, which ranged from 24.9% to 35.5% (Blanco *et al.*, 2006; Patel *et al.*, 2014; Van Ameringen *et al.*, 2014). A possible reason for the higher rate reported in this study is that we combined current and past BDZ use, whereas other studies did not assess past BDZ use. Another reason may be that study participants were drawn from tertiary care settings, possibly reflecting a more severely ill sample. The variation between the Brazilian sites in terms of the frequency with which BDZs were used is likely a consequence of different treatment orientations (predominantly pharmacotherapeutic vs. predominantly psychotherapeutic), different settings (inpatient vs. outpatient) and differences in patient characteristics (public vs. private). Also, rates of BDZ use were reported to be higher in Brazil than in most developed countries (Kapczinski *et al.*, 2001) and BDZs were regarded as being “overused” in Brazil (Brunoni *et al.*, 2013).

The vast majority (96.7%) of patients using BDZs took them in conjunction with other pharmacological agents, most commonly SRIs. This is in accordance with suggestions that use of BDZs to augment SRIs in OCD might be useful (Hewlett *et al.*, 1992; Hollander *et al.*, 2003; Crockett *et al.*, 2004).

In accordance with our hypothesis, clonazepam was the most frequently used BDZ. It is possible that this finding reflects the fact that the study was conducted in academic centres specialised in OCD, where prescribers were more likely to be aware that some research suggested possible efficacy of clonazepam for OCD. However, clonazepam, along with diazepam, is also the most commonly used BDZ in Brazil (Noto *et al.*, 2002; Firmino *et al.*, 2011; Brunoni *et al.*, 2013).

Users of BDZs were significantly older than the participants who never took BDZs, and current age was a significant, but weak predictor of BDZ use in this sample of OCD individuals. This is in agreement with findings about the use of BDZs in various countries (Lagnaoui *et al.*, 2004; Neutel, 2005; Petitjean *et al.*, 2007; Hollingworth and Siskind, 2010; Holm *et al.*, 2012; Sonnenberg *et al.*, 2012; Cloos *et al.*, 2015; Olfson *et al.*, 2015), as well as Brazil (Firmino *et al.*, 2011; Brunoni *et al.*, 2013), and may reflect tendencies in the general use of BDZs. Contrary to our hypothesis and findings from other studies, the proportions of women among BDZ users and BDZ non-users were almost identical, and female gender did not emerge as a significant predictor of BDZ use in OCD individuals. It is uncertain whether these findings are related to OCD or some other factor.

Our hypothesis that BDZ use in OCD is related to a greater severity, chronicity and complexity of OCD was only partially supported. The severity of OCD did not differ between

BDZ users and BDZ non-users and did not predict use of BDZs. In contrast, the mean duration of OCD was significantly longer among BDZ users, suggesting a more chronic course of OCD in those who were taking BDZs. Due to the cross-sectional nature of the study, the direction of possible causality between the chronic course of OCD and use of BDZs could not be ascertained. Furthermore, the duration of OCD did not emerge as a significant predictor of BDZ use.

The use of additional medications for OCD over time was more common in BDZ users, as indicated by the significantly greater mean number of additional medications for OCD in this group than in the group of BDZ non-users; the number of additional medications for OCD also predicted the use of BDZs. These findings suggest that BDZs are more likely to be used when OCD is more complex or more difficult to manage, prompting clinicians to try various pharmacological agents. Similar polypharmacy in OCD has been reported by others (Blanco *et al.*, 2006; Van Ameringen *et al.*, 2014). The present study sheds more light on this issue by suggesting that BDZs may often be used as part of various augmentation strategies.

The finding that lifetime rates of most co-occurring anxiety disorders did not differ significantly between BDZ users and BDZ non-users was surprising, because it has been suggested that BDZs might be useful in OCD patients with co-occurring anxiety disorders (Hollander *et al.*, 2003) and that higher rates of co-occurring anxiety disorders were expected among BDZ users. However, BAI-derived findings do suggest that BDZ users were characterised by currently higher general anxiety levels and that these were a significant, but weak predictor of BDZ use. These somewhat discrepant findings may indicate that clinicians take more into account patients' general anxiety levels than the presence of co-occurring anxiety disorders when prescribing BDZs.

We found that of all OCD dimensions, only sexual/moral/religious obsessions were more prominent in BDZ users than in BDZ non-users. However, neither the DY-BOCS sexual/moral/religious obsessions score nor the DY-BOCS aggressive obsessions score predicted BDZ use. These findings suggest that use of BDZs in this sample of OCD individuals was unrelated to the severity of these obsessions, but it remains to be ascertained whether patients with certain OCD features might be more responsive to BDZs, used either alone or in combination with SRIs.

The use of BDZs has been controversial, largely due to their habit-forming properties and some of their adverse effects, such as sedation and psychomotor impairment. Clinicians treating OCD patients need to balance the potentially detrimental effects of BDZs with the benefit of a quick relief of anxiety with these agents.

This study has a number of limitations. First, it is based on cross-sectional research, which did not allow us to examine any effects of BDZs or to assess changes in OCD and its treatment over time. Likewise, it was not possible to obtain data on the longitudinal patterns of BDZ use, including its duration and any changes in the doses of BDZs. Second, the study relied on participants' recall about medications that they have taken since the onset of their OCD, which is subject to recall bias. Third, data on the factors that might have influenced the prescription of BDZs (e.g., clinician or patient preferences and previous patient experience with BDZs) were not collected. Further, information on the use of hypnotic medications was not recorded. Since this class of pharmacological agents includes a number of BDZs, the rate of BDZ use in this sample may have been somewhat underestimated. However, our primary focus in this study was BDZ use for OCD and anxiety, not for sleep disturbance. Finally, the

interpretation of the findings should take into account tertiary care settings and the country in which the study was conducted; these factors also limit the generalizability of the findings.

In conclusion, this study sheds more light on the neglected issue of BDZ use in OCD and confirms that use of BDZs in adult OCD patients is more common than what would be expected on the basis of the available OCD treatment guidelines. Clonazepam was the most commonly used BDZ in this large Brazilian sample of OCD patients. It appears that BDZs are typically used in combination with several other pharmacological agents over time and in patients with marked anxiety, suggesting an association between BDZ use on one hand and greater complexity of OCD and difficulty in managing OCD on the other. This study did not find a link between BDZ use and specific features of OCD, raising a question as to whether there are any aspects of OCD itself that might suggest a need for treatment with BDZs. A paucity of high-quality studies of the efficacy of BDZs for OCD calls for further research. These efforts should ultimately clarify the role of BDZs in the treatment of OCD.

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Table 1. Demographic characteristics of benzodiazepine users and non-users.

Demographic characteristics	BDZ users (n = 367)		BDZ non-users (n = 588)			<i>p</i>
	Mean (Median; SD)		Mean (Median; SD)		Mann-Whitney <i>U</i> statistic	
Current age (in years)	37.58 (35; 12.80)		34.73 (32; 12.17)		93555.50	< 0.001
Education (in years)	14.60 (14; 4.85)		14.88 (14; 5.00)		104861.50	0.49
	n	%	n	%	χ^2 (<i>df</i> = 1)	
Female gender	213	58.0	342	58.2	0.001	0.97
Caucasian	299	81.5	493	83.8	0.90	0.34
Married/de facto relationship	148	40.3	228	38.8	0.23	0.63
Parenthood (having children)	154	42.0	236	40.1	0.31	0.58
Unemployed	63	17.7	90	15.6	0.74	0.39

BDZ = Benzodiazepine.

Table 2. Relevant clinical variables in benzodiazepine users and non-users.

Variables	BDZ users (<i>n</i> = 367) Mean (Median; SD)	BDZ non-users (<i>n</i> = 588) Mean (Median; SD)	Mann-Whitney <i>U</i> statistic	<i>p</i>
Y-BOCS total score	25.89 (26; 8.03)	25.41 (26; 7.09)	102536.50	0.20
DY-BOCS aggressive obsessions score	5.68 (6; 5.04)	5.21 (5; 4.97)	101637.00	0.12
DY-BOCS sexual/moral/religious obsessions score	4.85 (3; 5.02)	4.02 (0; 4.84)	96733.00	0.004
DY-BOCS symmetry and related obsessions and compulsions score	7.26 (8; 6.81)	7.74 (9; 5.88)	100860.00	0.09
DY-BOCS contamination and cleaning score	6.13 (6; 5.17)	6.30 (7; 5.19)	106296.00	0.69
DY-BOCS hoarding score	3.14 (0; 4.27)	3.22 (0; 3.98)	105178.00	0.48
DY-BOCS miscellaneous obsessions and compulsions score	7.36 (8; 4.76)	7.68 (9; 4.68)	103356.00	0.27
Duration of OCD (in years)	24.65 (23; 13.14)	22.12 (20; 12.60)	95424.00	0.003
BDI-II score	18.90 (18; 11.87)	15.35 (14; 10.49)	89737.50	< 0.001
BAI score	18.28 (17; 12.32)	15.06 (13; 10.51)	92363.50	< 0.001
Number of additional medications for OCD	3.84 (3; 3.01)	1.29 (1; 1.50)	42729.50	< 0.001

BDZ = Benzodiazepine; Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; DY-BOCS = Dimensional Yale-Brown Obsessive-Compulsive Scale; OCD = Obsessive-compulsive disorder; BDI-II = Beck Depression Inventory; BAI = Beck Anxiety Inventory.

Table 3. Lifetime rates of co-occurring anxiety disorders in benzodiazepine users and non-users.

Co-occurring anxiety disorders	BDZ users		BDZ non-users		χ^2 (<i>df</i> = 1)	<i>p</i>
	<i>(n</i> = 367)		<i>(n</i> = 588)			
	<i>N</i>	%	<i>n</i>	%		
Panic disorder with agoraphobia	42	11.4	25	4.3	17.92	< 0.001
Panic disorder without agoraphobia	15	4.1	29	4.9	0.37	0.55
Agoraphobia without history of panic disorder	15	4.1	30	5.1	0.52	0.47
Social anxiety disorder	114	31.1	198	33.7	0.70	0.40
Specific phobia	107	29.2	189	32.1	0.94	0.33
Generalized anxiety disorder	126	34.3	195	33.2	0.14	0.71
Posttraumatic stress disorder	39	10.6	58	9.9	0.14	0.70

BDZ = Benzodiazepine.

Table 4. Results of the logistic regression analyses predicting use of benzodiazepines.

Predictor variables	Unstandardised B (SE)	Wald test (z-ratio)	Exp(B)	<i>p</i>
Current age	0.02(0.005)	4.35	1.02	< 0.001
Gender	-0.06 (0.14)	-0.44	0.94	0.66
Y-BOCS total score	-0.016 (0.02)	-1.06	0.98	0.29
Duration of OCD	0.002 (0.006)	0.26	1.002	0.79
Number of additional medications for OCD	0.61 (0.04)	16.23	1.83	< 0.001
BDI-II score	0.01 (0.01)	0.88	1.01	0.38
BAI score	0.02 (0.01)	2.49	1.02	0.01
DY-BOCS aggressive obsessions score	-0.01 (0.02)	-0.50	0.99	0.49
DY-BOCS sexual/moral/religious obsessions score	0.01 (0.008)	1.87	1.02	0.06

$R^2 = 0.44$.

Y-BOCS = Yale-Brown Obsessive-Compulsive Scale; OCD = Obsessive-compulsive disorder; BDI-II = Beck Depression Inventory; BAI = Beck Anxiety Inventory; DY-BOCS = Dimensional Yale-Brown Obsessive-Compulsive Scale.