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Socio-demographic and clinical characteristics of benzodiazepine long-term users: Results from a tertiary care center

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Abstract

Objective: The use of benzodiazepines (BDZs) represents a critical issue since a long-term treatment may lead to dependence. This study aimed at evaluating socio-demographic and clinical characteristics of BZD long-term users who followed a detoxification program at a tertiary care center.
Method: Two hundred-five inpatients were evaluated. Socio-demographic (e.g., gender, age, education) and clinical information (e.g., BZD used, dose, reason of prescription) was collected. BZDs dose was standardized as diazepam dose equivalents and was compared via the Defined Daily Dose (DDD). Chi-square, Fisher test, ANOVA and Bonferroni analyses were performed.
Results: Females were more frequently BDZ long-term users than males. Hypnotic BZDs were frequently prescribed for problems different from sleep disturbances. Lorazepam, alprazolam, and lormetazepam were the most prescribed drugs. Lorazepam was more frequently used by males, consumed for a long period, in pills, and prescribed for anxiety. Lormetazepam was more frequently consumed by females with a high school education, having a psychiatric disorder, taken in drops and prescribed for insomnia. Lormetazepam had the highest DDD.
Conclusion: A specific profile of BZD long-term user seems to exist and presents different socio-demographic and clinical characteristics according to the benzodiazepine taken into account.

1. Introduction

For decades, benzodiazepines (BZDs) have been recommended as the standard treatment of anxiety and insomnia [1–4]. In late 1990s, the most frequent recommendation for the treatment of anxiety disorders changed to a selective serotonin reuptake inhibitor (SSRI) or to a serotonin norepinephrine reuptake inhibitor (SNRI) [5] and BDZs were replaced by newer antidepressants mainly due to the claimed BZD withdrawal, rebound, overuse, and abuse [6]. However, the new SSRI and SNRI classification of withdrawal syndromes, which includes persistent postwithdrawal disorders [7], suggested that newer antidepressants have similar problems of withdrawal and rebound as BZDs. In addition, the literature has provided evidence for a reappraisal of BZDs as first-line pharmacological treatment of anxiety disorders without depression; and major differences in terms of rebound syndrome, potency, risk of abuse, and pharmacokinetics have been shown among BZDs [6].

Analyses of possible predictors for BZD long-term use show that gender is of minor importance [8,9] although more women use than men and the long-term use is much more common among women than men [9,10]. Older age was found to be an important predictor [8–11] as well as previous use [8,9] and low level of education [12]. Patients who obtained BDZ prescriptions from doctors in hospital care and patients who obtained prescriptions from doctors working in different settings continued to use BZDs to a greater extent than those who received prescriptions from private practitioners or health centers doctors alone [9]. Also a combined use of hypnotics together with anxiolytics seems to be a significant factor in frequent or daily use [9]. Alcohol consumption, anxiety and tension have been positively related to long-term use, while exercise seems negatively related to it [13]. In addition, according to a recent survey, BZD hypnotics have been associated with increased risk of high-dose use among long-term users, compared to diazepam; BZD anxiolytics were associated with significantly

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lower risk of high-dose use, the lowest risk being with clobazam and clonazepam; finally, triazolobenzodiazepines (i.e., alprazolam and triazolam) were at risk for high-dose use among continuous users [11]. Thus, not all benzodiazepines seemed to be the same [14].

In this framework, we assessed socio-demographic and clinical characteristics of BZD long-term users who referred to a tertiary care center for detoxification with the aim to verify whether routine data are consistent with the results provided by population surveys.

2. Methods

2.1. Sample and procedure

BZD dependent patients who consecutively referred to the Addiction Unit (AU) of the Verona University Hospital (Verona, Italy) between January 2003 and December 2014 were evaluated. Exclusion criteria were: lifetime and current substance use disorders, other than nicotine and benzodiazepines; addiction to more than one BZD (cases with more than one BZD long-term use were excluded to prevent interpretive bias and allow a clear identification of a socio-demographic and clinical profile of the long-term users for each benzodiazepine).

Inclusion criteria were: age older than 18 years; diagnosis of BZD dependence according to the DSM-IV criteria [15]; BZD addiction lasting from at least 180 days [16]. Eligible patients provided written informed consent and were evaluated by the medical doctors of the AU via standardized questions already used in the past [17,18] which allowed to collect the following information: demographic characteristics; reasons for BDZ prescription; average daily BZD dose consumed in the last 180 days; duration of BZD use; route of administration; co-occurrent psychiatric disorder(s). The study protocol fully adhered to guidelines of the Ethic Committee of the Verona University Hospital, Verona, Italy.

2.2. Statistical analyses

The different BZD dose was compared via the Defined Daily Dose (i.e., 1 DDD is the therapeutic daily dose established by WHO for any drug) [19] and BZDs dose was standardized as diazepam dose equivalents using one of the most accepted conversion tables where 10 mg of diazepam is equal to: 1 mg of lorazepam, 2 mg of lormetazepam, 0.25 mg of triazolam, 3 mg of delorazepam, 0.5 mg of alprazolam [20], 6 mg bromazepam [11], 1.5 etizolam [21,22], 20 mg temazepam [11,23].

Comparisons were performed using the chi-square test and Fisher's exact test for dichotomous variables, and the analysis of variance (ANOVA) plus Bonferroni test as a post-hoc analysis for continuous variables.

Significance levels were set at $p \leq 0.05$ (two-tailed). All of the analyses were performed using SPSS, version 21.0 [24].

3. Results

Two hundred-five subjects were enrolled. Among them 132 were females (64.4%) and 73 males (35.6%), with a mean age of 46.39 ± 11.33 years. Most subjects had a high school diploma (n = 76, 37.1%), followed by middle school diploma (n = 55, 26.8%), university degree (n = 37, 18%), and primary school education (n = 11, 5.4%). Distribution of marital status included: 81 (50.93%) married, 76 (47.2%) unmarried, and 3 (1.86%) widowed. About 54% (n = 110, 55.7%) of the sample was employed, 16.1% (n = 33) was unemployed, 20.5% (n = 42) was retired or housewife. Almost the whole sample (93.2%, n = 191) had at least one psychiatric disorder. The most frequent mental illnesses were anxiety or depressive disorders (n = 151, 79.47%), followed by bipolar disorder (n = 17, 8.94%), personality disorders (n = 12, 6.31%), others (n = 8, 4.21%). The use of BZD lasted 80.87 ± 79.62 months.

Among anxiolytic BZDs, lorazepam had the highest rate of use in the total sample, followed by alprazolam. Among hypnotic BZDs, lormetazepam had the highest rate of use in the total sample (Table 1).

Lorazepam and delorazepam were more likely to be consumed by males while lormetazepam was more likely to be consumed by females (Table 1). No difference was found in terms of age (Table 2).

When the distribution by working activity, civil status, and education for each benzodiazepine was evaluated, statistically significant results were found only for education (diazepam: 2 subjects completed the primary school, 1 completed the middle school, and 1 the high school, $p = 0.01$, $df = 4$; lormetazepam: 6 subjects completed the primary school, 29 the middle school, 57 the high school, 29 the college, for 3 subjects the information was not available, $p = 0.02$, $df = 4$).

Lorazepam was more likely to be consumed in pills while lormetazepam was more likely to be consumed in drops (Table 1). The 5.36% of the prescriptions for anxiolytic BZDs was for insomnia and the 24.39% of prescriptions for hypnotic BZDs was for anxiety (98% of prescriptions was due to lormetazepam).

Lormetazepam was more frequently prescribed in cases with a diagnosis of at least one psychiatric disorder than those without psychiatric disorders (n = 13, 92.9% vs n = 123, 64.4%; $p = 0.03$).

When the benzodiazepines were compared in terms of diazepam equivalent dose and duration of use, no statistically significant results were found. Lorazepam was noted to have the longest duration of use while lormetazepam had the highest DDD (Bonferroni post-hoc $p < 0.001$) (Table 2).

4. Discussion

The present study shows that BZD long-term users asking for detoxification are females in about two thirds of cases,

Table 1
Rate of use of each benzodiazepine. Distribution of gender, formulation, and reasons for prescription. Chi-squared test for independent samples.

			Gender n = 205			Formulation n = 177			Prescribed for anxiety n = 205			Prescribed for insomnia n = 205		
			female	male	statistics	pills	drops	statistics	no	yes	statistics	no	yes	statistics
	N	Total %	N (column %)	N (column %)	p	N (column %)	N (column %)	p	N (column %)	N (column %)	p	N (column %)	N (column %)	p
BZDs anxiolytics														
lorazepam	31	15.1	14 (10.6)	17 (23.3)	**0.01**	28 (73.2)	0 (0.00)	**<0.001**	8 (7.5)	23 (23.2)	**0.002**	27 (23.3)	4(4.5)	**<0.001**
alprazolam	15	7.3	9 (6.8)	6 (8.2)	0.71	5 (13.2)	8 (5.8)	0.16[a]	3 (2.8)	12 (12.1)	**0.01**	12 (10.3)	3 (3.4)	0.057
bromazepam	9	4.4	8 (6.1)	1 (1.4)	0.16[a]	1 (2.6)	5 (3.6)	1.00[a]	2 (1.9)	8 (7.1)	0.09[a]	7 (6)	2(2.2)	0.30[a]
delorazepam	4	2	0	4 (5.5)	**0.01**[a]	1 (2.6)	1 (0.7)	0.38[a]	1 (0.9)	3 (3)	0.35[a]	3 (2.6)	1(1.1)	0.63[a]
diazepam	4	2	2 (1.5)	2 (2.7)	0.61[a]	0	3 (2.2)	1.00[a]	2 (1.9)	2 (2)	1.00[a]	3 (2.6)	1(1.1)	0.63[a]
etizolam	4	2	1 (0.8)	3 (4.1)	0.13[a]	1 (2.6)	2 (1.4)	0.51[a]	2 (1.9)	2 (2)	1.00[a]	4 (3.4)	0 (0.00)	0.13[a]
BZDs hypnotics														
lormetazepam	136	66.3	96 (72.7)	40 (54.8)	**0.01**	0 (0.00)	120 (86.3)	**<0.001**	87 (82.1)	49 (49.5)	**<0.001**	59 (50.9)	77(86.5)	**<0.001**
triazolam	1	0.5	1 (0.0)	0 (1.3)	1.00[a]	1 (2.6)	0 (0.00)	0.21[a]	1 (0.9)	0	1.00[a]	0 (0.00)	1(1.1)	0.43[a]
temazepam	1	0.5	1 (0.8)	0	1.00[a]	1(2.4)	0 (0.00)	0.22[a]	0 (0.00)	1 (1)	0.48[a]	1 (0.9)	0(0.00)	1.00[a]

BZDs: benzodiazepines.
[a] Fisher's exact test.

have a high-school level of education in about one third of cases, are married and employed in about half of cases, and have a mean age of about 46 years. The majority of subjects used lorazepam and alprazolam, among anxiolytic BZDs, and lormetazepam, among hypnotic BZDs. The prescription of anxiolytic BZDs was for sleep disturbances rather than for anxiety problems in about 5.36% of the cases, while the prescription of hypnotics BZDs was for anxiety rather than for sleep disturbances in about 24.39% of the cases. Among anxiolytic BZDs, lorazepam was more frequently used by males, consumed in pills, and used for a longer period. Even delorazepam was more frequently used by males. Among hypnotic BZDs, lormetazepam was more frequently used by females with a high school education, having a psychiatric disorder, and taken in drops. The highest DDD value was found for lormetazepam.

The findings on gender distribution are consistent with population surveys showing that BZDs intake is twice in women than in men [16,25–29] and with the Luxembourg national registry study which found significantly more high-dose long-term users among women than among men [11]. Interestingly, anxiolytic BZDs were more likely to be used by men while hypnotics BZDs were mostly consumed by women. Unfortunately, no data from the literature evaluated gender distribution among anxiolytic and hypnotic BZDs, thus comparisons on this issue are not possible.

The present sample seems to have a relatively high level of education; this result is only apparently not consistent with the literature [12] since Mant et al. (1988) referred to the general population while we evaluated tertiary care patients, who frequently have an intermediate level of education [30–32].

Among anxiolytic BZDs, lorazepam and alprazolam had the longest-term use while the most hypnotic BZD used was lormetazepam. These findings are consistent with earlier population surveys [11,18,28,33,34] and can be related to the pharmacological characteristics of BZDs which differentiate their dependence potential. Dependence on BZDs following continuous use is most notable for those with a medium elimination half-life such as lorazepam and lormetazepam [35] or for triazolobenzodiazepines, such as alprazolam, which are characterized by high level of lipid solubility [6].

The present research also reported a higher rate of prescriptions, which apparently do not match the indication (i.e., improper prescription), for hypnotics BZDs than for anxiolytic BZDs. Although it is widely known that BDZs may be prescribed improperly, the extent of this problem remains uncertain [36] since studies aimed at evaluating the pattern of prescription of BDZs have yielded mixed results. On one hand, a trend to prescribe anxiolytic BDZs mostly for anxiety disorder and hypnotic BDZs mostly for insomnia was shown [37]; on the other hand, some authors found that both anxiolytics and hypnotics are prescribed for sleep disorders and/or anxiety disorders [38,39]. It is also noteworthy that most of these studies [27,34,40,41] assessed BZDs as a whole rather than estimating the pattern of prescription of each BDZ.

Table 2
Descriptive (mean ± SD) of continuous variables. Analysis of variance (ANOVA) plus Bonferroni test was applied for age, Defined Daily Dose, diazepam equivalent dose, and duration of treatment.

	Age (years) N = 203			Dose (mg) N = 202		Times × Defined Daily Dose N = 202			Diazepam equivalent dose N = 201			Duration of use (months) N = 198		
	mean	SD	p	mean	SD	mean	SD	p	mean	SD	p	mean	SD	p
BZDs anxiolytics														
lorazepam	46.87	9.48		29.13	30.71	13.10	16.47		291.29	307.11		118.97	123.49	
alprazolam	46.93	9.68		14.27	10.36	14.27	10.36		285.33	207.26		74.93	71.26	
bromazepam	43.89	8.58		152.83	258.82	15.29	25.88		305.56	517.73		77.11	60.58	
delorazepam	40.50	12.71		15.67	13.58	5.23	4.52		53.33	45.09		55.50	51.23	
diazepam	40.25	17.15	0.45	85.00	75.05	8.50	7.51	<**0.001**	85.00	75.06	0.26	76.50	109.69	0.19
etizolam	37.25	10.21		29.50	24.17	–	–		–	–		44.00	27.71	
BZDs hypnotics														
lormetazepam	47.05	11.90		65.45	67.66	**65.45**	67.66		338.35	29.12		75.54	68.15	
triazolam	39	–		5	–	20	–		100	–		8	–	
temazepam	48.00	–		13.00	–	–	–		1	–		72.00	–	

BZDs: benzodiazepines.

Both anxiolytic and hypnotic BZDs seemed to be used mainly by patients with intermediate education. This finding can be explained by the fact that the sample under study mainly included subjects having a medium–high level of education.

Finally, lormetazepam had a higher DDD than lorazepam. The result is consistent with the literature [11] and, as already suggested [18], some features may make lormetazepam long-term use easier than that of other BDZs (i.e., high therapeutic index, formulation in drops having a 95% concentration of alcohol) [18].

Some limitations should be taken into account: (a) psychiatric diagnoses were formulated without a diagnostic tool, due to the use of routine data; (b) even though the sample was large, subgrouping according to the BZD type resulted in relatively small subgroups. Thus, we could infer a pattern of use only for the more largely used BZDs. However, in spite of the small subgroups, the presence of statistically significant results underlines the strength of the results.

On the basis of the present findings, some recommendations could be argued both in research and in clinical practice. From the research point of view, studies evaluating factors identifying subjects at risk to become long-term BZD users and replication studies are warranted. In addition, studies evaluating hypnotic and anxiolytic BZDs separately, and, when possible, each BZD per se, are needed. From a clinical point of view, BZDs should be prescribed on the basis of their pharmacokinetic and pharmacodynamic profiles, not being all the same [14]. In addition, cognitive behavioral therapy [3] should be considered as alternative treatment for those at risk of becoming long-term users. Finally, pros and cons of BZDs recommendation should be balanced under the light of behavioral toxicity and iatrogenic comorbidity [42–48]. Indeed, a drug within its dose range may produce alterations in mood, perceptual, cognitive, and psychomotor functions that can limit the capacity of the individual or constitute a hazard to his/her well-being (i.e., behavioral toxicity) [42–44,46]; in addition, a drug treatment can modify the course, characteristics, and responsiveness of the illness for which it was administered (i.e., iatrogenic comorbidity) [45–48].

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