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ORIGINAL ARTICLE

Dependence on hypnotics: a comparative study between chronic users of benzodiazepines and Z-drugs

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Objective: To evaluate dependence among chronic benzodiazepine and Z-drug users in Brazil.
Methods: Chronic users of benzodiazepines (n=94), Z-drugs (n=74), or both (n=11) were recruited from the community, underwent a psychiatric evaluation and completed self-report instruments on hypnotic dependence, insomnia, anxiety, and depression. Users of benzodiazepines and Z-drugs were compared using *t*-tests, and logistic regression models were employed to explore significant predictors of a dependence diagnosis.
Results: There was no difference in the prevalence of dependence among benzodiazepine (77.2%) and Z-drug (69.4%) users. Benzodiazepine users reported increased psychosocial aspects of dependence, anxiety, and depression. Preoccupation with the availability of medication (prevalence ratio [PR] = 2.39 [1.15-5.20]) and insomnia (PR = 1.10 [1.02-1.19]) were associated with a diagnosis of dependence (n=175).
Conclusion: The prevalence of dependence was similar among both drug classes. The increased self-reported dependence, anxiety, and depression among benzodiazepine users may be due to behavioral rather than pharmacological aspects of medication use. Behaviors related to hypnotic use were important predictors of dependence.

Keywords: Benzodiazepines; Z-drugs; hypnotics and sedatives; substance-related disorders; insomnia

Introduction

Benzodiazepines (BZDs), such as clonazepam, diazepam, and alprazolam, and Z-drugs (zolpidem, zopiclone, zaleplon, and eszopiclone) are psychotropic medications recommended for the short-term (maximum duration of 4 weeks[1]) management of anxiety and insomnia.[2,3] BZDs were introduced in the 1960s and represented an evolution of barbiturates, although worries about their side effects led to the development of Z-drugs in the late 1980s. A study evaluating the growth in hypnotic prescriptions between 1993 and 2007 found a seven-fold increase in the number of BZD prescriptions and a 30-fold increase in Z-drug prescriprtions.[4] A more recent study found a slightly decreasing trend for most hypnotic and anxiolytic drugs, except clonazepam and zolpidem.[5]

BZD and Z-drugs induce sleep by binding to subtype A of γ-aminobutyric acid receptors. However, Z-drugs show an increased selectivity for α_1 subunits, which are responsible for the hypnotic/sedative effects. Due to this more specific pharmacological profile and shorter half-life, it was hypothesized that Z-drugs would not cause the undesired side effects associated with BZD, such as the impairment of daytime activities due to dizziness and fatigue and the development of dependence.[2]

The initial evidence concerning the abuse and dependence potential of Z-drugs consisted of case reports involving high doses and individuals from at-risk populations for developing prescription drug dependence, such as users of alcohol and other drugs, and those with a history of somatic and psychiatric conditions. However, similar reports began appearing with respect to healthy individuals.[6,7] Subsequent studies have reported similarities between the drug classes regarding safety, effectiveness and cost-benefit ratio.[8,9]

An analysis of large-scale reports of adverse drug reactions related to Z-drugs by European pharmacovigilance agencies provided evidence of misuse, abuse, dependence, and withdrawal symptoms. The authors argued that the existing data may be an underestimation of the actual prevalence, since they are based on spontaneous reports, in addition to the fact that believing Z-drugs are safer alternatives may have prevented professionals from sending these reports.[10] Long-term use of BZD and Z-drugs can cause cognitive and psychomotor deficits that increase the risk of falls, fractures, traffic

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accidents, mortality, abuse, and dependence – among users of both high and therapeutic doses.[11,12] In addition to the existing literature, it is necessary to assess the dependence of both classes of drugs from the perspective of patients.

Historically, the prescription of hypnotics follows a pattern of substitution in which the newly discovered medications replace their predecessors as safer options. There is growing evidence that the side effects of Z-drugs are similar to those of BZDs, despite the belief that Z-drugs are associated with less risk.[2,13] Studies must be conducted to examine the similarities and differences between these two types of drugs to determine whether Z-drugs are safer substitutes for BZDs, especially regarding dependence potential.

This study employed self-report data and psychiatric evaluations to: 1) compare aspects of medication use, dependence, and psychiatric symptoms among users of BZD and Z-drugs, and 2) explore which aspects were associated with a diagnosis of hypnotic dependence. Our initial hypotheses were that the drug classes would not differ in dependence prevalence and would present similar characteristics regarding all evaluated aspects.

Methods

Study design

An observational cross-sectional study was conducted at the Drug Dependence Unit of the Universidade Federal de São Paulo (UNIFESP), São Paulo, Brazil. Data collection took place between July, 2017 and January, 2018.

Participants

Our sample included 179 chronic hypnotic users, who were recruited through social media, flyers, posters and other media, as well as through referrals from health professionals. The advertisements invited chronic users to learn more about their hypnotic consumption, undergo a psychiatric evaluation regarding the use of sleep aids, and participate in a meditation course aimed at decreasing insomnia symptoms. The inclusion criteria were: age 18 years or older; literacy in spoken and written Portuguese; having used BZD or Z-drugs for at least 90 days with a minimum frequency of once a week.[14]

Procedures

Screening

Individuals interested in participating were instructed to contact the research team and undergo a brief phone screening to determine whether they met the inclusion criteria. From those who did, we gathered information on the medication used, dosage, and frequency, and we scheduled an in-person psychiatric evaluation.

Psychiatric evaluation

After the phone screening, the participants underwent a psychiatric evaluation based on ICD-10 criteria for mental and behavioral disorders due to use of sedatives and hypnotics – dependence syndrome (F13.2). Psychiatric symptoms, medical supervision, and the participant's history of past sleep/anxiety medication use were also assessed.

Data collection

Self-report instruments were administered individually after the psychiatric evaluation, either through an online platform (RedCap) or with paper and pen, according to the participant's preference. Completion of all questionnaires was supervised by the main researcher and took approximately 30 minutes.

As an added bonus, free participation in a mindfulness-based relapse prevention course was offered. The program included meditation practice, discussion, and psycho-educational elements about hypnotic use[15] in 8 weekly, 2-hour sessions. This protocol was found to reduce insomnia severity in a recent randomized clinical trial we conducted.[16]

Measures

All participants completed the instruments described below.

Sociodemographics

Data on age, sex, monthly income, years of education, and marital status were collected.

Characterization of medication use

General usage characteristics, such as medication type, dosage, weekly frequency, duration of use, whether taken by prescription (if so, the medical specialty of the main prescriber was determined), and details of medical supervision. Defined daily dose (DDD) was employed as a standardized measure of hypnotic amount consumed per day. DDD represents the average dose that must be consumed per day for the drug to maintain its therapeutic effects.[17]

Benzodiazepine Dependence Self Report Questionnaire – Portuguese Version (BENDEP-SRQ PV)

This scale includes 20 items expressing the domains of 1) to what extent the respondent perceives their "problematic use" of hypnotics (α = 0.70); 2) "preoccupation" with obtaining the medication (α = 0.77); "lack of compliance" with the prescribed therapeutic regimen (α = 0.75); 4) the degree of distress caused by "withdrawal" symptoms (only those who had tried to reduce their use completed this section) (α = 0.84).[14,18]

Insomnia Severity Index (ISI)

This instrument contains seven items that evaluate difficulty in initiating and maintaining sleep, problems with early awakenings, sleep pattern satisfaction, interference in daily activities, self-perception of the distress caused by insomnia and the extent that others perceive the impact of insomnia on the respondent's quality of life. Each item is scored using a five-point Likert scale, with a higher score indicating more severe insomnia (α = 0.85).[19]

Center for Epidemiologic Studies Depression Scale (CES-D)

This scale consists of 20 items measured on a four-point Likert scale. Respondents indicate the frequency of depressive symptoms experienced in the week prior to the assessment (α = 0.92).[20]

State-Trait Anxiety Inventory – Trait subscale (STAI-T)

This instrument includes 20 items measured on a four-point Likert scale, with the participants responding to statements about how they generally feel regarding a number of anxiety symptoms (α = 0.92).[21]

Data analysis

Analyses were performed in R version 4.0.3, considering a significance level of 5%. The sample was divided according to drug type (BZD [n=94] or Z-drug [n=74]; users of both drugs [n=11] were not included) and dependence diagnosis (dependent [n=130] or non-dependent [n=45] based on the psychiatric evaluation and regardless of drug type; data was missing for four participants, and they were excluded from this analysis). The descriptive analyses were performed for the total sample, and the aforementioned groups were compared using independent *t*-tests (quantitative variables) and chi-square tests (categorical variables). Continuous variables were standardized with Z-scores, since normality could not be assumed.

To compare aspects of use and dependence among users of BZD and Z-drugs, *t*-tests were conducted with the following dependent variables: self-report measures of hypnotic dependence, anxiety, depression, and insomnia (n=168, considering only users of BZD or Z-drugs exclusively). Cohen's d was used as a measure of effect size to compare the groups. G*Power software was used for statistical power calculation. To achieve a power of 80%, with a 5% significance level and two groups of 94 (BZD) and 74 (Z-drugs) participants, a minimum effect size of Cohen's d = 0.44 was required.

Logistic regression models were used to determine which aspects were associated with a diagnosis of dependence (n=175, considering participants with no missing data regarding the ICD-10 criteria for hypnotic dependence). The analytical process was conducted in three steps. First, we used univariate models to assess the association of each self-report measure and hypnotic dependence individually. The same models were then repeated, but the covariates of age, sex, education, income, marital status, current medication, and past BZD use were included.

Sociodemographic variables were added to the multivariate models to adjust for confounding factors, due to their influence on hypnotics use and dependence, as demonstrated in previous studies. Female sex and age close to menopause are associated with insomnia and the increased use of hypnotics,[22] while current marriage and greater social support are protective factors.[23] Income was included because it is known to impact access to medication and health care services. Current medication type was a main variable of interest and was added to control for the particular characteristics of each drug class. In addition, prior BZD use was added because our sample included Z-drug users who switched from BZD after Z-drugs were introduced into the market.[2]

To find a parsimonious model with good fit and discriminative potential, all predictors and control variables were simultaneously entered into a single model, and significant predictors were selected using a stepwise algorithm with backward elimination. Model fit was evaluated with the Hosmer-Lemeshow test and area under the receiver operating characteristics curve plots.

Ethics statement

All procedures were approved by the UNIFESP research ethics committee (protocol 2.423.738). Written consent was obtained from all participants.

Results

Descriptive statistics

Sociodemographic and hypnotic usage data are shown in Tables 1 and 2, respectively, for the total sample, according to drug type, and according to diagnosis of dependence. No differences were found in these characteristics between dependent and non-dependent participants. Compared to the Z-drug group, BZD users were more frequently widowed, had lower incomes (Table 1), and consumed hypnotics for longer periods at lower doses (Table 2).

The reported BZDs included clonazepam (n=64), alprazolam (n=26), lorazepam (n=8), diazepam (n=4), bromazepam (n=3), estazolam (n=1), clobazam (n=1), cloxazolam (n=1), flurazepam (n=1), and chlordiazepoxide (n=1). The reported Z-drugs included zolpidem (n=84) and zopiclone (n=1). Use of only one medication was reported by 167 (93.3 %) participants; 11 (6.1%) participants took two hypnotics concomitantly, and one (0.6%) participant reported the simultaneous use of three drugs.

Prevalence of dependence

The participants were divided into three groups according to the drug type they were using at the time of data collection: 94 (52.5%) used only BZDs, 74 (41.3%) used only Z-drugs, and 11 (6.2%) used both classes of drugs simultaneously. The percentage of participants diagnosed as dependent (according to the ICD-10 criteria) and the 95% confidence interval (95%CI) regarding the prevalence of dependence were calculated. Among BZD users the dependence prevalence was 77.2% (95%CI 67.2-85.3), among Z-drug users it was 69.4% (95%CI 57.5-79.8), and for users of both drugs it was 81.8% (95%CI 48.2-97.7). The difference in dependence prevalence among the groups was not significant ($\chi^{2}_{[2]}$ = 1.61, p = 0.447).

Table 1 Sociodemographic characteristics of the total sample according to drug type and ICD-10 diagnosis of dependence based on the psychiatric evaluation

		Drug type[†]			Dependence[‡]		
	Total (n=179)	BZD (n=94)	Z-drug (n=74)	Test statistic, p-value	Yes (n=130)	No (n=45)	Test statistic, p-value
Age, median (IQR) Missing = 0	54 (19.5)	54 (18.8)	54 (20.8)	t = 0.54, 0.593	54 (19.5)	51 (20)	t = 0.52, 0.604
Gender (female) Missing = 1	164 (91.6)	86 (91.5)	69 (93.2)	χ^2 = 0.18, 0.673	121 (93.1)	39 (86.7)	χ^2 = 1.75, 0.186
Marital status				χ^2 = 8.43, 0.038*			χ^2 = 4.78, 0.188
Single	52 (29.0)	26 (27.7)	22 (29.7)		36 (27.7)	16 (35.6)	
Married	76 (42.5)	37 (39.4)	34 (46.0)		52 (40.0)	22 (48.9)	
Separated/divorced	40 (22.4)	21 (22.3)	18 (24.3)		33 (25.4)	5 (11.1)	
Widowed	11 (6.1)	10 (10.6)	0 (0)		9 (6.9)	2 (4.4)	
Missing = 0							
Schooling				χ^2 = 9.00, 0.174			χ^2 = 3.75, 0.711
Incomplete primary education	10 (5.6)	7 (7.5)	3 (4.1)		7 (5.4)	2 (4.4)	
Primary education	9 (5.0)	7 (7.5)	2 (2.7)		7 (5.4)	1 (2.2)	
Incomplete secondary education	5 (2.8)	2 (2.1)	1 (1.4)		5 (3.9)	0 (0)	
Secondary education	33 (18.5)	21 (22.3)	9 (12.2)		24 (18.5)	9 (20.0)	
Incomplete higher education	21 (11.7)	13 (13.8)	8 (10.8)		17 (13.1)	4 (8.9)	
Higher education	57 (31.8)	25 (26.6)	28 (37.8)		40 (30.8)	16 (35.6)	
Graduate school	44 (24.6)	19 (20.2)	23 (31.1)		30 (23.1)	13 (28.9)	
Missing = 0							
Monthly income[§]				χ^2 = 12.23, 0.032*			χ^2 = 5.83, 0.323
0-1	18 (10.3)	13 (14.13)	4 (5.63)		11 (8.73)	7 (15.91)	
1-6	84 (48.3)	50 (54.35)	28 (39.44)		66 (52.38)	16 (36.36)	
6-10	28 (16.1)	14 (15.22)	13 (18.31)		19 (15.08)	8 (18.18)	
10-15	20 (11.5)	7 (7.61)	10 (14.08)		12 (9.52)	8 (18.18)	
15 +	20 (11.5)	6 (6.52)	14 (19.72)		15 (11.9)	4 (9.09)	
Unknown	4 (2.3)	2 (2.17)	2 (2.82)		3 (2.38)	1 (2.27)	
Missing = 5							

Data presented as n (%), unless otherwise specified.
IQR = interquartile range.
[†] Incudes only participants who were exclusive users of benzodiazepines (BZDs) or Z-drugs. Users of both drug classes simultaneously were not included in this analysis.
[‡] Includes participants with no missing data on the ICD-10 diagnosis of dependence, regardless of type of drug.
[§] Calculated in multiples of the Brazilian minimum monthly salary.
* $p < 0.05$.

Comparison between users of BZDs and Z-drugs

Participants who used both classes of drug simultaneously were not included in the analysis (n=11).

As shown in Table 3, compared to Z-drug users, BZD users had significantly higher scores on the BENDEP-SRQ PV domains of problematic use, preoccupation, and lack of compliance, as well as anxiety and depression. The groups were equivalent in terms of withdrawal symptoms and insomnia.

Comparison between patients diagnosed as dependent or not according to the ICD-10

Participants were divided into two groups: those who were diagnosed as dependent (n=130) or non-dependent (n=45) according to ICD-10 criteria in the psychiatric evaluation, regardless of drug type. Logistic regression models were used to determine significant predictors of dependence.

The dependence variable was binary: a diagnosis of dependence corresponded to a positive response. In the univariate logistic regression models that predicted dependence, significant associations were found with problematic use, preoccupation, lack of compliance, insomnia, and depression (Table 4). All of these variables were associated with a higher chance of being diagnosed as dependent.

When running the stepwise algorithm to find a multivariate logistic regression model that best predicted dependence according to the ICD-10, all predictors and control variables were entered and eliminated backwards. This model included the variables preoccupation (prevalence ratio [PR] = 2.39 [1.15-5.20]), insomnia (PR = 1.10 [1.02-1.19]), and all covariates. Model fit was confirmed with the Hosmer-Lemeshow test with division in 10 groups ($\chi^{2[8]}$ = 7.89, p = 0.444) (Table 4). Receiver operating characteristics analysis was performed to assess the overall accuracy in discriminating dependent from non-dependent users. Both predictors (insomnia and preoccupation) and the covariates were included. An area

Table 2 General hypnotic consumption characteristics of the total sample according to drug type and ICD-10 diagnosis of dependence based on the psychiatric evaluation

		Drug type[†]			Dependence[‡]		
	Total (n=179)	BZD (n=94)	Z-drug (n=74)	Test statistic, p-value	Yes (n=130)	No (n=45)	Test statistic, p-value
Duration of use (months), median (IQR) Missing = 4	12 (43.0)	16 (55.0)	7 (20.0)	t = -3.34, 0.001*	12 (43)	10 (43)	t = -1.66, 0.099
Age of use onset, median (IQR) Missing = 6	42 (23.0)	41 (23.0)	40 (22.5)	t = -0.24, 0.812	43 (23)	40 (22)	t = -0.48, 0.632
Duration of past use (months), median (IQR)[§] Missing = 2	30 (78.0)	33 (88.0)	30 (57.0)	t = -0.47, 0.637	33 (63)	24 (110)	t = 0.63, 0.532
Defined daily dose, median (IQR) Missing = 1	0.5 (0.8)	0.3 (0.4)	1 (0.5)	t = 6.22, $<$ 0.001*	0.5 (0.8)	0.5 (0.8)	t = -1.67, 0.097
How the medication is obtained							
Public health service	31 (17.4)	23 (24.5)	6 (8.2)	χ^2 = 7.82, 0.05	23 (17.8)	8 (17.8)	χ^2 = 0.30, 0.961
Private practice	112 (62.9)	53 (56.4)	51 (69.9)		81 (62.8)	27 (60.0)	
Hospital	12 (6.8)	7 (7.5)	5 (6.8)		9 (7.0)	3 (6.7)	
No medical supervision	23 (12.9)	11 (11.7)	11 (15.1)		16 (12.4)	7 (15.6)	
Missing = 1							
Doctor evaluates consumption of sleep medication (Yes)[‖] Missing = 3	104 (59.1)	50 (55.0)	48 (64.9)	χ^2 = 1.67, 0.197	73 (57.0)	28 (63.4)	χ^2 = 0.59, 0.443
Doctor evaluates sleep (Yes)[¶] Missing = 3	99 (56.3)	51 (56.0)	41 (55.4)	χ^2 = 0.007, 0.935	68 (53.1)	28 (63.6)	χ^2 =1.47, 0.226

Data presented as n (%), unless otherwise specified.
IQR = interquartile range.
[†] Incudes only participants who were exclusive users of benzodiazepines (BZDs) or Z-drugs. Users of both drug classes simultaneously were not included in this analysis.
[‡] Includes participants with no missing data on the ICD-10 diagnosis of dependence, regardless of type of drug.
[§] n=65 participants reported previous hypnotic use in the total sample.
[‖] Participants were asked whether the doctor who prescribed the hypnotics conducted an evaluation of the effectiveness of the sleep aid or only renewed a previously issued prescription.
[¶] Participants were asked whether the doctor who prescribed the hypnotics conducted an evaluation of the participant's sleep quality or only renewed a previously issued prescription.
* $p < 0.05$.

Table 3 *t*-tests comparing standardized scores on self-report measures for the group of users of BZD and Z-drugs (n=168)

Self-report measure	BZD (n=94)	Z-drugs (n=74)	*t*-test	p-value	Cohen's *d*
Problematic use (BENDEP-SRQ PV)	0.17 (0.85)	-0.25 (0.76)	-3.39	< 0.001*	0.53
Preoccupation (BENDEP-SRQ PV)	0.12 (0.65)	-0.18 (0.64)	-3.03	0.003*	0.47
Lack of compliance (BENDEP-SRQ PV)	0.13 (0.82)	-0.22 (0.65)	-3.07	0.003*	0.47
Withdrawal (BENDEP-SRQ PV)	0.17 (1.39)	-0.17 (1.17)	-1.74	0.083	0.27
Insomnia (ISI)	0.05 (1.02)	-0.09 (0.97)	-0.88	0.377	0.13
Anxiety (STAI-T)	0.19 (1.05)	-0.26 (0.90)	-2.91	0.004*	0.45
Depression (CES-D)	0.20 (1.03)	-0.26 (0.95)	-2.99	0.003*	0.47

Data presented as mean (standard deviation).
BENDEP-SRQ PV = subscales of the Benzodiazepine Dependence Self Report Questionnaire – Portuguese Version (total scores on the scales); BZD = benzodiazepine; CES-D = Center for Epidemiologic Studies Depression Scale; ISI = Insomnia Severity Index; STAI-T = State-Trait Anxiety Inventory – Trait subscale.
* $p < 0.05$.

Table 4 Logistic regression models predicting whether a participant would belong to the dependent (n=130) or non-dependent group (n=45) according to ICD-10 criteria

	Crude models			Adjusted models†			Stepwise†		
Variable	PR	95%CI	p-value	PR	95%CI	p-value	PR	95%CI	p-value
Problematic use (BENDEP-SRQ PV)	1.85	1.19-2.98	0.009*	2.37	1.34-4.39	0.004*			
Preoccupation (BENDEP-SRQ PV)	2.19	1.26-3.98	0.007*	2.61	1.33-5.41	0.007*	2.39	1.15-5.20	0.023*
Lack of compliance (BENDEP-SRQ PV)	2.01	1.20-3.62	0.013*	2.35	1.27-4.72	0.010*			
Withdrawal (BENDEP-SRQ PV)	1.17	0.90-1.52	0.252	1.16	0.85-1.59	0.339			
Insomnia (ISI)	1.08	1.02-1.14	0.009*	1.11	1.03-1.20	0.005*	1.10	1.02-1.19	0.017*
Anxiety (STAI-T)	1.02	0.99-1.06	0.102	1,03	0.99-1.07	0.081			
Depression (CES-D)	1.04	1.00-1.07	0.030*	1,05	1.00-1.10	0.031*			

95%CI = 95% confidence interval; BENDEP-SRQ PV = subscales of the Benzodiazepine Dependence Self Report Questionnaire – Portuguese Version (total scores on the scales); CES-D = Center for Epidemiologic Studies Depression Scale; ISI = Insomnia Severity Index; PR = prevalence ratio; STAI-T = State-Trait Anxiety Inventory – Trait subscale.
† Adjusted for age, sex, education, income, marital status, current medication use and prior benzodiazepine (BZD) use (reference group = non-dependent).
* $p < 0.05$.

under the curve value of 0.78 was found, indicating acceptable accuracy at discriminating the groups.

Discussion

The main findings of this study are: 1) there was no significant difference in the prevalence of dependence between the BZD and Z-drug groups; 2) compared to Z-drug users, BZD users had a longer duration of medication use, higher scores regarding problematic use, preoccupation about the unavailability of medication, lower treatment compliance, higher anxiety and depression, and used lower doses; and 3) greater preoccupation about the unavailability of medication and insomnia severity were significant predictors of a diagnosis of dependence.

Based on the long duration of use (34.8 months), the percentage of participants who report medical supervision (87.1) and a mean DDD value < 1 (the minimum recommended to maintain the therapeutic effects), the majority of our sample consisted of low-dose dependent users.[24] Regarding medical supervision and repeat prescriptions, just over half of the patients reported that their doctor assessed their sleep or medication use, with the remainder simply renewing the prescription. This is consistent with studies showing that prescriptions are often provided without direct contact between the doctor and patient[25,26] and it supports the notion that hypnotics are not always properly prescribed.[27]

That the prevalence of dependence did not differ between the groups is in accordance with the literature, which has shown that BZDs and Z-drugs produce similar levels of dependence.[6,28] No significant difference was found in insomnia severity between the groups. Despite being long-term users of sleep aids, our sample still had insomnia symptoms, which corroborates evidence about tolerance in both classes of drugs.[29,30]

Although the prevalence of dependence according to ICD-10 criteria did not differ between groups, BZD users had higher scores for all BENDEP-SRQ PV measures of the psychosocial aspects of dependence: problematic use, preoccupation, and lack of treatment compliance. Although hypnotic users often do not perceive themselves as dependent,[31] they might acknowledge dependence-related behaviors when they are presented as questionnaire items.[18] The lack of awareness reported by Z-drug users could be due to general practitioners and pharmacists being more favorable towards the safety and efficacy of Z-drugs, beliefs that are not based on current evidence and guidelines.[32-34] In addition, BZDs and Z-drugs are not subject to the same type of prescription control; the rules for BZDs are stricter and more explicit regarding the risk of dependence.[35]

The BENDEP-SRQ PV withdrawal domain represents how distressed respondents felt by withdrawal symptoms at any time when they tried to reduce their medication use. No differences were found in withdrawal symptoms between the drug classes. Similarly, a patient perspective

study[28] and a controlled trial comparing aspects of withdrawal between both drug classes[36] found no differences in the prevalence of withdrawal symptoms.

The BZD group had been using hypnotics for more months than the Z-drug group, which is consistent with the fact that BZD were released onto the market in the 1960s 13] and Z-drugs were introduced only in the 1990s.[8] Having been available for much longer, it could be expected that the duration of BZD use would be longer. The current sample includes patients who have been using BZD for over 40 years, and the majority of this period was before Z-drugs were introduced into the market. The longest treatment duration for Z-drugs in our sample was 12 years. This pattern has also been found in previous studies.[37,38] Longer treatment[39,40] is related to decreased compliance, which explains why BZD users scored higher in the BENDEP-SRQ PV lack of compliance domain.

The median DDD consumed by users of Z-drugs was 1, whereas BZD users consumed significantly lower doses. DDD can be understood as the average dose per day required to maintain a drug's therapeutic effects for its primary indication in adults.[17] Prescription guidelines for both classes of drugs state that the lowest possible effective dose should be prescribed,[1,41] which means that BZD users were closer to an "ideal" situation. A study assessing the consumption of BZD and Z-drugs from 2001 to 2016 in Manitoba, Canada found that Z-drug consumption, intensity, prevalence and pharmacological exposure increased, whereas BZD increased only in intensity, with a reduction in prevalence.[42] This illustrates the widespread use of higher doses of Z-drugs than BZDs.

BZD users reported more depression and anxiety than Z-drug users. In a bidirectional manner, studies have shown that depressive symptoms are a risk factor for chronic BZD use,[43] which, in turn, is associated with worsening depression.[41]

The finding that anxiety is increased among BZD users agrees with their expected pharmacological effects, which are anxiolytic and hypnotic. However, Z-drugs only have sleep-related effects. The presence of anxiety symptoms in BZD users can be taken as evidence of tolerance. The first-line pharmacological treatment for anxiety is serotonergic agents. Since their effects can be delayed, it is common practice in clinics to initially prescribe a BZD for quick symptom relief until the serotonergic agent takes effect (although this does not comply with the prescription guidelines). Nevertheless, the use of BZD often continues while the antidepressant does not,[41,44] increasing the duration of untreated illness.[45]

A greater concern with medication availability and greater insomnia severity increased the chance of being diagnosed with dependence. However, this model had low discriminatory potential. Important characteristics of insomnia could be responsible for our results. Studies on barriers and facilitators of hypnotic discontinuation highlight the impact of insomnia on quality of life[46] and the fear of recurrent symptoms.[31]

Another factor to consider is that insomnia is a cyclic disorder. Ong et al.[47] proposed a metacognitive model of insomnia in which the disorder is promoted and perpetuated by components called primary and secondary arousal. Primary arousal reflects cognition directly related to the inability to sleep, such as thoughts and beliefs about lack of sleep. Secondary arousal, on the other hand, refers to the emotional valence attributed to the primary cognitions, which can significantly increase attentional bias. Without adequate cognitive flexibility to deal with these thoughts, they become aggravating factors, perpetuating the vicious cycle of insomnia.[47]

A relationship was found between preoccupation with drug availability and dependence, ie, the greater this preoccupation, the greater the probability that the participant would be diagnosed as dependent. The items in the preoccupation domain reflect behavioral aspects of dependence and craving, which manifests itself as anxiety about having the medication at hand or having the next dose available.[3] Thus, our results indicate behaviors that can guide clinical conduct: carrying tablets, the need to have them close by or constantly thinking about them can be viewed as a warning that measures against dependence must be taken.

The fact that dependence was predicted by insomnia severity and preoccupation is in accordance with the way users perceived themselves as dependent through withdrawal symptoms (mainly rebound insomnia) and anticipating a lack of medication.[31] Withdrawal was not a predictor of dependence, either independently or in the multivariate model. Although this result does not diminish the importance of withdrawal as a sign of dependence, our model points to important psychological components that must be observed, which do not derive from the physical character of dependence, but from observing behavior associated with hypnotic use.

This study compared two classes of widely used hypnotics, BZDs and Z-drugs. The high rates of prolonged use for both of these drugs indicate that their use is an important public health problem.[4]

The study has some limitations; the relatively small sample size means that the prevalence ratio values produced in the logistic regression analyses, which were very close to 1 and considered statistically significant, should be interpreted with caution. Due to the cross-sectional design, causality may not be implied in the relationships presented. The sample size also prevented a comparison of specific aspects of dependence for each drug. In addition, dependence was not diagnosed through structured interviews, despite being based on the ICD-10 criteria, and we were unable to control the logistic regression models for previous psychiatric diagnoses and symptoms.

A possible selection bias may have occurred due to the recruitment method, which included a free mindfulness-based intervention. This could have selectively attracted people more motivated to stop using hypnotics, which would hamper the generalizability of our findings to other types of users. Regarding the homogeneity of the sample, all the participants were classified as low-dose dependent users, with none reporting abuse and few using more than one therapeutic dose per day.

The present study stimulates further research into non-pharmacological and pharmacological alternatives for

long-term insomnia treatment. Regarding the comparison between BZDs and Z-drugs, further studies could assess use and dependence in large Brazilian population samples. Particularly regarding Z-drugs, it is important to disseminate information based on the current scientific evidence to dispel the erroneous beliefs of patients and health professionals and, from a broader perspective, to direct legislation about the control of BZDs and Z-drugs.[35] It is important that future studies include other groups of hypnotics users, such as abusers or people who take them during treatment for alcohol use disorders.

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Disclosure

The authors report no conflicts of interest.

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