Benzodiazepine Use in an Opioid Maintenance Program in Portugal: Risks and Clinical Outcomes

Uso de Benzodiazepinas em Programa de Manutenção Opióide em Portugal: Riscos e Características Clínicas

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ABSTRACT

Introduction: The co-association of benzodiazepines and opioids is associated with an increased risk of overdose, death, and poorer psychosocial prognosis. The aim of this study is to characterize the prevalence, pattern of use, and primary clinical outcomes in benzodiazepines users in a public opioid maintenance treatment unit.

Material and Methods: We conducted a cross-sectional study involving 236 patients treated with opioid substitutes (methadone and buprenorphine). We conducted a descriptive, bivariable, and multivariable analysis to determine clinical differences between benzodiazepines users and non-users.

Results: The prevalence of consumption of benzodiazepines was 25.4% (60). The benzodiazepines were obtained with a medical prescription (49.8%) or on the black market (42.6%). The most prescribed benzodiazepine was diazepam (29.1%), and the main reasons were to relieve insomnia (27.7%) or anxiety (26.9%) and to enhance the psychoactive effects of other drugs (19.7%). Regarding the clinical outcomes, we highlight: a very high prevalence of hepatitis C (51.7%); severe ongoing consumption of psychoactive drugs (73.7%); and a high rate of depression and anxiety (> 60%), significantly higher in the benzodiazepines-user group. In the multivariable analysis of benzodiazepine use, we found alcohol consumption (OR 0.482; IC 95% 0.247, 0.238) had a negative association and having hepatitis C (OR 2.544, IC 95% 1.273, 5.084) or anxiety symptoms (OR 5.591; IC 95% 2.345, 13.326) had positive associations.

Discussion: Our results suggest the BZD users had a complex drug addiction problem and underline the importance of adequately addressing BZD use, contemplating psychological and psychiatric approach in this particular population.

Conclusion: Past or current use of benzodiazepines is associated with poor clinical and psychiatric outcomes. A multidisciplinary approach with a focus on infectious diseases and mental health is critical in order to enhance the treatment effectiveness and overall prognosis.

Keywords: Benzodiazepines; Buprenorphine; Methadone; Opiate Substitution Treatment

RESUMO

Introdução: A co-associação entre benzodiazepinas e opióides associa-se a risco aumentado de *overdose*, morte e pior prognóstico psicossocial. Pretendemos determinar a prevalência, o padrão de consumo e as principais co-morbilidades do uso de benzodiazepinas, em utentes sob tratamento de manutenção opióide.

Material e Métodos: Conduzimos um estudo transversal, envolvendo 236 doentes tratados com substitutos opióides (metadona e buprenorfina). Realizou-se uma análise descritiva, bivariável e multivariável das características clínicas entre os usuários de benzodiazepinas e os não-usuários de benzodiazepinas.

Resultados: A prevalência do uso de benzodiazepinas foi de 25,4% (60). A obtenção de benzodiazepinas foi através de prescrição médica (49,8%) ou mercado negro (42,6%). A substância mais prescrita foi o diazepam (29,1%), e as principais razões para a toma foi insónia (27,7%), ansiedade (26,9%), e para potenciar os efeitos psicoativos de outras drogas (19,7%). No que respeita aos resultados clínicos sublinhamos: prevalência elevada de hepatite C (51,7%); elevado consumo continuado de substâncias psicoativas (73,7%); elevada taxa de depressão e ansiedade (> 60%), significativamente mais elevada nos utilizadores de benzodiazepinas. Na análise multivariável para o uso de benzodiazepinas, verificámos que o consumo de álcool (OR 0,482; IC 95% 0,247, 0,238) tem associação negativa; a hepatite C (OR 2,544; IC 95% 1,273, 5,084) e a ansiedade (OR 5,591; IC 95% 2,345, 13,326) tiveram associações positivas.

Discussão: Os resultados obtidos sugerem que os utilizadores de BZD têm um problema complexo de dependência de drogas e sublinham a importância de abordar adequadamente o uso de BZD, contemplando uma abordagem psicológica e psiquiátrica nesta população em particular.

Conclusão: O uso de benzodiazepinas, no passado ou atualmente, associa-se a piores indicadores físicos e psiquiátricos. A abordagem multidisciplinar com foco nas doenças infeciosas e na saúde mental é uma necessidade crítica para a efetividade do tratamento e prognóstico global.

Palavras-chave: Benzodiazepinas; Buprenorfina; Metadona; Tratamento de Substituição de Opiáceos

INTRODUCTION

Benzodiazepines (BZD) were introduced into clinical medicine in the early 1960s, and since then they have been used to treat many conditions, including insomnia, anxiety disorders, alcohol dependence, and epilepsy.[1] Buprenorphine (BUP) and methadone (MET) are effective options used in opioid maintenance treatment (OMT) for opioid

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abstinence and treating opioid dependence.[2,3] The practice of prescribing BZD to OMT patients is causing concern, since the combination of opioids with BZD is significantly associated with overdose death,[3] higher risk behaviours, and drug-related harm, such as using high doses of drugs, needle sharing, and intoxication-related accidents.[3-6] The prevalence of BZD use in OMT patients is not well established, and it is described between 13% and 47%.[4,7,8] The higher risk behaviours associated with opioid and BZD co-consumption seem to translate into many physical and psychological health problems, including a higher risk of human immunodeficiency virus (HIV) infection, psychopathology, and poorer treatment and social outcomes.[9-12] According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), this topic should be addressed seriously due to the potential risks to both the individual and public health.[13]

Historically, in the 1980s – 1990s, Portugal faced an opioid crisis, with high rates of drug-related deaths and HIV infection rates. To combat this public health emergency, Portugal decriminalized the possession of all drugs for personal use in 2001, and shifted towards a more healthcare-centred approach to drug use, as well as broader health and social policy changes.[14] Notably, Portugal coupled its decriminalization with a public health reorientation that directed additional resources towards treatment and harm reduction.[15] Surprisingly, due to the dramatic success with a massive reduction of HIV infections and drug-related deaths, Portugal has become an international model for drug policy reform.[14,15]

However, new challenges have emerged, as the International Narcotics Control Board and other studies identify Portugal as one of the European countries with the highest rates of BZD consumption in Europe.[16-20] Nonetheless, we did not find any data characterizing BZD use in OMT.

The aim of this study is to characterize the prevalence and consumption pattern of BZD in a public OMT unit and the primary clinical outcomes regarding physical and psychiatric comorbidities in BZD users.

MATERIAL AND METHODS

Study design

We conducted a cross-sectional study. Our sample included patients who attended a public OMT program in a drug addiction treatment unit. In 2018, 496 patients attended this public OMT program. The unit offers medical and psychosocial treatment to patients provided by a multidisciplinary team that includes psychiatrists, general practitioners, psychologists, social workers, and nurses. A psychiatrist or a nurse administers the opioid medication (BUP or MET), and the psychology team monitors adherence.

Entering the study was entirely voluntary, and all the participants provided written informed consent. The inclusion criteria were: individuals 18 years old and over; being enrolled in OMT for at least one month; individuals providing free, informed consent. The exclusion criteria were: participation in the pilot study; being less than 18 years old; being enrolled in the OMT program for less than one month; and 4) individuals declining to participate in this study. A total of 236 participants met the inclusion criteria (47.6%).

Data collection was performed between April and September 2018. The attending psychologist or nurse filled out a questionnaire about BZD during the patients' visit to the unit. The applied questionnaire was structured, replicated, and adapted from the literature, and it was pre-tested randomly in 10 patients attending the public opioid treatment program in the drug addiction treatment unit in order to assess face validity. Minor adjustments were made.

This study was approved by the Ethics Committee of the Regional Health Administration of Lisbon and Tagus Valley (authorization number 11086 / CES / 2017).

Background variables

The questionnaire was divided in four sections and assessed the following variables:

1) Sociodemographic characterization (gender, age, education level, professional status, civil status, living conditions, and forensic background);

2) BZD prevalence and pattern use (route of drug administration, frequency, type, and daily dose of BZD concerning past and current use; the acquiring methods and the main reasons for taking BZD; the evolution of BZD consumption during the OMT program; the subjective perspective about BZD dependence and motivation for stopping BZD use, divided into two levels: a high level of motivation: 'want to stop', 'want to try and will probably succeed', and a low level of motivation: 'don't want to stop', 'could try to stop but will probably fail');

3) Physical factors (prevalence of HIV, hepatitis B, and hepatitis C; overdose episodes; psychoactive drug consumption in the last 30 days);

4) Psychiatric factors (application of a Likert scale (0 – 5: always/very often/sometimes/rarely/never). In order to assess the intensity of depression, suicidal thoughts, anxiety, irritability, and anger symptoms, we considered a low rate of psychiatric symptoms when answering 'rarely/never' and a high rate of psychiatric symptoms when answering 'always/very often/sometimes'.

Statistical analysis

The data obtained from the questionnaire were recorded in a data matrix developed for this purpose in the IBM SPSS Statistics® version 24.0 and analyzed using the features of this program.

The statistical analysis consists of two parts: descriptive analysis and comparative bivariable analysis. In the descriptive analysis, we calculated the binary variables, mean, standard deviation, and minimum and maximum. For the categorical variables, the absolute and relative frequencies were calculated. When the numerical variables did not follow a normal distribution, we used the median.

In the bivariable analysis, for the categorical variables, we used the chi-square test, and when not applicable, we used Fisher's exact test; for the binary variables, we used

the *t*-student test for independent samples or, if not applicable, the Mann–Whitney test. We calculated the *p* - value for the statistical test associated with each independent variable of the study.

We developed cross-tables containing absolute and relative frequencies for categorical variables and the mean and the mean deviation for numerical variables. All the numerical variables followed a normal distribution.

For the binary variables, the magnitude of the association was calculated through the difference of means and the respective 95% confidence interval (CI), while for the categorical variables we calculated the respective 95% CI. All analyses were performed with a significance level of 0.05.

In the multiple regression analysis, we included the variables that, in the bivariate analysis, had statistically significant results (p value < 0.05) and the variables with p values under 0.20. The magnitude of the associations was obtained by calculating the exponential value of the regression coefficients, resulting in the adjusted odds ratios (OR). In order to reach the final value of each adjusted OR for each variable, throughout the multivariate analysis process, the variable with the highest p value was removed each time, obtaining an optimized model with a final table with the variables whose association with the use of BZD was statistically significant (p value < 0.05). For the analysis of the fit quality of the logistic regression model, we used the area under the receiver operator characteristic (ROC) curve.

RESULTS

Sociodemographic characterization: a descriptive analysis

Of the 236 participants, 91.1% (215) were male, with a median age of 47 years (range: 27 – 64 years). Regarding the education level, 67.8% (160) had nine years or less of education. Concerning the professional status, 33.9% (80) were unemployed, 52.5% (124) held a full-time job, 6.4% (15) had a part-time job, and 7.2% (17) were retired.

Regarding the civil and paternity status, 67.4% (159) were not married, and 57.6% (136) had at least one child. The majority (69.9%, 165) of the participants lived with someone (family or friends) and owned a house (50.8%, 120). Regarding the legal background, 66.5% (157) had legal problems in the past, and from that group, 28.4% (67) were convicted and received prison sentences.

The psychiatric diagnoses were coded by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) from the World Health Organization Version for 2016. All the participants had an opioid dependence syndrome (F11.2), and 38.1% (90) had a comorbid psychiatric diagnosis. The most frequent diagnoses were specific personality disorder (F60) (27.8%, 25), other anxiety disorders (F41) (25.6%, 23), and depressive episodes (F32) (22.2%, 20), followed by bipolar affective disorder (F31) (18.9%, 17) and schizophrenia (F20) (5.6%, 5).

Table 1 shows that BZD users and non-users do not differ in relevance regarding sociodemographic characterization.

BZD pattern of use

a) Current BZD users

The prevalence of current BZD consumption was 25.4% (60). Of these, 69.4% (43) used BZD for at least 24 months, and 85.0% (51) took only one BZD type. The types of BZD prescribed were diazepam (29.1%, 23), alprazolam (15.2%, 12), oxazepam (12.6%, 10), ethyl loflazepate (11.4%, 9), clonazepam (10.1%, 8), midazolam (6.3%, 5), lorazepam (5.1%, 4), bromazepam (5.1%, 4), dipotassium clorazepate (2.5%, 2), cloxazolam (1.3%, 1), and flurazepam (1.3%, 1).

Table 1 – Bivariate statistical analysis for sociodemographic characterization

Variable in analysis	Categories of the variable	BZD users	Non-BZD users	Odds ratio (IC 95%)	*p*-value
Age	Mean ± SD Min - max	46.7 ± 6.8 31 - 61	46.8 ± 7.1 27 - 64	0.083 (-1.977, 2.144)	0.937
Gender	Male	54 (90.0%)	161 (91.5%)	1.193 (0.441, 3.228)	0.729
	Female	6 (10.0%)	15 (8.5%)		
Civil status	Not married	46 (76.7%)	113 (64.2%)	0.546 (0.279, 1.070)	0.075
	Married	14 (23.3%)	63 (35.8%)		
Educational level	≤ 9 years	39 (65.0%)	121 (69.9%)	1.253 (0.673, 2.234)	0.477
	> 9 years	21 (35.0%)	52 (30.1%)		
Parental status	No	21 (35.0%)	79 (44.9%)	1.513 (0.823, 2.778)	0.181
	Yes	39 (65.0%)	97 (55.1%)		
Professional status	Not employed	25 (41.7%)	55 (31.3%)	0.639 (0.348, 1.164)	0.141
	Employed/retired	35 (58.3%)	121 (68.8%)		
Legal issues	No	20 (33.3%)	59 (33.5%)	1.009 (0.542, 1.877)	0.979
	Yes	40 (66.7%)	117 (66.5%)		
Convicted to prison sentence	No	42 (70.0%)	127 (72.2%)	1.111 (0.584, 2.113)	0.749
	Yes	18 (30.0%)	49 (27.8%)		

BZD: benzodiazepine

We calculated the mean daily doses of BZD using a conversion table of BZD equivalent doses to diazepam,[20] finding a result of 33.82 mg (S.D. = 51.9) of diazepam per day. In the bivariable analysis, we found a higher average daily dose of MET in the BZD-user group compared with the non-BZD users (79.66 mg *vs* 62.81 mg; *p*-value = 0.047). Although in the BUP patients the BUP doses were slightly higher in the BZD-user group (6.61 mg *vs* 6.13 mg), this difference was not statistically significant (*p*-value = 0.625) (Table 2).

b) History of BZD use

Addressing the previous BZD consumption, 71.2% (168) of the sample admitted having a regular consumption (> 3 times/week) in the past. Of these, the majority, 94.6% (177), used BZD in the oral formulation, 3.2% (6) took BZD by intravenous form, and the remaining 2.2% (4) administered BZD by inhalation.

The selected ways to obtain BZD (209 in total, because more than one option could be selected) were mostly through a medical prescription (49.8%, 104) and from the black market (42.6%, 89), followed by friends/family (7.6%, 16).

The reasons identified for BZD intake (249 in total, because more than one reason could be selected) were because of its hypnotic effect (27.7%, 79), its anxiolytic effect (26.9%, 67), the intention to enhance other psychoactive drugs' effects (19.7%, 49), the intention to reduce hangover symptoms related with other drug abuse (13.3%, 33), medical indication (15.0%, 6), the desire to feel happier (4.4%, 11), and the intention to enhance the MET/BUP effect (2.0%, 5).

By performing a bivariable analysis we found that BZD users with regular BZD use in the past have 5x higher odds to consume BZD currently than those who did not consume BZD in the past ($p < 0.001$) (Table 2).

c) BZD use evolution during the OMT

We found that 69.4% (43) of participants were in a substitution program for at least 24 months. At OMT admission, the prevalence of BZD consumption was 47.9% (113), and at the time of the survey this prevalence was 25.4% (60), which means that 46.9% (53) stopped, 35.4% (40) decreased, 13.3% (15) maintained, and only 4.4% (5) increased BDZ use.

d) Potential BZD dependence risk acknowledgment and evaluation

From the 236 participants, 85.5% (201) acknowledged the potential BZD dependence risk, but only 53.3% (32) of the current regular BZD users consider themselves as having BZD dependency. From the current users (n = 60), 63.3% (38) expressed a high level of motivation to stop the BZD intake, choosing the option 'I want to stop' or 'I want to try and will probably succeed'. The remaining 36.7% (22) marked the option 'I could try to stop but will probably fail' or 'I do not want to stop', expressing a low level of motivation for stopping BZD intake.

Health and risk behavior factors

a) Physical factors

Regarding the information available in the literature, we identified infectious diseases (HIV, hepatitis B, and hepatitis C) and overdose episodes as the main negative physical factors related with BZD intake. In this context, we found the following infectious disease prevalence estimates: hepatitis C: 51.7% (122); HIV: 15.7% (37); and hepatitis B: 8.5% (20). Moreover, 15.8% (35) of individuals had at least two or more of these diseases combined.

In the bivariable analysis, we found that the BZD users had a higher prevalence of hepatitis C when compared with the non-user group (70.0% *vs* 46.2%, $p = 0.001$). The same was not found regarding HIV (20.0% *vs* 14.5%, $p = 0.311$)

Table 2 – Bivariate statistical analysis for BZD pattern use and physical outcomes

Variable in analysis	Categories of the variable	BZD users	Non-BZD users	Odds ratio or difference of means (IC 95%)	*p*-value
Daily dose of BUP (mg)	Mean ± SD Min - max	6.61 ± 3.20 2.0 - 16.0	6.13 ± 3.67 1.5 - 16.0	0.483 (- 1.483, 2.250)	0.625
Daily dose of MET (mg)	< 60	14 (23.3%)	61 (34.7%)	1.743 (0.888, 3.420)	0.111
	> 60	46 (76.7%)	115 (65.3%)		
History of BZD intake	No	6 (10.0%)	62 (35.2%)	4.895 (1.993, 12.019)	< 0.001
	Yes	54 (90.0%)	114 (64.8%)		
HIV	No	48 (80.0%)	148 (85.5%)	1.480 (0.691, 3.169)	0.311
	Yes	12 (20.0%)	25 (14.5%)		
Hepatitis B	No	52 (86.7%)	164 (93.2%)	2.103 (0.815, 5.423)	0.118
	Yes	8 (13.3%)	12 (6.8%)		
Hepatitis C	No	18 (30.0%)	93 (53.8%)	2.713 (1.448, 5.082)	0.001
	Yes	42 (70.0%)	80 (46.2%)		
History of overdose variable in analysis	No	48 (80.0%)	144 (81.8%)	1.125 (0.537, 2.357)	0.755
	Yes	12 (20.0%)	32 (18.2%)		

SD: standard deviation; BZD: benzodiazepine

or hepatitis B (13.3% *vs* 6.8%, *p* = 0.118) (Table 2).

From the 236 individuals, 18.6% (44) had at least one overdose episode. We did not find a statistically significant difference between BZD users and non-users concerning having a history of overdose episodes (20.0% *vs* 18.2%, *p* = 0.755) (Table 2). However, we found that lifelong regular consumption of BZD was associated with an increased risk of overdose (90.9% *vs* 9.1%, *p* = 0.001; OR 5.000; 95% CI: 1714 – 14 587).

When asked about the type of drug associated with the overdose episodes, heroin was the most identified drug (17.8%; 42), followed by BZD (4.2%; 10), alcohol (3.4%; 8), and cocaine (2.9%; 7). In four cases (4.7%), the overdose occurred in a polydrug context: heroin with BZD and alcohol (3), and heroin with guanfacine (1). From those who had an overdose episode, 85.2% (201) of the individuals acknowledged the increased risk of overdose related with BZD abuse when associated with other drugs.

b) Psychiatric factors

As described previously, the main psychiatric factors associated with BZD intake in OMT populations were a higher consumption of other drugs and a higher level of psychiatric symptoms.

o In order to characterize those domains, we asked about the consumption of other drugs in the last 30 days and applied a Likert scale, considering a high rate of psychiatric symptoms when answering 'always/very often/sometimes'. On the other hand, a low rate of symptoms corresponded to 'rarely/never' answers.

Our results showed a prevalence of other psychoactive drug consumption (cannabinoids, cocaine, heroin, alcohol) in the last 30 days of 73.7% (174). The main type of substance of abuse was alcohol (58.9%; 139), followed by cannabinoids (31.4%; 74) and cocaine (17.4%; 41). Polydrug abuse was found in more than half of the individuals (52.9%; 92), consuming two or more drugs combined in the last 30 days.

By applying a bivariable analysis, we found that BZD users had a higher consumption of cannabinoids (41.7% *vs* 27.8%, *p* = 0.046) and lower consumption of alcohol in the last 30 days when compared with non-users (46.7% *vs* 63.1%, *p* = 0.026) (Table 3).

Regarding psychiatric symptoms, we found a high rate of psychopathology, such as depression (62.3%; 147), anxiety (63.6%; 150), irritability and anger (29.2%; 69), and suicidal thoughts (8.1%; 19). In the bivariable analysis, we found that BZD users had a higher rate of psychopathology, such as depression (81.7% *vs* 55.7%, *p* = < 0.001), suicidal thoughts (18.3% *vs* 4.5%, *p* = 0.002), and anxiety (88.3% *vs* 55.1%, *p* = < 0.001), when comparing with non-users (Table 3).

Optimized logistic regression model

The following variables were included in the logistic regression model: daily dose of MET, history of BZD intake, civil status, parental status, professional status, hepatitis C, hepatitis B, alcohol consumption in the last 30 days, cannabinoid consumption in the last 30 days, depression symptoms in the last 30 days, suicidal thoughts in the last 30 days, and anxiety symptoms in the last 30 days (Table 4).

Table 3 – Bivariate statistical analysis for psychiatric outcomes

Variable in analysis (in the last 30 days)	**Categories of the variable**	**BZD users**	**Non-BZD users**	**Odds ratio or difference of means** (IC 95%)	***p*-value**
Alcohol consumption	No	32 (53.3%)	65 (36.9%)	0.512 (0.283, 0.927)	0.026
	Yes	28 (46.7%)	111 (63.1%)		
Cocaine consumption	No	50 (83.3%)	145 (82.4%)	0.935 (0.428, 2.045)	0.867
	Yes	10 (16.7%)	31 (17.6%)		
Heroin consumption	No	55 (91.7%)	162 (92.0%)	1.052 (0.362, 3.054)	1.000
	Yes	5 (8.3%)	14 (8.0%)		
Cannabinoid consumption	No	35 (58.3%)	127 (72.2%)	1.851 (1.006, 3.407)	0.046
	Yes	25 (41.7%)	49 (27.8%)		
Amphetamine consumption	No	60 (100.0%)	176 (100.0%)	-	-
	Yes	0 (0.0%)	0 (0.0%)		
Depressive symptoms	Low rate	11 (18.3%)	78 (44.3%)	3.545 (1.729, 7.272)	< 0.001
	High rate	49 (81.7%)	98 (55.7%)		
Suicidal thoughts	Low rate	49 (81.7%)	168 (95.5%)	4.714 (1.797, 12.370)	0.002
	High rate	11 (18.3%)	8 (4.5%)		
Anxiety	Low rate	7 (11.7%)	79 (44.9%)	6.166 (2.656, 14.317)	< 0.001
	High rate	53 (88.3%)	97 (55.1%)		
Irritability and anger	Low rate	40 (66.7%)	127 (72.2%)	1.296 (0.690, 2.433)	0.419
	High rate	20 (33.3%)	49 (27.8%)		

BZD: benzodiazepine

Table 4 – Optimized logistic regression model

Variable in analysis	Categories of the variable	Odds ratio (IC 95%)	*p*-value
History of BZD intake	No Yes	3.726 (1.444, 9.617)	0.007
Alcohol consumption in the last 30 days	No Yes	0.482 (0.247, 0.238)	0.032
Anxiety	Low rate High rate	5.591 (2.345, 13.326)	< 0.001
Hepatitis C	No Yes	2.544 (1.273, 5.084)	0.008

BZD: benzodiazepine

The logistic regression model obtained was statistically significant (Omnibus test < 0.001), with a good fit (Hosmer and Lemeshow test 0.741 and area under the ROC curve 80.2%), achieving 76.8% of predictions. The optimized logistic regression model included the variables related with consumption of BZD in the past, hepatitis C, alcohol consumption in the past 30 days, and anxiety symptoms in the last 30 days.

We concluded that alcohol consumption in the last 30 days has a negative association with BZD use, with a relative reduction of 51.8% in BZD use (adjusted OR 0.482, $p = 0.032$). On the other hand, having a history of BZD intake increases 4x the odds of BZD use (adjusted OR 3.726, $p = 0.007$); having hepatitis C increases 2.5x the odds of BZD use (adjusted OR 2.544, $p = 0.008$); and having anxiety symptoms increases 6x the odds of BZD use (adjusted OR 5.591, $p < 0.001$). These three variables have a positive association with BZD.

DISCUSSION

To our knowledge, this is the first Portuguese study to examine BZD use in an OMT population. Our analyses showed that despite clinical guidelines cautioning against prescribing BZD in patients using opioids, about a quarter (25.6%) of the 236 patients in OMT had regular BZD consumption. This percentage is lower compared to most studies described in the literature.[4,7,8,22-24] We also found that 69.4% (43) took BZD for at least 24 months, suggesting a high prevalence of chronic BZD use, which is not recommended in BZD use and prescription guidelines.[1,20]

By analyzing the BZD pattern of use variables and comparing with the literature, we found that:

1. The EMCDDA explained the most common BZD types are the ones with a faster onset of action (e.g., diazepam, alprazolam),[13] and our study found concordant facts, with diazepam, alprazolam, and oxazepam as the top three most used BZD.
2. Concerning the ways of obtaining BZD, our results showed a high percentage of street-level marketing, described in 42% of the cases. The available data suggests an increase of BZD purchase at the street level and online,[13] which seems to represent an uncontrolled and unclarified problem for health authorities. On the other hand, we found a high percentage of medical prescriptions (49.8%), which should warn practitioners to be more aware of possible abusive BZD consumption.
3. Our findings were also in agreement with the main reasons given for taking BZD in the literature.[23-26] Nearly a quarter of the participants found BZD helpful for relieving psychiatric symptoms, such as insomnia and anxiety. Jones *et al* (2012) explain that BZD was also used to enhance the opioid effects of reducing the withdrawal symptoms associated with underdosing on the substitution treatment. In our study, this was found in only 2% of the cases, which could indicate a reasonable control of opioid doses.
4. Finally, evidence shows that entering an OMT program has a positive impact on reducing the intake of other drugs, including BZD.[23,26] Our study showed the same results. We found that almost half (46.9%) of the participants completely stopped BZD use, and more than one-third (35.4%) reduced the daily dose intake. These findings suggest that a reasonable control of opioid dependence and being enrolled in an OMT unit have a significant impact on the misuse of other drugs, even when not directly addressed.

Regarding physical factors, our study revealed a substantial prevalence of hepatitis C of 51.7%, probably reflecting high-risk drug-related behaviors, such as needle sharing. As described by many authors, this percentage was higher in BZD users,[5,6,9,12] highlighting the risks associated with BZD misuse by opioid users. In this context, BZD use also seems to be related with overdose episodes and drug-related deaths.[3,24] Our data revealed that BZD was identified in 10 of the 44 overdose cases, which underlines the importance of adequately addressing BZD use in this particular population.

Considering psychiatric factors, specifically polydrug consumption, known to be present in individuals with opioid and BZD co-use,[3,27] we found an almost three-quarter prevalence (73.7%) of consumption of other psychoactive drugs (cannabinoids, cocaine, heroin, alcohol) in the last 30 days. Comparing the BZD users with the non-users, the BZD users had a higher consumption of cannabinoids and needed a higher daily MET dose, suggesting that these

individuals probably have a severe and complex drug addiction problem.

Finally, as explained before, the BZD intake seemed to be related with psychological suffering, generalized anxiety disorder, and major depressive disorder in significant percentages.[3,28] We found that more than 60% of the patients felt depressed or anxious, with significantly higher rates in the BZD-user group, suggesting that a proper psychological approach and psychiatric evaluation are necessary for the treatment of dual disorders.

Strengths and limitations

As far as we know, this is the first Portuguese study to assess the BZD use prevalence and characterize, the BZD consumption and related factors in a public OMT unit. We achieved a reasonable participation rate, and our results match the international published data.

Nevertheless, this study had several limitations. First, besides the use of a structured questionnaire replicated and adapted from the literature, we did not apply any validated scale to characterize psychiatric symptoms or disorders. Second, being a retrospective study with some items related with past experiences, the information is vulnerable to the subjectivity inherent to individual memory bias. In order to address concerns about measurement bias, we used both prescription- and patient-level analyses to assess the concomitant use of BZD and opioid substitutes. Finally, the use of self-report introduces the possibility of bias; however, self-report in non-coercive circumstances by this population is generally accepted as a reliable and valid form of evidence.[29,30]

CONCLUSION

We found a prevalence of regular BZD consumption of 25.6%. The primary outcomes of this population were a higher prevalence of psychiatric symptoms and higher polydrug use in the BZD-user group. This study also found a reduction of BZD intake in half of the cases.

We concluded that alcohol consumption in the last 30 days has a negative association with BZD use. However, having a history of BZD intake, having hepatitis C, and having anxiety symptoms had a positive association with BZD use.

This aspect reinforces the need to address BZS intake in OMT patients. Due to infectious diseases, a high level of prescribed BZD, and a high prevalence, it also seems appropriate to have a proper articulation with primary and secondary medical care services.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

CONFLICTS OF INTEREST

The authors reported no potential conflict of interest.

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