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

**Benzodiazepine Use in an Opioid Maintenance Treatment Programme: Risks and Clinical Outcomes**

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**Short title:** BZD use in OMT: Risks and Clinical Outcomes

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**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.

Materiais e Métodos: Conduzimos um estudo transversal, envolvendo 236 pacientes 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 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: 1) prevalência elevada de Hepatite C (51.7%); 2) elevado consumo continuado de substâncias psicoativas (73.7%); 3) elevada taxa de depressão e ansiedade (> 60%), significativamente mais elevada nos usuários de benzodiazepinas. Na análise multivariável para o uso de benzodiazepinas, verificámos que o consumo de álcool tem associação negativa; a hepatite C e a ansiedade tiveram associações positivas.

Discussão e 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; Tratamento de Manutenção Opióide; Buprenorfina; Metadona.

**ABSTRACT**

Background: The co-association of benzodiazepines (BZD) and opioids is associated with an increased risk of overdose, death, and poorer psychosocial prognosis. This study aims to characterise the prevalence, pattern of use, and primary clinical outcomes in BZD users from 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 BZD users and non-users.

Results: The prevalence of BZD consumption was 25.4% (60). The BZD were obtained with a medical prescription (49.8%) or on the black market (42.6%). The most prescribed BZD was diazepam (29.1%), and the main reasons were to relieve insomnia (27.7%) or anxiety (26.9%) and to enhance other drugs’ psychoactive effects (19.7%). Regarding the clinical outcomes, we highlight: 1) a very high prevalence of hepatitis C (51.7%); 2) severe ongoing consumption of psychoactive drugs (73.7%); and 3) a high rate of depression and anxiety (>60%), significantly higher in the BZD-user group. In the multivariable analysis of benzodiazepine use, we found alcohol consumption had a negative association and having hepatitis C or anxiety symptoms had positive associations.

Discussion and Conclusion. Using BZD in the past or currently is associated with poor clinical and psychiatric outcomes. A multidisciplinary approach with a focus on infectious diseases and mental health is critical to enhance the treatment effectiveness and overall prognosis.

*Keywords*: benzodiazepines, opioid maintenance treatment, buprenorphine, methadone

**1. 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 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 seems 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 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 decriminalised the possession of all drugs for personal use in 2001, shifting towards a more health-centred approach to drug use, as well as broader health and social policy changes.14 Notably, Portugal coupled its decriminalisation 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 that characterise BZD use in OMT, making this study a significant starting point to understand this issue.

This study aims to characterise 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.

**2. Materials and Methods**

***2.1 Study design***

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

Entering the study was entirely voluntary, and all the participants provided written informed consent. The inclusion criteria were 1) individuals 18 years old or more; 2) being enrolled in the OMT for at least one month; and 3) providing free, informed consent. The exclusion criteria were 1) participation in the pilot study; 2) being less than 18 years old; 3) being enrolled in the OMT programme for less than one month; and 4) declining to participate in this study. A total of 236 participants met the inclusion criteria (47.6%).

Data collection was performed between April 2018 and September 2018. The reference psychologist or nurse filled out a questionnaire about BZD during the patients´ visit to the unit. The questionnaire applied was structured, replicated, and adapted from the literature, and it was pre-tested randomly on 10 patients attending the public opioid treatment programme in the drug addiction treatment unit 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 (authorisation no. 11086 / CES / 2017). The work described in this paper did not receive any grant or funding from the public, commercial, or non-profit sector and was fully supported by the authors.

***2.2 Background variables***

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

 1) Sociodemographic characterisation (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 programme; 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’.

***2.3. 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 analysed using the features of this programme.

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 numeric 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 ​​< 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). 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 optimised model with a final table with the variables whose association with the use of BZD was statistically significant (p value <0.05). For analysis of the fit quality of the logistic regression model, we used the area under the receiver operator characteristic (ROC) curve.

**3. Results**

***3.1. Sociodemographic characterisation: 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 codified by the International Statistical Classification of Diseases and Related Health Problems (ICD-10) – 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 characterisation.

*Insert Table 1*

***3.2. BZD pattern of use***

*3.2.1 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).

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).

*3.2.2. History of BZD use*

Addressing the previous BZD consumption, 71.2% (168) of the sample assumed 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).

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).

*3.2.3. BZD use evolution during the OMT*

We found that 69.4% (43) of participants were in a substitution programme 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.

*3.2.4. 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.

***3.3 Health and risk behaviour factors***

*3.3.1. Physical factors*

Regarding the information available in the literature, we identified infectious diseases (HIV, hepatitis B, and hepatitis C) and overdose episodes as the principal negative physical factors related to BZD intake. In this context, we found the following infectious disease prevalences: 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) or hepatitis B (13.3% vs 6.8%, p=0.118) (Table 2).

*Insert 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: 1.714–14.587).

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 to BZD abuse when associated with other drugs.

*3.3.2* *Psychiatric factors*

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

In order to characterise 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 73.7% (174) of other psychoactive drug consumption (cannabinoids, cocaine, heroin, alcohol) in the last 30 days. The principal 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.

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).

*Insert Table 3*

***3.4*** ***Optimised 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.

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 optimised logistic regression model included the variables related to 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 51.8% relative reduction odd in the 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.

*Insert Table 4*

**4. 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 less than the data majority described in the literature.4,7,8,22,23,24 We also found that 69.4% (43) took BZD for at least 24 months, suggesting a high prevalence of chronical BZD use, which is not recommended in BZD use and prescription guidelines.1,20

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

1. 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. Available data suggest an increase of BZD selling 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 programme 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 tremendous impact on the misuse of other drugs, even when not directly addressed.

Regarding physical factors, our study revealed a massive 51.7% prevalence of hepatitis C, probably reflecting high-risk drug-related behaviours, 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 to 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 to psychological suffering, generalised 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.

***4.1. Strengths and limitations***

As far as we know, this is the first Portuguese study to assess the BZD use prevalence and characterise, with an expansive view, 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 characterise psychiatric symptoms or disorders. Second, being a retrospective study with some items related to past experiences, the information is vulnerable to the subjectivity inherent to individual memory bias. 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

**5. Conclusions**

We found a prevalence of 25.6% regular BZD consumption. 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.

**Conflicts of interest**

The authors reported no potential conflict of interest.

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TABLES

Table 1. Bivariate statistical analysis for sociodemographic characterisation

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Variable in analysis  | Categories of the variable | BZD users | Non-BZD users | Odds ratio (IC 95%) | p-value |
| Age | Mean ± SDMin–max | 46.7 ± 6.831-61 | 46.8 ± 7.127-64 | 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%) |

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 ± SDMin–max | 6.61 ± 3.202.0-16.0 | 6.13 ± 3.671.5-16.0 | 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 overdosevariable in analysis  | No | 48 (80.0%) | 144 (81.8%) | 1.125 (0.537, 2.357) | 0.755 |
| Yes | 12 (20.0%) | 32 (18.2%) |

Note: SD: standard deviation; BZD: benzodiazepine

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%) |

Note: BZD: benzodiazepine

Table 4. Optimised Logistic Regression Model

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

Note: BZD: benzodiazepine