

INTERACTION BETWEEN BENZODIAZEPINES, CONGENERES, AND ALCOHOL WITH OTHER SUBSTANCES IN PATIENTS OF THE CAPS OF THE CITY OF MARINGÁ-PR"

INTERAÇÃO ENTRE BENZODIAZEPÍNICOS, CONGÊNERES E ÁLCOOL COM OUTRAS SUBSTÂNCIAS EM PACIENTES DO CAPS DA CIDADE DE MARINGÁ-PR

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ABSTRACT: Mental disorders, such as anxiety, and their consequential impacts on the use of pharmaceuticals to remedy this situation, prove to be fertile ground for problems, particularly when considering, in addition to this scenario, the historical consumption of alcohol and other drugs in Brazil. Thus, drug interactions between benzodiazepines, hypnotics used in the treatment of mental disorders such as anxiety, with other widely used and addictive substances, particularly in a portion of the population already at risk, such as patients treated in institutions related to the treatment of psychiatric pathologies, become a significant concern. The objective of this study was to identify, among individuals using benzodiazepines and other sedative hypnotics, those who do so concurrently with the use of alcohol and, primarily, tobacco. A quantitative analysis and field research were conducted through a questionnaire to collect data from patients treated at the Psychosocial Care Center (CAPS) in the city of Maringá-PR. It was identified that there is a substantial number of patients concurrently using both alcohol and benzodiazepines as well as tobacco, which can bring about health problems ranging from mild to potentially fatal, even though the risks may often go unnoticed. Thus, the aim is to promote greater understanding among the general population in the future, as well as to contribute to more specific instructions and greater adherence to the correct treatment.

Keywords: Alcohol; Anxiolytics; Tobacco

RESUMO: Os transtornos mentais, como a ansiedade, e seus consequentes impactos na utilização de fármacos para remediar essa situação se mostram terreno fértil para problemas, principalmente ao se analisar, em adição a esse cenário, o histórico consumo de álcool e outras drogas no Brasil. Dessa forma, as interações medicamentosas entre os benzodiazepínicos, hipnóticos usados no tratamento de transtornos mentais como a ansiedade, com outras substâncias de uso disseminado e com caráter viciante, principalmente em uma parcela da população já em risco, vide os pacientes atendidos em instituições ligadas ao tratamento de patologias psiquiátricas. O objetivo do presente trabalho foi detectar, entre os indivíduos que utilizam benzodiazepínicos e outros hipnóticos sedativos, aqueles que o fazem concomitante ao uso de álcool e, principalmente, tabaco. Dispôs-se de análise quantitativa e pesquisa de campo através de questionário para coletar dados dos pacientes atendidos pelo Centro de Atenção Psicossocial (CAPS) da cidade de Maringá-PR. Identificou-se que há uma quantidade substancial de pacientes realizando o uso concomitante tanto de álcool com benzodiazepínicos quanto com tabaco, os quais podem trazer problemas de saúde tanto leves quanto potencialmente fatais, mesmo que muitas vezes não se tenha noção desse risco. Dessa forma, objetiva-se futuramente promover maior entendimento pelas pessoas no geral, além de contribuir para instruções mais específicas e maior adesão ao tratamento correto.

Palavras chave: Álcool; Benzodiazepinas; Tabaco

1. INTRODUCTION

According to 2017 data from the World Health Organization (WHO), the prevalence of anxiety disorders (AD) worldwide is 3.6%, affecting 5.6% of the population in the Americas and 9.3% of the population in Brazil, representing the highest number of AD cases in the world. Additionally, there is a suggestion of increased anxiety following the COVID-19 pandemic in the Brazilian population, with a 44.2% increase in prevalence (SOUZA et al., 2021).

Insomnia ranks as the second most prevalent mental disorder, still lacking efficient available treatments, and is associated with alcohol consumption when analyzing adolescents and young adults. This association is due to short-term effects caused by depression in the Central Nervous System (CNS) by the substance acting on GABA receptors, as well as its antagonistic effects on NMDA glutamatergic receptors, leading to a decrease in the transition latency between wakefulness and sleep states (DA SILVA-FONSECA et al., 2021).

Benzodiazepines are psychotropic medications recommended for the control of anxiety and insomnia (CURADO et al., 2022). According to the Health Sciences Descriptors (DeCS), drug interaction is defined as the "action of a drug that can affect the activity, metabolism, or toxicity of another drug," potentially acting as a potentiator or inhibitor of another drug's action at different scales. Pharmacological or clinical responses can also occur due to food or other chemicals acting on another medication (LEÃO et al., 2014).

In a Brazilian national sample, KRAWCZYK et al. (2021) demonstrated that concurrent use of benzodiazepines and alcohol is prevalent, particularly among women over 25 years old and employed individuals, potentially more prescribed in Brazil due to the high historical rate of alcohol use. In these individuals, self-reported anxiety was more likely, indicating greater morbidity, and it was also associated with tobacco use. The types of polysubstance use were determining factors in the demographic risk presented. Finally, the authors suggest strategies regarding guidance on polysubstance use concurrent with alcohol misuse.

According to a study from North America and the United Kingdom, between 5 and 33% of the older population received a prescription for a benzodiazepine for a sleep problem (TAVARES et al., 2021), and nationally, the prevalence of various classes of benzodiazepines continues to increase, mainly related to ages between 45 and 59 years old (MADRUGA et al., 2019).

Associated with this, alcohol consumption is historically widespread in the country (KRAWCZYK et al., 2021), posing a severe public health problem, related to higher rates of mortality and morbidity due to its potential to cause disease and its relation to loss of quality of life. Moreover, according to the II National Survey on Alcohol and Drugs in 2012, the prevalence of harmful alcohol use and alcohol dependence was 16% and 6.8%, respectively. Meanwhile, a multicenter study conducted in the same year reported that

alcohol abuse and alcohol dependence were the second and third most prevalent life disorders (DOS SANTOS et al., 2019).

Establishing relationships regarding the increase in national epidemiology of both drugs, according to MADRUGA et al. (2019), and alcohol, as mentioned by KRAWCZYK et al. (2021), and the pre-existence of drug interactions involving different pharmacological classes, it becomes necessary to delve into how one interacts with the other and create specific relationships in prescription, consumption, and adherence to treatment in cases where drugs from both benzodiazepine and non-benzodiazepine classes are associated with alcohol consumption, whether acutely or chronically.

In light of the above, this study seeks to analyze the possible interaction between benzodiazepines and zolpidem with alcohol and tobacco consumption. Does concurrent consumption of these medications with alcohol and/or tobacco occur? What is the risk for individuals if this interaction occurs? Are consumers aware of this situation? How does this pharmacological relationship affect the general population?

2. METHODOLOGY

This is a cross-sectional, descriptive study conducted at the Psychosocial Care Center (CAPS), located at the intersection of Pioneiro João José Queiroz Street and Igenes Gongora Street, S/N - Jardim Ipanema, in the municipality of Maringá, in the northern region of Paraná, with an estimated population of 409,657 inhabitants (IBGE, 2022).

The sample universe consisted of 39 adult patients of both genders over 18 years old who were being treated at CAPS, on the waiting list, or after treatment and who expressed a desire to participate in the research following all applicable ethical procedures. Individuals underwent an interview through a structured questionnaire with objective and descriptive questions to determine the use of benzodiazepines, related drugs, alcohol, and cigarettes, as well as the drug effect of their combined application, and their correlations in the socio-economic context.

Patients responded to a questionnaire regarding the assessment of drug interaction between alcohol and medications, aiming to elicit responses from patients, users of the Unified Health System (SUS) in the city of Maringá-PR, who were prescribed benzodiazepines, as well as to delineate those within this group whose consumption is associated with alcohol and other drugs.

Inclusion criteria were individuals of both genders over 18 years old who signed the Informed Consent Form (ICF) in duplicate. Those who did not meet the criteria were automatically excluded.

Furthermore, the research was based on pharmacodynamics and pharmacokinetics studies of these drugs, through authors such as Goodman and Gilman, among others. In addition, scientific articles from the Pubmed, Uptodate, Sciencedirect, and Scielo databases relevant to the topic were used.

All intervention procedures in this study were submitted to the Ethics and Research

Committee of UniCesumar for approval, CAAE 66694923.6.0000.5539, opinion number 5.900.606, and were only carried out with full approval. Qualitative and quantitative data were tabulated and subsequently analyzed using descriptive statistics based on frequency distribution and central tendency, and ANOVA Blocked, respectively. The significance level adopted was 5%.

3. RESULTS

Table 1. Distribution of participants assisted at the CAPS AD in the municipality of Maringá-PR according to sociodemographic characteristics.

Gender	Male (71,8%)
Age (29-38)	33,3%
Race	White (53,8%)
Marital status	Single (53,8%)
Diabetes	5,12%
Asthma	7,69%
Cardiovascular disease	12,82%
Renal disease	2,56%
Educational level	Incomplete high school education (35,9%)
Neighborhood	Morangueira neighborhood (12,8%)

Source: research findings

Of the 39 participants, 28 (71.8%) were male, while 11 (28.2%) were female. Regarding skin color, 21 (53.8%) self-identified as white, 7 (17.9%) as black, 9 (23.1%) as mixed race, and 2 (5.1%) as other. Regarding marital status, there were 21 (53.8%) single individuals, 11 (28.2%) legally separated, 5 (12.8%) married, 1 (2.6%) widowed, and 1 (2.6%) chose not to disclose (Table 1).

In terms of age, 7 (17.9%) respondents were aged 18 to 28, 13 (33.3%) were aged 29 to 38, 6 (15.3%) were aged 39 to 48, 7 (17.9%) were aged 49 to 58, and 6 (15.3%) were aged 59 or older. Regarding education level, 3 (7.7%) had completed higher education or more, 13 (33.3%) had completed high school or had incomplete higher

education, 14 (35.9%) had completed elementary school or had incomplete high school, and 9 (23.1%) had no formal education or incomplete elementary school (Table 1).

When collecting data on underlying diseases, 2 (5.1%) had diabetes, 3 (7.7%) had asthma, 5 (12.8%) had some cardiovascular disease, such as systemic arterial hypertension and arrhythmia, and 1 (2.56%) had chronic kidney disease.

The most prevalent regions were: 1 (2.6%) patient in Conjunto Ney Braga, Conjunto Thaís, Jardim Alvorada III, Jardim Atlanta, Jardim Continental, Jardim Guairacá, Jardim Kakogawa, Jardim Liberdade, Jardim Monterrei, Jardim Pinheiros, Jardim Quebec, Jardim Requião, Oásis, Paris III, Parque Hortênciã I, Parque Laranjeiras, Parque Residencial Tuiuti, Sarandi, Vila Morumbi, Vila Operária, Vila Santo Antônio, Zona 04, and Zona 02. The regions Conjunto Requião, Jardim Universo, Jardim Alvorada, and Iguatemi had 2 (5.1%) patients each, 3 patients (7.7%) were from Zona 07, while 5 (12.8%) were from Vila Morangueira (Table 1).

Regarding alcohol, the age of onset of consumption among patients (Table 2) was as follows: 25 (64.1%) began consumption before the age of 18, while 12 (30.7%) began consumption at age 18 or older. Regarding concurrent use during treatment provided by CAPS, 24 (61.5%) did not consume alcoholic beverages, 13 (33.3%) consumed alcoholic beverages, and 2 (5.1%) were not yet in treatment.

When categorizing alcohol use chronologically, 25 (65.8%) of the respondents did not fit the grading conditions, while 6 (15.8%) consumed alcohol 1 to 2 days a week, 4 (10.5%) consumed alcohol 3 to 6 days a week, and 3 (7.9%) consumed alcohol 7 days a week. Regarding the quantity consumed in the last month, 21 (53.8%) did not fit the conditions, 1 (2.6%) consumed one drink, 1 (2.6%) consumed four drinks, and 16 (41%) consumed 5 drinks or more.

Regarding self-perception of drinking habits with treatment offered by CAPS, 19 (50%) believed that the habit interfered with both health and treatment, 2 (5.3%) believed it interfered with health but not treatment, while 1 (2.6%) believed it did not interfere with either health or treatment, and 16 (42.1%) did not apply to the question.

In terms of the relationship between drinking habits and treatment, 17 (43.6%) believed that the former negatively impacted the latter, 3 (7.7%) believed that the habit improved the effectiveness of treatment, and 2 (5.1%) denied any relationship between the two. 17 (43.6%) did not apply to the question.

Table 2. Relationship to alcohol, age of onset of consumption among participants assisted in the CAPS AD of the municipality of Maringá-PR.

Age of onset (years)	Less than 18 years 25 (64,1%)
Alcohol use	34,2%
Concurrent use during treatment at CAPS	33,3%
Maximum amount consumed in a single session in the last month	1 dose (53,8%)
Self-perception of the interference of drinking behavior on treatment and health	The habit interferes with health and interferes with treatment (50%)
Assessment of the relationship between the form of interference of drinking behavior on treatment tra	Worsens the treatment (43,6%)

Source: research findings

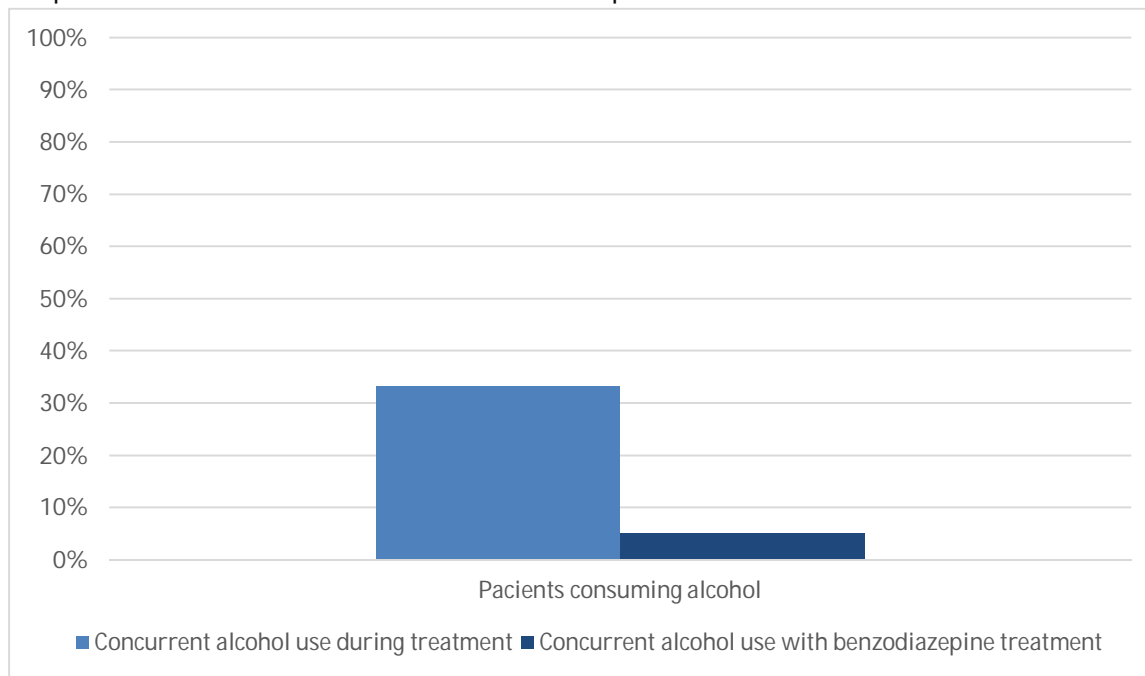
Graph 1 depicts the relationship between concurrent alcohol use and benzodiazepine treatment. We observe that 33.3% of the interviewed patients use alcohol concurrently with treatment, and only a small percentage (5.1%) use benzodiazepine medication alongside alcohol consumption. Therefore, 15% of the interviewed patients in treatment who use alcohol associate its use with benzodiazepine drugs, which correlates with the data presented by KRAWCZYK et al. (2021), which measures a total of 0.4% of patients falling into this criterion, showing some discrepancy compared to this literature.

In current literature sources, such as KRAWCZYK et al. (2021) and ZAMBONI et al. (2022), the epidemiological profile of patients who drink during psychiatric treatment generally tends to be female. However, during the data collection at CAPS, it is evident that the patients included are mostly male (65.5%). The explanation for this discrepancy may be confined to the sampling space itself - where the male portion constitutes 71.8% of the whole - demonstrating a higher demand from male audience in the specific CAPS unit.

Another alarming factor regarding alcohol consumption is the age of onset of the habit, specifically during legal minority (18 years), which represents 64.1% of the total interviewed. This factor is explained, according to COURTNEY et al. (2020), by the extensive alteration and neuromodulation caused by early drug consumption in the individual's behavioral and reward system, which can consequently lead to greater vulnerability of the user's neurodevelopment and increase the chances of future

dependence, resulting in an epidemiological profile of psychiatric patients marked by early exposure to alcohol consumption, as clearly evidenced by the profile of the patients addressed in the interview.

Graph 1 - Concurrent Alcohol Use with Benzodiazepine Treatment



Group 1 (light blue bar): concurrent drinking with treatment.

Group 2 (dark blue bar): patients who use alcohol concurrently with benzodiazepines.

When questioning the interview participants about concurrent smoking with the treatment provided by CAPS (Table 3 and Graph 2), 12 (30.8%) denied consumption, 24 (61.5%) stated they use cigarettes, and 3 (7.7%) stated they are not undergoing treatment. Regarding the self-perception of smoking habit with treatment, 15 (38.5%) believe the habit interferes with both health and treatment, 9 (23.1%) state it interferes with health but not treatment, 4 (10.3%) believe it does not interfere with either health or treatment, and 11 (28.2%) do not apply to the question.

The duration of the cigarette consumption habit is organized as follows: 9 (23.1%) have been consuming for 1 to 10 years, 15 (38.4%) for 11 to 20 years, 4 (10.2%) for 21 to 30 years, and 3 (7.7%) for 30 years or more. 8 (20.5%) stated they have never smoked cigarettes. In terms of daily cigarette pack usage, 9 (23.1%) use less than one pack/day, 15 (38.4%) consume one pack/day, and 5 (12.8%) consume more than one pack/day. 10 (25.6%) stated they consume zero packs/day.

Regarding how this habit interferes with treatment, 8 (20.5%) claim it improves its effectiveness, 8 (20.5%) claim it worsens its effectiveness, 11 (28.2%) claim there is no relationship between the habit and treatment, and 12 (30.8%) patients do not apply to the

question. Thus, it becomes apparent how a harmful habit to well-being and supportive in the process of dependence (LEKKA et al., 1997) ends up having its meaning distorted, especially in the population addressed by psychiatric therapies, including those seeking to eliminate addictions. This reflects in morbidity consequences for the patient themselves, who internalize or soften the treatment process with smoking, which, in parallel, generates other problems that go beyond the psychiatry field.

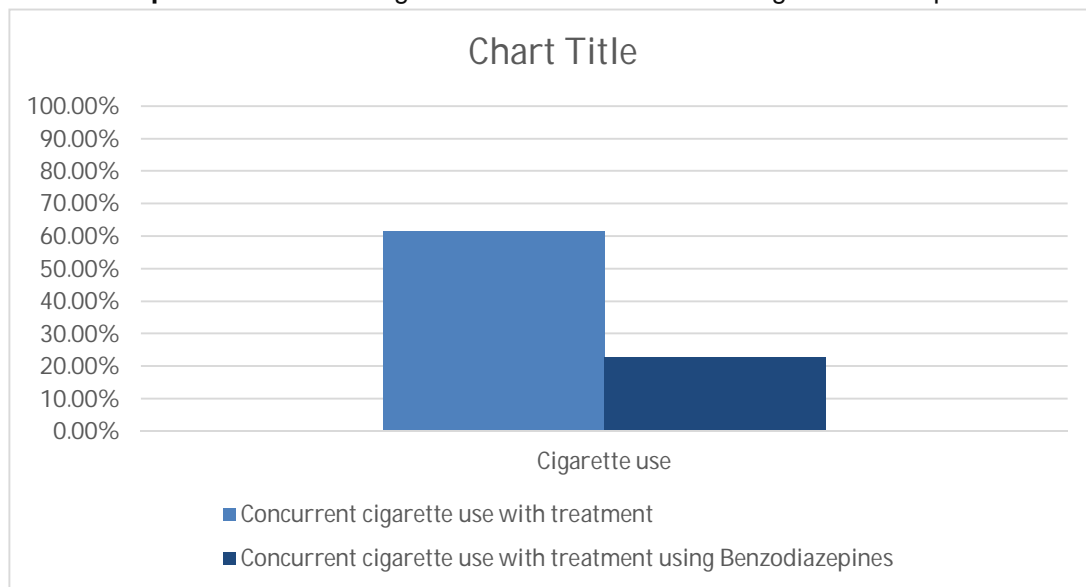
Table 3. Concurrent Cigarette Use with Treatment among Participants Assisted at the CAPS AD in the Municipality of Maringá-PR.

The correlation of cigarettes with the patients

Duration of the habit (years)	11-20 (38,4%)
Daily quantity of cigarettes	20 (38,5%)
Concurrent use during treatment at CAPS	Yes (61,5%)
Self-perception of the interference of smoking on treatment and health	The habit interferes with health and treatment (38,5%)
Assessment of the relationship between the way smoking interferes with treatment	The habit does not interfere with treatment (28,2%)

Source: research findings

Graph 2 - Concurrent Cigarette Use with Treatment using Benzodiazepines.



Graph 2. Group 1 (light blue bar): concurrent smoking with treatment; Group 2 (dark blue bar): patients who use cigarettes concurrently with benzodiazepines.

Regarding the medications provided by the CAPS and most commonly used by the patients (Table 4), we observe that the anticonvulsant sodium valproate was the most prescribed medication (33.3%), followed by the mood stabilizer lithium carbonate (20.51%), the benzodiazepine Diazepam (20.51%), and the antidepressant venlafaxine (25.64%).

The concurrent use of alcohol and benzodiazepines leads to the coactivation of the GABA-A receptor in inhibitory, GABAergic synapses, excessively depressing the CNS due to the transmembrane domains of the receptors containing solvent-accessible cavities. Consequently, its allosteric potentiation extends beyond therapeutic and/or recreational use, generating potential drug interactions between the inadvertent use of different depressants that modulate these receptors (ZHU et al., 2018). These findings are supported by the meta-analysis of ALPERT et al. (2022), whose results showed that one of the leading causes of alcohol-associated death involved toxicity from the concurrent use of drugs, especially benzodiazepines (although the literature is epidemiologically imprecise regarding which drugs are most associated with alcohol use), leading to overdose, which can occur even at low levels of substances.

Table 4. Most Used Medications by Participants Assisted at CAPS AD in the Municipality of Maringá-PR.

**Medications used by patients
provided by CAPS**

Valproic Acid/Sodium Valproate	33,3%
Amitriptyline	7,69%
Bupropion	2,56%
Carbamazepine	2,56%
Lithium Carbonate	20,51%
Clonazepam	5,12%
Chlorpromazine	10,25%
Diazepam	20,51%
Fluoxetine	7,69%
Haloperidol	7,69%
Levomepromazine	7,69%
Risperidone	17,94%
Thiamine	2,56%

Thioridazine	2,56%
Venlafaxine	25,64%
B-Complex Vitamin	7,69%

Source: research findings

When questioned about treatment adherence, 30 (76.9%) stated they correctly take the treatment medications, 4 (10.3%) denied adherence, and 5 (12.8%) did not respond to the question. In response to the question about episodes of intoxication, 31 (79.5%) denied subsequent episodes, while 7 (17.9%) reported subsequent episodes, and 1 (2.6%) did not respond to the question.

Regarding episodes of acute benzodiazepine intoxication, when reported during the interview, typical signs found were nausea, vomiting, and dizziness, which is consistent with data found in PENNINGA et al. (2015) research and literature sources depicting typical signs of this intoxication, which may pose greater risks in patients using polypharmacy or alcohol due to pharmacological interactions.

Regarding other medications used by patients (Table 5), we can observe that antipsychotics (20.5%) were the most used medications by the patients, and according to SANTOS et al. (2009), anticonvulsants represent a class of psychotropic drugs that generally have a binding capacity to plasma proteins and interfere with other drugs through protein displacement, which, in turn, can lead to an increase in the free fraction of the anticonvulsant with potential risk of toxicity. Thus, the need for caution in their use is noted, given the potential interactional risk.

Table 5. Most Used Medications by Participants Assisted at CAPS AD in the Municipality of Maringá-PR.

**Medications used by patients obtained
through other means.**

Hypoglycemic agent	3 (7,69%)
Antihypertensive	3 (7,69%)
Antipsychotic	8 (20,51%)
Antileptics	2 (5,12%)

Source: research findings

3. FINAL CONSIDERATIONS

Through the process applied in the research and comparison with current literature, the epidemiological profile of patients at the CAPS in the specific region of Maringá, PR, was observed, highlighting facts that demonstrate not only the relevance of the association of benzodiazepine drugs with alcohol but also other classes of drugs incident in the treatment offered by the public network and in clarifying their associations - whether purely

pharmacological or in the overall treatment -, as well as the relationship between the age of onset of consumption and the seeking of psychiatric support in the future. Thus, it is clear how the effects of alcohol and its associations are prevalent in this area of health, resulting in a range of consequences observed in the literature such as higher rates of treatment relapses, lower response and adherence to the therapeutic proposal, and seeking of health services related to drug dependence.

In parallel, the misinformation and limited self-perception of patients also contribute to this issue, especially concerning the concurrent use of tobacco during treatment.

Therefore, through the data presented in the research, the importance of the health worker's guiding role responsible for the patient is emphasized, elucidating data such as those found to highlight how important it is to refrain from certain habits that negatively impact the treatment in question. These facts need to be presented to the patient in a didactic and comprehensive manner to steer them away from habits that negatively impact their health process.

Thus, the contribution of this survey to both the academic and social spheres is evident. Amidst a society marked by these habits - even though constantly warned of their respective harm - this project serves its function of exposing and proposing solutions to reverse this biopsychosocial morbidity.

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