






Benzodiazepine and Z-drug consumption in a national social security organization in Argentina: rational or excessive use?


Consumo de benzodiazepinas y fármacos Z en una organización de la seguridad social nacional argentina: ¿uso racional o excesivo?

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ABSTRACT Benzodiazepines and “Z-drugs” (BZD/Z) are overprescribed in many countries. This study evaluates their consumption in a social security sector health insurance provider with national coverage in Argentina. With a descriptive and observational approach, outpatient dispensations of BZD/Zs were analyzed for people over 18 years old from April 2020 to March 2021, disaggregated by sex, age, active ingredient, and half-life. An annual prevalence of use of 11.6% was found among the 431,445 adult affiliates, with higher rates in women and in those over age 60. Overall consumption of BZD/Zs was 77.6 defined daily doses (DDD) per 1000 enrollee-days. The average user received 5.1 annual dispensations and the equivalent of 1.4 DDD for each day of the year. BZD/Zs with long half-life were the most used. We found high levels of BZD/Z consumption and for longer periods than recommended. It is necessary to improve the quality of consumption and reduce the negative impact of inappropriate use of these drugs among treated individuals.

KEY WORDS Benzodiazepines; Drug Utilization; Pharmacoepidemiology; Social Security; Argentina.

RESUMEN Las benzodiazepinas y los “fármacos Z” (BZD-Z) se prescriben en exceso en muchos países. Este estudio evaluó su consumo en una organización de la seguridad social (obra social) de Argentina de alcance nacional. A partir de un diseño observacional descriptivo se analizó la dispensa ambulatoria de BZD-Z, entre abril 2020 y marzo 2021, a mayores de 18 años; desagregada por sexo, edad, principio activo y vida media. Se encontró una prevalencia anual de uso del 11,6% entre los 431.445 afiliados adultos, con valores más elevados en las mujeres y mayores de 60 años. El consumo global de BZD-Z fue de 77,6 dosis diarias definidas (DDD) cada 1.000 afiliados-día. El usuario promedio recibió 5,1 dispensas anuales y el equivalente a 1,4 DDD por cada día del año. Las BZD-Z más usadas fueron las de vida media larga. El consumo de BZD-Z resultó elevado y más prolongado que lo recomendado. Es necesario mejorar la calidad en el consumo y reducir el impacto negativo del uso inapropiado de estos fármacos entre los individuos tratados.

PALABRAS CLAVES Benzodiazepinas; Utilización de Medicamentos; Farmacoepidemiología; Seguridad Social; Argentina.

INTRODUCTION

Benzodiazepines are one of the most widely used pharmacological groups due to their anxiolytic, hypnotic, muscle relaxant, and anticonvulsant properties. Their use often lasts for longer periods than recommended, and that is why they continue to cause controversy globally.⁽¹⁾ The so-called “Z-drugs”, such as zolpidem and zopiclone, which are closely associated with benzodiazepines, were developed as hypnotics that do not produce tolerance and physical dependence, but these problems were identified when their consumption increased.⁽²⁾

The prevailing way of life and the requirements of modern times lead individuals to undergo worryingly difficult and stressful situations, both in the workplace and at home.⁽³⁾ Those who commercialize drugs have made a determined effort to show that psychoactive substances are the solution to these problems. This is the reason why individuals and prescribing professionals link benzodiazepines and Z-drugs (BZD/Zs) to various uses such as sleep improvement, anxiety reduction, enhanced performance in daily activities, improved personal performance, or mitigation of unwanted social situations, to name but a few purported uses.⁽³⁾

The use of this type of drugs varies according to the studied population, and in the adult population across Argentina it ranges from 4.3% to 8.1%^(4,5); while in Brazil it accounts for 5.6%⁽⁶⁾; in Uruguay it accounts for 7.4%,⁽⁷⁾ and in Spain the rate is 11.4%.⁽⁸⁾

Other authors warn about the existence of an extraordinary diversity in consumption according to sex, age, profession or even the activity undertaken by the studied population.⁽⁹⁾ For instance, within the military forces of the Spanish Navy, the percentage of BZD/Z consumption is 1.8%⁽⁹⁾; among the nursing staff this percentage varies (from 10% to 32%) according to the country being studied^(10,11,12,13); and regarding other occupations and professions, variation is still higher.⁽¹⁴⁾

In all cases, indiscriminate use of BZD/Zs will result in chronic users, who are more

likely to develop tolerance and dependence. This does not generally occur when they are prescribed for conditions such as anxiety or insomnia on a temporary basis, according to the guidelines of the World Health Organization.^(15,16) Suddenly quitting long-term treatments can lead to forms of anxiety, panic attacks, hyperventilation, moderate tremors, sleep disorders, muscle spasms, anorexia, weight loss, visual alteration, sweating, or dysphoria.^(17,18,19)

For this reason, treatment duration should be the shortest possible, ideally not exceeding a period of four weeks when treating insomnia, and no more than three months when treating anxiety, including the period of tapering off up to drug discontinuation.⁽²⁰⁾

Therefore, it is important for each place, institution or health financing agency to know the reality regarding the profile of BZD/Z consumption, not only to avoid an unnecessary use of these drugs, but also to prevent unwanted associated effects. It is within this framework that the authors decided to conduct this research work within a social security organization (employment-based health insurance provider) with national coverage in Argentina, with the aim of inquiring into outpatient BZD/Z use among affiliates aged 18 years and older, the amount and type of BZD/Zs dispensed during a period of 12 months, and duration of drug use.

METHODOLOGY

Design and study population

Drug use was analyzed with a descriptive and observational approach. The employment-based health insurance provider with national coverage, having enrollees across the 24 provinces in Argentina, provides services to a population amounting to 577,000 affiliates of different age groups, out of whom 20.1% are over 60 years old, performing duties in the armed forces and national law enforcement agencies, including active workers, their dependents, retired persons, and pensioners.

Data source and studied variables

The information was obtained from the database of outpatient dispensations, which includes pharmacies run by the institution itself and other third-party pharmacies. Each record states the dispensation date, patient's identification details, number of containers, and composition of the drugs dispensed.

Outpatient dispensations were analyzed for the total number of affiliates over 18 years old that used drugs between April 1st, 2020 and March 31st, 2021. The analysis was focused on all benzodiazepines and benzodiazepines analogs with hypnotic action (eszopiclone, zolpidem, and zopiclone), in their presentations as monodrugs or as fixed dose combinations (FDCs).

Although a drug provision does not necessarily imply its effective use, in this work, for convenience purposes, the term "user" will refer to the person receiving a dispensation whereas the term "affiliates" will refer to the entire population covered by the employment-based health insurance.

In order to explore the indication for BZD/Z drugs, the diagnosis, if any, described on the prescription was recorded. To quantify the various drugs with a common unit, the defined daily dose (DDD) was used, which is the average maintenance dose per day for a drug, used for its main indication in adults. An international committee approved by the World Health Organization establishes the Anatomical Therapeutic Chemical (ATC) Classification System for drugs and their corresponding DDD.⁽²¹⁾

Under the ATC classification system, clonazepam is labeled as an anticonvulsant and the assigned DDD is 8 mg, according to this indication. However, the prevailing use of clonazepam among adults is as an anxiolytic, in which case the usual doses are substantially lower. To appropriately reflect the contribution of clonazepam to the total exposure of the population to BZD/Z drugs, we followed the literature that assigns an anxiolytic DDD of 1 mg to this drug.^(7,22,23,24) As for FDCs, the assigned DDDs depended on the BZD/Z component.

User's sex and age were recorded as well as the active principle and its corresponding ATC code, the DDD value⁽²¹⁾ and half-life of the drug.^(1,25) BZD/Z drugs were classified as having short, medium or long half-life, depending on whether they were under 6 hours, from 6 to 24 hours or more than 24 hours, respectively.⁽²⁵⁾

The total milligrams and total DDDs dispensed during the annual period per each drug were quantified and with this information the DDDs for each drug dispensed on a daily basis per 1,000 enrollees (DDD per 1,000 inhabitants per day = DID) were established, using the following formula⁽²⁶⁾:

$$DID = \frac{\text{mg of drug dispensed per year}}{\text{DDD mg} \times 365 \text{ days} \times \text{N}^\circ \text{ of affiliates}} \times 1,000$$

The annual prevalence of use for each sex and age group was calculated as well as the percentage of affiliates that received at least one package of BZD/Zs during the period under study.⁽²⁷⁾ The average quantity of BZD/Zs dispensed throughout the year for each user was also defined, stated in packages and DDD per year, also disclosed as DDD/user/day.

As an approach to the duration and continuity of use, we explored the total number of months in which each user was dispensed at least one container of BZD/Zs and the maximum period of uninterrupted dispensation in consecutive months. Concomitant dispensation during the same month of other pharmaceuticals with potential drug interactions with BZD/Z drugs was recorded, in accordance with the cited reference text.⁽²⁸⁾

With respect to statistical analysis, information was consolidated on a single database and later analyzed using statistical software "R" version 4.0. Data are described as average figures and their standard deviations or percentages, according to the type of variable.

All the data were encoded to hide given names, surname, number of affiliate, and any other detail that could reveal users' identity. The protocol used in this study was authorized by the Ethics Committee of the Institution (D19-20).

RESULTS

During the study period (starting April 1st, 2020 and ending March 31st, 2021), the employment-based health insurance provider had a total of 431,445 adult affiliates over 18 years old, out of whom 48.3 % were female, the mean age being 46.5 (+/- 19.7) years.

During the 12 months of the study, we analyzed 4,833,768 dispensations, out of which 273,311(5.7%) accounted for BZD/Z drugs, directed at 50,049 different users (61.9% female; mean age 64.1 +/- 16.0 years).

The users received about 6.6 containers of BZD/Z drugs per year, containing 78.7 DDD per container on average, accounting for a total of 518 annual DDD per user, which amounts to 1.4 DDD per day.

The percentage of affiliates over 18 years old that received at least one dispensation of BZD/Z drugs during the year of study was 11.6 %. An increment of BZD/Z-drug consumption was observed as the age of the

affiliates increased, being always higher in women (Figure 1).

The total average dispensation of BZD/Z drugs measured in DID was 77.6 daily DDD per 1,000 enrollees. The main BZD/Zs dispensed during the period were clonazepam with a DID of 36.8 and alprazolam with a DID of 27.6 (Table 1). They were followed, according to the quantities dispensed, by lorazepam (DID 5.4), zolpidem (DID 3.8), diazepam (DID 1.8), and bromazepam (DID 0.9). The least commonly dispensed BZD/Z drugs were eszopiclone and zopiclone, both with a DID lower than 0.1 (Table 1).

The main FDCs were bromazepam + trimebutine, bromazepam + domperidone + simethicone, chlordiazepoxide + sulphiride, alprazolam + domperidone, alprazolam + sulphiride.

Taking into account the half-life of the BZD/Z drugs dispensed, 50.7% of the total DDD accounted for a long half-life, 44.2% for a medium half-life and only 5.1% for a short half-life (Table 1).

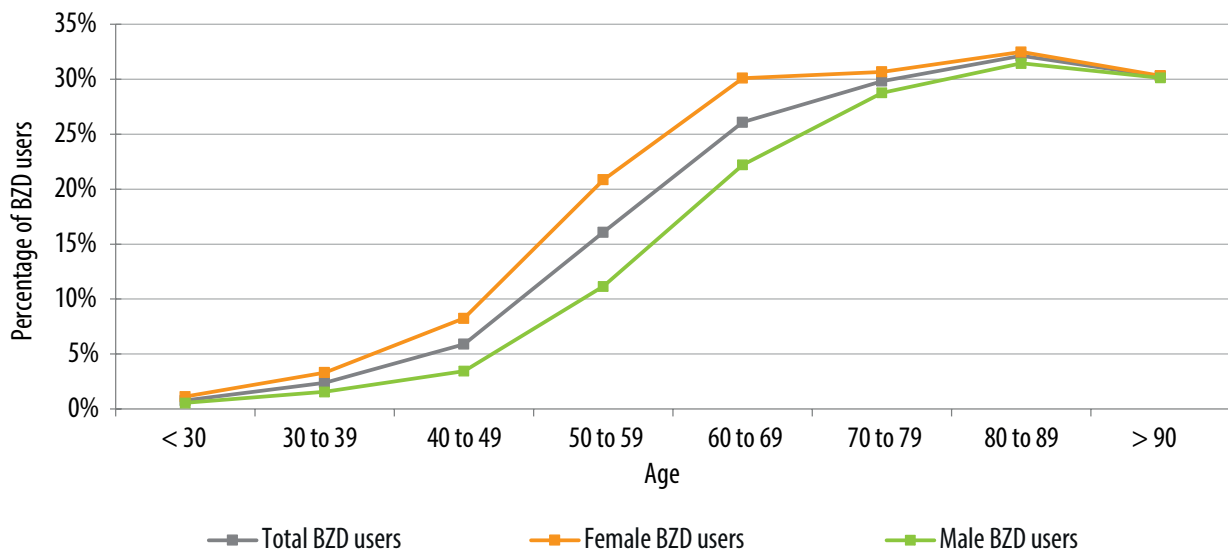


Figure 1. Annual prevalence of benzodiazepines and Z-drug use, according to age group and sex, in a social security organization (employment-based health insurance provider). Argentina, from April 1st, 2020 to March 31st, 2021.

Source: Own elaboration based on data provided by Instituto Obra Social de las Fuerzas Armadas y de Seguridad.
BZD= Benzodiazepines.

Table 1. Dispensation of benzodiazepines and Z-drugs by a social security organization (employment-based health insurance provider). Argentina, from April 1st, 2020 to March 31st, 2021.

Active ingredient	Half-life	DDD (ATC)	Total Milligrams	DID (DDD/1,000 enrollees /day)	Accumulated percentage of DID dispensed
Clonazepam*	Long	1	5,801,502	36.84	47.38
Alprazolam	Medium	1	4,350,442	27.63	82.92
Lorazepam	Medium	2.5	2,124,982	5.40	89.86
Zolpidem	Short	10	5,917,576	3.76	94.69
Diazepam	Long	10	2,891,394	1.84	97.05
Bromazepam	Medium	10	1,426,952	0.91	98.22
Clobazam	Long	20	2,249,820	0.71	99.14
Flunitrazepam	Medium	1	42,021	0.27	99.48
Midazolam	Short	15	486,025	0.21	99.75
Clordiazepóxido	Medium	30	485,025	0.10	99.88
Zopiclona	Short	10	131,152	0.08	99.98
Eszopiclona	Short	10	18,748	0.01	100.00

Source: Own elaboration based on data provided by Instituto Obra Social de las Fuerzas Armadas y de Seguridad.

DDD= defined daily doses; ATC= Anatomical Therapeutic Chemical Classification System; DID= defined daily dosis per 1,000 inhabitants per day.

*Regarding the DDD of 1 mg for clonazepam, we followed the works by Speranza et al,⁽⁷⁾ Quaglia Planas et al,⁽²²⁾ Zorzanelli et al,⁽²³⁾ Kurko et al.⁽²⁴⁾

Regarding the estimated duration and continuity of treatment, each user received on average 5.1 ± 3.1 dispensations throughout the year, with a maximum average period of consecutive dispensations of 3.0 ± 2.4 months.

The main reasons for prescription were anxiety (88.4%) and insomnia (11.6%). Nevertheless, diagnoses of these clinical conditions could be registered only in 24.2% of the patients.

We observed potential drug interactions of BZD/Z drugs, including the concomitant use with antacids in 1.3% of the cases, with antidepressants (1.1%), with estrogens/ progestogens (0.9%), with antipsychotics 0.8%, and with opioid derivatives (0.1%).

DISCUSSION

In an employment-based health insurance provider with national coverage in Argentina, the total dispensation of BZD/Z drugs, evaluated with a series of different parameters, proved to be really high. The most general indicator is population exposure measured as DID, which accounted for 77.6 DDD

dispensed on a daily basis per 1,000 affiliates over 18 years old. This quantity proved to be somewhat lower than the 112.4 DID registered in the study of an Argentine employment-based health insurance provider with provincial coverage,⁽²⁹⁾ and than the 82.9 DID consumed in a municipality near Rosario.⁽²²⁾ When compared to other studies conducted in other countries, the value found was just lower than the values registered in European countries with higher consumption such as Spain or Portugal (89.3 and 96.0 DID, respectively, in 2012)^(30,31,32) and higher than the findings reported in several studies conducted in Australia, Costa Rica, Honduras, Denmark, among others.^(33,34,35,36,37,38) Out of 26 countries of the Organization for Economic Cooperation and Development (OECD), ranked according to their consumption combining sedatives and hypnotics, the employment-based health insurance provider under review would be placed in the highest fifth position.⁽³⁹⁾

It should be noted that, given the predominance of consumers among individuals over 60 years old, the age composition of the study population determines the aggregate results and may limit comparability among

research studies. In this sense, the 20.1% of individuals over 60 years old registered with the employment-based health insurance provider being studied is somewhat lower than the 23.1% in North America and the 25.7% in Europe.⁽⁴⁰⁾ If the population distribution was leveled with the distribution in these regions, the values presented in this study could be somewhat higher.

Thanks to the information about users, we could calculate the prevalence of BZD/Z consumption, where 11.6 % is a value that is practically identical to the value reported in Spain.⁽³⁰⁾ When the analysis was performed based on sex and age, we could confirm that the use of BZD/Z drugs was higher in women than in men, and that consumption increased with age, the highest peak being among octogenarian individuals, in line with the findings reported by other authors that studied this type of consumption in different countries.^(41,42,43)

As to intensity of consumption, an average of 1.4 DDD per user and per day clearly surpass the values of 1.1 reported in the cited Argentine research study and the 0.8 reported in a study conducted in Spain.^(29,30) The general panorama is then a population with a high frequency and intensity of use of these psychotropic drugs.

With respect to the selection of the drugs used, the profile of consumption observed in this work was, mainly, BZD/Z drugs of a long half-life such as clonazepam, followed by drugs of a medium half-life such as alprazolam, which coincides with the observations described in other works carried out in Argentina, Brazil, and Uruguay.^(7,22,23,29,44) This preference for long-acting pharmaceuticals is contrary to the recommendations on the use of BZD/Zs in older adults, who are most of the users in this study. Beers's criteria⁽⁴⁵⁾ and the recommendations to review potentially inappropriate medications (PIM) included in the Screening Tool of Older Persons Prescriptions (STOPP) - Screening Tool to Alert Doctors to Right Treatment (START)⁽⁴⁶⁾ highlight that they imply a higher risk of prolonged sedation, confusion, balance disorder, and falls.

Potential drug interactions detected here were relatively rare. The most common drug interactions include the combination of BZD/Z use with antacids, female hormones, and antidepressants, which is an aspect already observed by other researchers.⁽²⁸⁾ The combined administration of these drugs can produce changes in their plasmatic concentration modifying their effects.

In analyzing the factors that determine consumer demand of BZD/Z drugs within a population, it can be postulated that the different prevalence rates of clinical conditions explain the different patterns of consumption of sedatives and hypnotics among countries, but existing evidence does not go in that direction. When comparing data of prevalence of anxiety disorders of the initiative Global Burden of Disease (GBD) with the data on consumption of sedatives and hypnotics by the Organization for Economic Cooperation and Development (OECD) mentioned above, the prevalence rate of anxiety conditions for the year 2017 ranged from 3.7% to 9.0% (a ratio of 2.5 between extreme values) while the consumption of BZD/Zs varied between 1.9 DID and 110.8 DID (a quotient of 58.3)^(39,47) If we take into account countries such as Portugal, which has maximum values of prevalence of anxiety and consumption of BZD/Zs, the correlation between pathology and treatment would be confirmed. However, countries like Spain and Italy, with practically identical levels of anxiety (6.0 and 6.1% respectively), have diametrically opposed levels of consumption of BZD/Zs (88.0 and 2.9 DID, respectively).^(39,47) According to the data reported by the Global Burden Disease (GBD) study, there is prevalence of anxiety disorders of 5.5% for Argentina, while values of 77.6 DID found in our study, along with the findings in other works,^(22,29) place us in a high-consumption pattern, similar to the situation in Spain.

It seems then that differences in the prescription of BZD/Z drugs have to do, to a considerable extent, with prescriptive habits inherent in each society. It has been argued that among the determinants we could identify the training of professionals, the health

system organization, legal regulations on psychotropic drugs, systems of medication coverage, and the degree of medicalization of non-pathological discomforts and of the social problems.⁽⁴⁸⁾

This set of factors will result in a definite incidence of new treatments with BZD/Z drugs that, according to the literature consulted, can range from 1.2% to 7.5% of the adult population every year, varying according to country, sex, and age of patients.^(49,50,51,52) Once the drug treatment is commenced, and due to its potential to generate dependence, a percentage of the patients under treatment will become chronic users of BZD/Z drugs, a fraction that is estimated to be 20% in a careful study with a 10-year follow-up.⁽⁵³⁾ In this way, the increasing prevalence of chronic BZD/Z users is shaped year after year, which in our study shows a fast growth between 40 and 60 years old, then reaching a plateau in the last decades of an individual's lifetime (Figure 1).

From a qualitative approach, a study conducted in Belgium on the motivations of primary care professionals to initiate a treatment with benzodiazepines showed that, although they perceive themselves as cautious, the pressure to offer an answer to a patient's psychosocial problem prevails. Among the reasons given, they mention lack of alternative proposals and lack of time during consultation, arguing that benzodiazepines are "the lesser evil," without perceiving that the addictive nature of these drugs is a problem in itself. It should be noted that demands from patients were not identified in this study as a factor for prescription.⁽⁵⁴⁾ In another US study, doctors highlighted efficacy and speed of action of benzodiazepines for treating anxiety, with great satisfaction from the patient. The use in older adults was not considered to be problematical since there was no increase in the dose or drug craving suggesting addiction. The professionals tended to be skeptical about the risks of chronic use and little optimistic as to the chances of achieving a reduction or suspension of drug use by their patients.⁽⁵⁵⁾

The appropriate way of using BZD/Zs continues to be controversial at an international level, showing largely different prescriptive practices. On the one hand, adverse effects deriving from a long-term use, psychological and physical dependence, and absence of research studies backing up efficacy from the continued use of these pharmaceuticals over years or for decades are highlighted.^(1,56,57) It can be argued that the example of countries with low level of BZD/Z use demonstrates that a substantial part of the chronic use in countries like Argentina proves to be unnecessary. On the other hand, some authors endorse the need to give an answer to problems having a difficult solution, in which the use of psychotropic drugs would constitute the lesser evil.⁽⁵⁴⁾ Other authors highlight that, despite decades of research in the field, a lot of key aspects of the discussion still require more conclusive evidence.⁽⁵⁸⁾ The search of efficacious non-pharmacologic alternatives for treating anxiety and insomnia proves to be crucial in this sense.⁽⁵⁹⁾

Limitations of this study

The duration and continuity of treatments could only be approached with indirect indicators, like number of annual dispensations per user and the maximum period of monthly consecutive dispensations. These show a minimum value for these variables, assuming that each dispensation covers up only a month of treatment. However, considering that dispensations account, on average, for 78.7 DDD per container, one would expect that each of them would cover – for many users – treatment for over a month. It is known that the use of BZDs over four months is a factor of high risk for developing adverse effects, especially among older adults.^(60,61)

The studied period coincided with the emergence of COVID-19 pandemic in Argentina. It is interesting to consider the possible role of economic and social crises in the consumer demand of BZD/Z drugs, taking into account research studies that have explored whether an increase in emotional stress may

result in a higher consumption of psychotropic drugs.^(62,63) However, a slant in the opposite direction is possible, since restrictions on citizens mobility and suspension of non-essential activities – including habitual medical care – may have hindered access to medication. As it was not possible to make a comparison with consumption data from previous years, the present work is not sufficient to determine the direction of the net effect.

Another limitation of this study was impossibility to register the reason for prescription of BZD/Z drugs in all cases, since a diagnosis is not always required or registered on the medication database of dispensations. Based on available data, it was observed that anxiety was the main reason for use, as opposed to other research studies conducted in Argentina in which indication for insomnia prevailed.⁽⁴⁴⁾

Based on the results obtained in this investigation, institutional actions were implemented for the purpose of giving rationality to BZD/Z prescription, such as educational interventions directed at the professionals of the employment-based health insurance provider, which included auditing prolonged

treatments, training prescribing professionals to limit terms of dispensation of BZD/Z drugs to the period suggested by the WHO, and proper communication by being in contact with the affiliates and health-care professionals to warn about potential drug interactions and expected adverse effects deriving from the use of this therapeutic group of drugs.

CONCLUSION

Consumption of BZD/Z drugs by the population of affiliates of the studied employment-based health insurance provider with national coverage in Argentina proved to be high, which does not conform to the good international practices of rational use of this group of psychotropic drugs. Implementation of corrective actions based on the results obtained in this study may not only control this situation, but also improve the quality of consumption, reducing the negative impact of inappropriate use of these drugs among treated individuals.

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CONFLICT OF INTERESTS

The authors of this work declare that, even though part of the research team works for the institution that facilitated the data explored in this study, they took all the necessary measures to make sure that this linkage does not represent a conflict of interest or does not influence the type of analysis and the findings presented in this article.

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