

Inappropriate use of benzodiazepines and their side effects*Uso inapropiado de benzodiazepinas y sus efectos secundarios**O uso inadequado de benzodiazepínicos e seus efeitos colaterais***Jéssica Bicalho Resende Lemos de Freitas¹**

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Abstract

Benzodiazepines (BZDs) are drugs that act on the central nervous system, generally used for their anxiolytic and sedative-hypnotic functionalities. The aim of the study is to demonstrate that the chronic and indiscriminate use of BZDs can bring many adverse events, which can lead to tolerance, dependence and withdrawal crises. This is a qualitative, descriptive research, carried out through an integrative literature review, in the SciELO, Google Scholar, Capes Journal Portal, and PubMed search bases. Ten studies were selected, which met the scope of the work. For the discussion, the following categories were listed: Benzodiazepines, The lack of guidance from a specialized doctor and its consequences in the use and Factors that influence the inappropriate use of benzodiazepines. Therefore, we sought to expand the offer of available studies on benzodiazepine drugs, alerting to the consequences arising from the prolonged use of drugs of this class.

Descriptors: Benzodiazepine; Drug Tolerance; Adverse Effects; Prescription Medicines; Substance Abuse.**Resumén**

Las benzodiazepinas (BZDs) son fármacos que actúan sobre el sistema nervioso central, generalmente utilizados por sus funcionalidades ansiolíticas y sedantes-hipnóticas. El objetivo del estudio es demostrar que el uso crónico e indiscriminado de BZD puede traer muchos eventos adversos, que pueden conducir a crisis de tolerancia, dependencia y abstinencia. Se trata de una investigación cualitativa, descriptiva, realizada a través de una revisión integradora de literatura, en las bases de búsqueda SciELO, Google Scholar, Capes Journal Portal y PubMed. Se seleccionaron 10 estudios, que cumplieron con el alcance del trabajo. Para la discusión, se enumeraron las siguientes categorías: Benzodiazepinas, La falta de orientación de un médico especialista y sus consecuencias en el uso y Factores que influyen en el uso inadecuado de las benzodiazepinas. Por lo tanto, buscamos ampliar la oferta de estudios disponibles sobre las benzodiazepinas, alertando sobre las consecuencias derivadas del uso prolongado de drogas de esta clase.

Descriptores: Benzodiazepina; Tolerancia a las Drogas; Efectos Adversos; Medicamentos Recetados; Abuso de Sustancias.**Resumo**

Os benzodiazepínicos (BZDs) são drogas que agem no sistema nervoso central, geralmente utilizados por suas funcionalidades ansiolíticas e sedativo-hipnóticas. O objetivo do estudo é demonstrar que o uso crônico e indiscriminado dos BZDs pode trazer muitos eventos adversos, podendo levar a tolerância, dependência e crises de abstinência. Trata-se de uma pesquisa qualitativa, do tipo descritiva, realizada por meio de uma revisão integrativa da literatura, nas bases de pesquisa SciELO, Google Acadêmico, Portal de Periódicos da Capes, e PubMed. Selecionou-se 10 estudos, que atendiam ao escopo do trabalho. Para a discussão, elencaram-se as seguintes categorias: Benzodiazepínicos, A falta de orientação de um médico especializado e suas consequências no uso e Fatores que influenciam no uso inadequado dos benzodiazepínicos. Portanto, buscou-se ampliar a oferta de estudos disponíveis sobre os fármacos benzodiazepínicos, alertando para as consequências oriundas do uso prolongado dos medicamentos desta classe.

Descriptores: Benzodiazepina; Tolerância a Medicamentos; Efeitos Adversos; Medicamentos com Prescrição; Abuso de Substâncias.

Introduction

The class of benzodiazepines (BZDs) includes drugs that have been on the market for a few decades, having direct action on the Central Nervous System (CNS), providing a feeling of mental rest, in addition to sedation, granting the user relaxation. The high efficiency of this class makes them addictive for those who use them, emphasizing the need to be controlled drugs and used only with the presentation of a medical prescription^{1,2}.

In addition, the use of BZDs is not indicated when used for periods that exceed four months, as, after this period in use, there is a reduction in the expected anxiolytic effect and in its effectiveness as a sleep inducer, so that adverse events begin to appear and even overcome its therapeutic effect³.

Still, there are doctors who, due to the indiscriminate demand by patients, end up medicalizing the presence of any psychological or physical suffering of the patient, such as personal and work conflicts. In addition, the abuse of BZDs can configure physiological and psychological dependence³.

Thus, the widespread use of psychotropic drugs of the benzodiazepine class is an obstacle faced by several countries in the world. In view of this, contemporary society suffers from a very high state of anguish, frenzy and changes that disturb the entire human emotional state, which restricts sleep and increases fatigue. These variables raise the search for substances that alleviate these pains, and the use of benzodiazepines has been the answer to these questions for decades, even if in a wrong and unjustified way. In Brazil, this is confirmed by the data, which demonstrate that this type of drug is among the best-selling controlled drugs in the country¹⁻⁴.

Accordingly, prolonged and indiscriminate use of benzodiazepines is directly linked to several side effects, including dementia, cognitive impairment, psychomotor disorders, traffic accidents, all-day sleepiness, tolerance and dependence, in addition to restricted mobility and greater introspection in the elderly, in these, the risk of falls and fractures is included. As a result, all benzodiazepines are identified as drugs with inappropriate potential, their prescription should be avoided and they should only be prescribed under a relevant need, evaluated by the physician⁵.

However, despite such a recommendation, the use of benzodiazepines has increased exponentially; becoming a worrying fact since the risk of adverse events also increases considerably⁵.

This study is justified by the events frequently seen in everyday life, given that the misuse of BZDs seems to bring together both patients and doctors, as they prescribe the medication and pharmacists who make them unnecessary. In this way, the information that is not disseminated and the lack of understanding is responsible for the consequences that this misuse will cause a posteriori from the misuse of BZDs.

The study was motivated by the great reports in the Family Health Program (PSFs), by the teams of health agents, of the excessive use of BZDs by a large portion of the population, thus, there is a need to understand the dependence on these drugs and prolonged use and its consequences.

This review aims to expand the offer of available studies on benzodiazepine drugs, alerting to the consequences arising from the prolonged use of drugs of this class, mainly due to the lack of adequate follow-up in psychiatric treatment.

Methodology

This is a qualitative, descriptive research, which aims to obtain a detailed and complex view, to understand the human phenomena related to the use of benzodiazepines, in order to understand the side effects to which they were analyzed.

Thus, the description of the phenomenon will make it possible to enumerate the importance of controlling the use of benzodiazepines for human health, as well as the collection of information, with variables, so that they compose the consequences of their indiscriminate use. For this, an integrative literature review will be used, which aims to survey theoretical references already written and case reports produced in the study area to explain veiled information⁶⁻⁸.

A search was carried out in scientific articles related to the topic under debate, in the search platforms Scientific Electronic Library Online (SciELO), Google Scholar, Portal of Periodicals of the Coordination for the Improvement of Higher Education Personnel (Capes) and PubMed. Additionally, a Pharmacology book was consulted.

The survey of articles was carried out considering the following descriptors: benzodiazepine, drug tolerance, adverse events, prescription drugs, substance abuse. Concurrently with the use of the Boolean operator "AND".

During the selection of theoretical references, the following inclusion criteria were adopted: to be related to the theme and to respond to the guiding question, as well as the full online availability, published in the Portuguese or English language. It was adopted as temporal cut, scientific productions published from 2018 to 2022, however, during the selection process, a production dated 2017 was identified, in which the theme includes important data, so it was decided to include there.

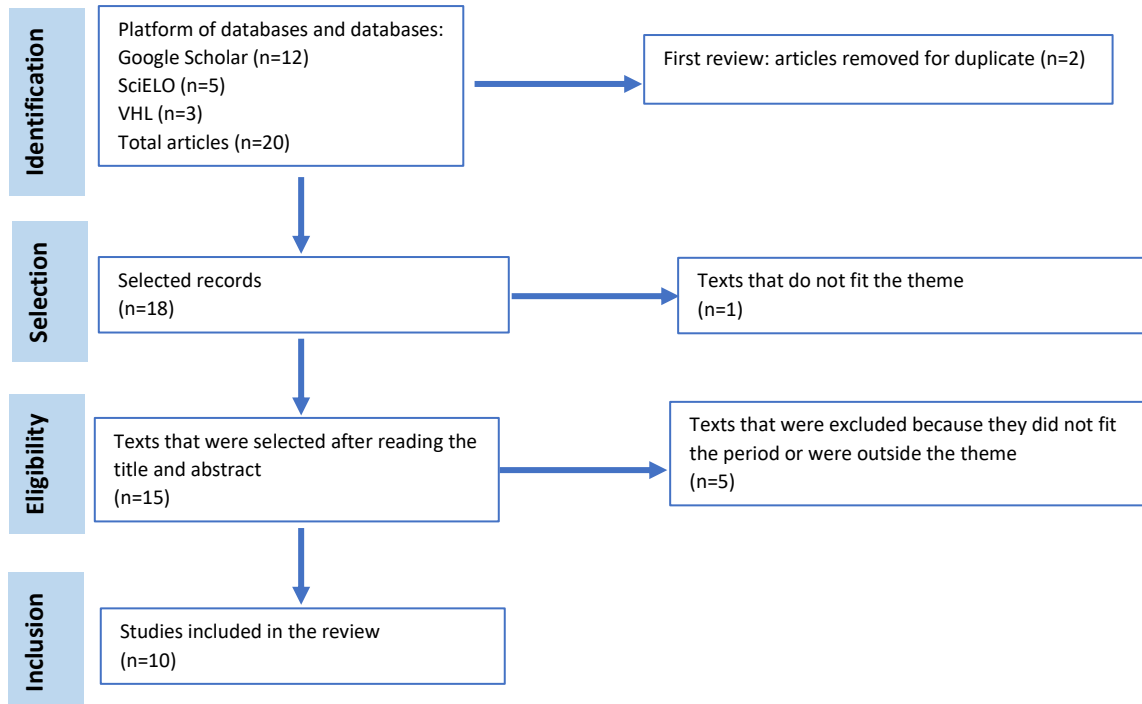
As an exclusion criterion was considered repeated articles and saturation of the content.

Figure 1 presents the stages of search and selection of the articles found, according to the pre-established eligibility criteria to reach the funnel where the works used as the basis for this research are concentrated.

Data analysis will be carried out by categorical content analysis, which consists of breaking up the text into analogically grouped categories, since it is the best alternative to study from qualitative data⁹.



Figure 1. Flowchart used in the selection of studies. Matipó, MG, Brazil, 2022



Results and Discussion

After reviewing the articles, 10 works were highlighted, all of them of Brazilian origin. Only one article has data collected in the field in another country, in the case of Cuba, which is quantitative and all the others have qualitative characteristics^{1,9}.

Therefore, Chart 1 is intended to demonstrate the highlighted articles collected that led to the realization of this article with its main findings. The summary table presented below makes it clear that all studies present discussions and data on the use of benzodiazepines and their adverse effects when poorly administered.

Chart 1. Characteristics of the selected articles. Matipó, MG, Brazil, 2016-2022

ID	Title	Year	Objective	Main Findings
A01 (Sousa et al., 2020)	AS CONSEQUÊNCIAS E OS EFEITOS DECORRENTES DO USO INDISCRIMINADO E PROLONGADO DE BENZODIAZEPÍNICO: UMA REVISÃO DA LITERATURA	2020	Identify the consequences resulting from the indiscriminate use of benzodiazepines, age group and gender of users and the risks of their prolonged use.	The study emphasizes the relevance of BZDs in the treatment of anxiety disorder. However, it emphasizes the need for care in use due to the adverse effects caused by prolonged use. The high rate of inappropriate prescriptions was also highlighted. In addition to the fact that they report that consumers who stand out in terms of age are elderly and in terms of gender, most are women.
A02 (Senra et al., 2021)	EFEITOS COLATERAIS DO USO CRÔNICO E INDISCRIMINADO DE BENZODIAZEPÍNICO: UMA REVISÃO NARRATIVA	2021	Demonstrate the side effects of chronic and indiscriminate use of benzodiazepines and the damage that this practice can cause in the individual, social and physical spheres of individuals who use this medication.	It refers to the high therapeutic index of BZDs, which makes them safe drugs. In addition, it warns of the lack of guidance on the part of the doctor with the patient. In Brazil, the main place of prescription is primary care, where the scarcity of long-term integrated care facilitates inappropriate use, resulting in several dose-dependent adverse effects, possible irreversibility and difficulty in weaning.
A03 (Fegadoll i et al., 2019)	USO E ABUSO DE BENZODIAZEPÍNICO NA ATENÇÃO PRIMÁRIA À SAÚDE: PRÁTICAS PROFISSIONAIS NO BRASIL E EM CUBA	2019	Understanding of sanitary practices in the provision of benzodiazepines in primary care and the meanings that health professionals attribute to these.	It highlights the disarticulation between primary care and the psychiatric specialty, resulting in a process of renewal of undue prescription in the basic health unit (UBS). In addition, it warns of unjustifiable prescriptions and renewals, mainly due to quick consultations at the UBS and a concept that identifies the consequences resulting from the indiscriminate use of benzodiazepines, age group and gender of users and the risks of their prolonged use. "necessary evil". The indication of this class for menopausal women and the elderly represents a common and worrying action.



A04 (Andrade et al., 2020)	USO CRÔNICO E INDISCRIMINADO DE BENZODIAZEPÍNICO: UMA REVISÃO DE LITERATURA	2020	Identify which benzodiazepines are most used in Brazil, as well as outline the profile of users.	The objective is to identify which BZDs are most used in Brazil, outlining the profile of users of this pharmacological class. In the studies listed, the most consumed BZDs was Lorazepam, but for cases of anxiety, Clonazepam is the drug of first choice. Regarding the profile of users, the age group that most uses these drugs are the elderly. As for sex, women use it more, since they are the ones who most seek the health system. With regard to males, consumption is more frequent among younger people, mainly for recreational use and association with other psychoactive substances.
A05 (Silva et al., 2021)	O USO DE BENZODIAZEPÍNICOS ENTRE AS MULHERES NO CONTEXTO DA RAPS	2021	Conduct a literature review about the use of benzodiazepine drugs by women who are assisted in services offered by RAPS.	From the data analysis, most benzodiazepine users are women and make indiscriminate use of the drug, due to the fact that drug treatment is often not justified, resulting in an irrational use of the drug. The mean age of the study users was 52.45 years. According to Silva, Lima and Ruas (2018), countless causes favor the irrational use of medication, factors that appear in their own life history and subjectivity, but which come from a social demand that wants a socially constructed woman. Silveira et al. states that if there is a need to use medication to treat women with pain that is born in a social field, a clinic will not be being made, and the intervention will always be traced in this medicalizing method. This justification of the need to continue domestic work is pointed out by Mendonça et al. (2008) as a reaffirmation of gender roles, as the drug causes calm to extinguish women's reactions to certain social models of behavior.
A06 (Freire et al., 2021)	UTILIZAÇÃO DE BENZODIAZEPÍNICOS EM IDOSOS BRASILEIROS: UM ESTUDO DE BASE POPULACIONAL	2021	Evaluate the use of benzodiazepines (BZDs) in Brazilian elderly.	According to the study, the most used BZDs in Brazil were clonazepam and diazepam, both free in the SUS. In addition, there was a higher prevalence among women, elderly people between 70 and 79 years old, individuals with depression and comorbidities, and who were hospitalized in the last 12 months. There were no correlations between class medications and socioeconomic status. In addition, the percentage of BZDs obtained over-the-counter was less than 9%, underscoring the importance of physician awareness aimed at patient independence and autonomy.
A07 (Che 2016)	USO INADEQUADO DE BENZODIAZEPÍNICOS EM IDOSOS: PROJETO DE INTERVENÇÃO	2016	Develop an intervention plan aimed at reducing the use of benzodiazepines by users of the elderly population enrolled in the family health team at UBS Morada de Sol.	The study analyzes the inappropriate use of BZDs in the elderly in the community of Cianorte in Santa Catarina, which, through the planning of Primary Care, found the high rate of use of BZDs in the elderly age group, which for reasons such as: lack of education by the UBS, free access to many drugs and drug interactions with other drugs used continuously. This problem is considered a risk to their quality of life. The article aims to develop an intervention plan in order to minimize the use of BZDs by the elderly in the UBS described.
A08 (Martins, et al., 2017)	O QUE NÃO TEM REMÉDIO NEM NUNCA TERÁ": UM ESTUDO A PARTIR DO USO ABUSIVO DE BENZODIAZEPÍNICO EM MULHER	2017	Analyze, from the feminine singularity, the abuse of benzodiazepine drugs of a woman and the role of the nurse in the assistance to the singular psychic suffering.	The exacerbated use of benzodiazepines in women is explained by factors related to both social issues and power relations where male people exercise a controlling role in society, over female people. Epidemiology shows a higher prevalence of benzodiazepine use in women, as such data are up to three times higher than in men. Brazilian women have these higher rates, especially when divorced or widowed, with low income and, on average, between 60 and 69 years of age. The study used psychoanalysis as a research reference, which made it possible for the study to be more focused on the uniqueness of each woman.
A09 (Prado, et al., 2019)	IMPLANTAÇÃO DE GRUPOS DE APOIO PARA PACIENTES COM DIAGNÓSTICO DE INSÔNIA E DEPENDÊNCIA A	2016	Improve the therapeutic and behavioral approach of patients diagnosed with insomnia and/or dependence on benzodiazepine drugs, at UBS Tabuleiro II in Matinhos / PR.	Insomnia is defined as the recurrent difficulty in initiating or maintaining sleep, it can also be characterized by early awakenings and non-restorative sleep. Insomnia is often associated with dependence on benzodiazepine medications. The study shows that in most of these patients we can find an association with other clinical



	BENZODIAZEPÍNICO: EXPERIÊNCIA NA UNIDADE BÁSICA DE SAÚDE TABULEIRO II DE MATINHOS – PR			disorders, being called secondary insomnia. The prevalence is higher in the elderly, being 60% and in women.
A10 (Lopes, et al.,2019)	UTILIZAÇÃO CRÔNICA DE BENZODIAZEPÍNICOS NO TRATAMENTO DA ANSIEDADE NO ÂMBITO DA ATENÇÃO PRIMÁRIA: UMA REVISÃO DE LITERATURA	2019	Evaluate the age group and gender of patients who chronically use this class of medication, inform according to literary refinement the maximum time of use of benzodiazepines, know the most prescribed BZD today for the treatment of anxiety and identify the main risks and effects adverse effects with chronic use of benzodiazepines in the treatment of anxiety in primary care.	This article highlights that the benzodiazepine most transcribed is clonazepam, in addition to being recommended to patients without the help of a psychiatrist, in addition to the lack of information about these drugs by professionals in primary care. This factor is directly related to chronic use, therefore, it generates several health risks. Among the exemplified risks are: anterograde amnesia, decrease, sedation, of cognition, reduction of coordination, increased risk of accidents and tolerances. In the elderly, a risk group for the use of benzodiazepines is presented because of incorrect use: fractures resulting from falls, psychomotor retardation and excessive sedation.

Benzodiazepines

One of the main treatments related to anxiety requires the use of benzodiazepines. However, there is concern about the use of this drug, due to its potential for abuse and dependence, and it has negative effects on the areas of cognition and memory. It acts adversely on the person's motor control and potentiates the effects of other sedatives such as alcohol.

In the acute treatment of anxiety, only benzodiazepines and β -adrenergic antagonists are effective. Benzodiazepines are effective in the long and short term of treatment, with persistent or recurrent attacks of anxiety. Withdrawal of benzodiazepines cannot occur crudely and quickly, as it can increase anxiety and risk of seizures. Because of this, it is extremely important that the discontinuation of this medication is done gradually, that the weaning is done correctly¹⁰.

Benzodiazepine sedative-hypnotics are not capable of causing generalized CNS depression, as they do not produce anesthesia or fatal intoxication, unless other drugs with depressant actions are administered concomitantly. However, coma may occur with the use of very high doses¹⁰.

An important fact to be seen is that in Brazil, in 2019, more than 13 million people were estimated to use this drug, also showing that 1 in 10 Brazilians have already been treated with benzodiazepines. In 2020, there was a great demand from patients on chronic use of benzodiazepines without proper medical follow-up, several reports about weaning this medication incorrectly, resulting in CNS problems and addictions. In addition, this medication needs correct follow-up with psychology and medicine professionals, offering better support to the patient and seeing him as a whole^{11,12}.

The lack of guidance from a specialized doctor and its consequences in the use

In Brazil, most benzodiazepine prescriptions come from primary care services, and in the vast majority of cases, inadequately. Much is heard about the lack of time for a well-designed consultation, leading to difficulty in developing alternative therapeutic strategies. Basic health

units have a great demand for care, and the doctor, due to overload, or lack of interest, does not seek to understand his patient as a whole or the reasons that led him to use the medication¹³.

Studies show that it is difficult for primary care professionals to initiate treatment, when in fact they only continue previous prescriptions, most of them with inadequate indication⁴. This fact leads to an intense search for revenue renewal, without worrying about the time of use or the real need for continuation. The great demand and lack of knowledge of professionals contribute to the chronic use of psychotropic drugs, causing numerous side effects, such as ataxia, sedation, amnesia and dependence.

The search for a trained professional is as important as the treatment itself, the way in which the patient receives guidance, along with continuous care, results in the use in an appropriate way, including time of use and weaning, in addition to enabling identification and correction of possible adverse effects. Despite the fact that the Family Health Strategy (ESF) is also an environment that provides services aimed at mental health, due to the proximity of the teams to the families and the community, there is a certain distance between primary care and psychiatry. Workers in primary care seek to identify minor mental disorders, whose signs and symptoms need to be addressed so as not to trigger disorders that are more complex. In this sense, research indicates that insomnia is one of the most common symptoms, with benzodiazepines being the most prescribed drugs. But the lack of skilled monitoring results in misuse leading to side effects and risk of addiction^{13,14}.

It is necessary to recognize that there are numerous obstacles to the rational use of BZDs, since there is self-medication, misinformation, a wide variety of products, in addition to pharmacists and sellers who do not respect national legislation and, mainly, inadequate prescriptions. All these practices can be serious for the health of the population, causing drug dependence, which is very common in the use of psychotropic substances, and even serious side effects.

Therefore, according to the literature used for this study, it is clear that the use of controlled drugs has its



particularities, as the effects appear with different intensities. The action profile of these drugs is related to the type of medication prescribed, and must be in accordance with the pharmacological criteria established with the diagnosed disease. In this sense, the health professional should seek to prescribe them in the lowest possible therapeutic dose and for short periods, according to the diagnosed pathology, thus reducing the risk of dependence¹³. The authors point out that the use of BZDs should not exceed a period of four months, because after that time, there is a reduction in the anxiolytic effect and a decrease in its efficiency as a sleep reducer, so that adverse events begin to appear and, including overcoming its therapeutic effect. However, it is important to emphasize that even respecting the time of use; the withdrawal of benzodiazepines can generate signs and symptoms suggestive of withdrawal. However, after an initial period of 5 weeks, an improvement in the quality of life of patients can be seen, including a reduction in anxiety³.

Although there is no consensual way to wean BZDs, studies suggest measures for their withdrawal, such as, for patients on low-dose use, a 50% reduction of the dose already in use per week should be reduced until its total withdrawal. For users who are subjected to high doses, or with difficulties in their withdrawal, the reduction can be reduced to 25% every two weeks or reduced by 10% of the original dose every 2 weeks until reaching 20% of the original dose. and from there, reduce by 5% every 2 weeks. However, they are suggestive strategies, what will determine this reduction, and speed, is the clinical response of the user and their reactions to the process, which should always be adjusted according to their particularities¹⁵.

Factors influencing inappropriate use of benzodiazepines

For years, the indiscriminate use of BZDs in the world has been noted, especially their use for long periods and in unnecessary situations⁴, making it impossible to carry out a more in-depth and individualized analysis carried out by a specific professional in the area, thus triggering another factor, which is the non-individualization of each patient, not taking into account some risk factors, such as lung diseases and increasing age. Such factors make the inappropriate use of BZDs become something progressive, causing chronic dependence on its users. This is because users of BZDs are not properly instructed regarding the drugs that, most of the time, think that it is a lifelong treatment, while it is not the treatment proposal, in which it must have a beginning, middle and end.

One of the groups most affected by the inappropriate use of BZDs are women, with insomnia as the main reason. Historically, women have always been disadvantaged when compared by gender, causing several factors of this difference to directly influence mental and physical health. As factors, we can mention: domestic work, marital status, number of children, labor rights, exposure to physical and sexual violence, maternity factors and double or triple shifts¹⁶. This historical heritage makes women more and more one of the most affected groups, with the

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aggravating age and also because they are usually more concerned about their health than men, the majority being in doctors' offices and basic health units.

Another group affected on a large scale are the elderly, in which the constant use of these drugs generates some side effects, such as fractures resulting from falls, psychomotor slowness and excessive sedation¹³. Therefore, the use of BZDs can cause the quality of life of the elderly to decrease considerably and what was a solution, becomes a problem, as caused by inappropriate use, that is, it can be reversed so that it does not occur in new treatments, under the supervision of a psychiatrist.

Neglect in relation to the treatment of elderly users of BZDs is a public health problem, since, even with the recommendations, the number of elderly people who are long-term dependent on BZDs is increasing. It is then noted that the protocol is flawed, making it impossible to have a unique and individual view of each patient and the ideal treatment for each case, hindering the progression of health in the cases, since, even though they are efficient, the BZDs are being used inappropriately. This form of application can cause numerous side effects, of different categories and intensity, which can be moderate or even severe. According to data, the predominant groups are women between 70 and 79 years of age, those with poor and very poor self-perception of health, or multimorbidity, with emphasis on women and the elderly^{5,17}.

Self-medication is yet another factor that influences this inappropriate use of benzodiazepines, and this practice deserves special attention among students in the health area, configuring a vicious behavior, mainly due to prior knowledge of pharmacological bases. The indiscriminate use of some benzodiazepines is part of the routine of young students, who, based on their pharmacological knowledge, seek relief from symptoms, try to minimize frustrations and health problems. In this way, students feel more confident when self-medicating, but the lack of follow-up by a qualified professional can result in numerous consequences and adverse effects. Therefore, the health risks due to self-medication are also considered a public health problem, since the consequences of this practice can become serious¹⁸.

Final Considerations

There is a large gap between theory and practice in the use of benzodiazepines, which directly influences the treatment of individuals with psychiatric disorders and, consequently, their quality of life.

In order to be effective in prescribing benzodiazepines, some actions are necessary, such as: psychiatric medical professionals trained to diagnose and prescribe, primary health care units with psychiatric care, multidisciplinary mental health care - with psychiatrists, nurses, psychiatrists, psychologists, social workers -, expansion of the means of light and light-hard technology in health education, greater rigidity in the release of drugs of the benzodiazepine class by pharmaceutical professionals and even the creation of new mechanisms to



control these drugs, as it becomes very clear that the indiscriminate use of benzodiazepines is a risk to the health of society.

It is expected that the present study will arouse the interest of health unit managers, as well as government agencies, to implement stricter control strategies and fines.

As well as other researchers, in order to continue studies on this topic, putting an end to the scarcity of published scientific evidence, which results in the critical-reflective evaluation of assistant professionals about their performance with the patient who seeks mental health assistance.

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