The Rational Use of Benzodiazepines: The Importance of Medical and/or Pharmaceutical Guidance

O Uso Racional de Benzodiazepínicos: Importância da Orientação Médica e/ou Farmacêutica

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ABSTRACT

A growing demand for drugs that may relieve symptoms such as stress and anxiety, with inappropriate prescriptions and unprepared professionals, contribute to the increasing misuse of benzodiazepine class drugs, increasing the likelihood of adverse reactions, intoxication, and dependence on these drugs. Chronic and indiscriminate use can lead to the development of tolerance and dependence to BZDs. Then, the present work aimed to prepare a narrative bibliographic review addressing the use of benzodiazepines and medical and/or pharmaceutical guidance/advice on the risks of the main adverse effects of them. The papers were obtained by direct search, using the following keywords: benzodiazepines, dependence, indiscriminate use. Two publications were found, one Brazilian and one Lebanese. Although the publications are almost 20 years apart and were published in different countries, we observed that data such as frequency of use of the drug, lack of counseling/incomplete counseling and duration of use of the drug by the majority of the population are preserved. These results, together with the high rate of use of benzodiazepines as a measure to relieve insomnia and anxiety, reinforce the idea of the need to develop deprescription policies and, when the drug is really necessary, to provide correct and complete guidance on the risk of the main adverse effects of this class of drugs.

Keywords: Benzodiazepine. Indiscriminate use. Patient guidance.

RESUMO

A crescente procura por medicamentos que venham aliviar sintomas como estresse e ansiedade, juntamente com prescrições inapropriadas de profissionais pouco preparados contribuem para o crescente uso indevido de medicamentos da classe dos benzodiazepínicos (BZDs) aumentando a probabilidade de reações adversas, intoxicação e também dependência a esses fármacos. O uso crônico e indiscriminado pode levar ao desenvolvimento de tolerância e dependência aos BZSDs. Assim, este trabalho teve como objetivo avaliar, através de uma revisão bibliográfica narrativa, o uso de benzodiazepinas e a orientação / aconselhamento médico e/ou farmacêutico sobre os riscos dos seus principais efeitos adversos. Os artigos científicos foram obtidos por busca direta, utilizando as seguintes palavras-chaves e suas correspondentes em inglês: benzodiazepínicos, dependência, uso indiscriminado. Duas publicações foram encontradas, uma brasileira e uma libanesa. Embora as publicações tenham uma diferença de quase 20 anos e tenham ocorrido em países diferentes, observamos que dados, como freqüência de utilização do fármaco, falta de aconselhamento / aconselhamento incompleto e tempo de consumo do medicamento pela maioria da população são conservados. Tais resultados, em conjunto com a alta taxa de utilização das benzodiazepinas como medida de alívio de insônia e ansiedade, reforçam a idéia da necessidade de elaboração de políticas de desprescrição e, quando o medicamento for realmente necessário, orientar correta e completamente sobre o risco dos principais efeitos adversos dessa classe de medicamentos.

Palavras-chaves: Benzodiazepínicos.Uso indiscriminado.Orientação ao paciente.

INTRODUCTION

Changes in the population's lifestyle habits have led to an increasing demand for medications designed to alleviate symptoms such as stress and anxiety. These increased demands, together with inappropriate prescriptions from poorly trained professionals, contribute to the growing indiscriminate use of medications responsible for alleviating these symptoms, belonging to the class of benzodiazepines (BZDs). This indiscriminate use contributes to the increase in adverse reactions, poisoning and also to dependence on these drugs (Auchewski et al., 2004; Soyka, 2017; Ait-Daoud et al., 2018; Liu et al., 2020).

BZDs are drugs that have the ability to depress the Central Nervous System (CNS), and are considered the most widely used group in the treatment of anxiety and insomnia. The main beneficial effects of this class are: reduction of anxiety, sedation, muscle relaxation and anticonvulsant effect (Ait-Daoud et al., 2018; Zahran et al., 2022; Smid, Mlakar & Stukovnik, 2024).

The use of substances to induce sleep, obtain sedation and relief from everyday stresses seems to have accompanied man since ancient

times. There are reports of the use of substances capable of producing stupor and a certain degree of unconsciousness, a state in which religious and "magical" rituals and medical procedures were carried out, in writings from all ancient cultures (Hollister, 1983; Harvey, 1985; Ait-Daoud et al., 2018; Zahran et al., 2022; Smid, Mlakar & Stukovnik, 2024).

Over time, knowledge has deepened and new compounds have been synthesized with the therapeutic purpose of reducing anxiety. The first BZD, chlordiazepoxide, was synthesized by accident in 1961, and the unusual seven-membered ring was produced as a result of a reaction that went wrong in the Hoffman-la Roche laboratories. Their unexpected pharmacological activity was recognized in a routine screening procedure and benzodiazepines soon became the most widely prescribed drugs in the pharmacopoeia (Rang, Dale & Ritter, 2015).

From structural changes in the original molecule, several benzodiazepine derivatives were synthesized (Swanson, 1975; Yu, Greenblatt & Greenblat, 2022; Peng, Morford & Levander, 2022). In 1963, diazepam was launched on the market, which emerged as an alternative to chlordiazepoxide, not because it was more effective than the latter, but because some consumers found the original compound to be a little "bitter" (Ayd, 1980; Allgulander, 1986). Other derivatives, such as nitrazepam and oxazepam, were introduced in 1965, and lorazepam and flurazepam in 1970 (Swanson, 1975; Peng, Morford & Levander; Yu, Greenblatt & Greenblat, 2022). Since their introduction on the market, several studies have been carried out with the aim of evaluating the extent of consumption of sedative-hypnotic drugs (Ayd, 1980; Allgulander, 1986).

METHODOLOGY

The strategy used was a narrative bibliographic review, a modality that uses a systematic and orderly process to identify, analyze, evaluate and synthesize studies related to a selected topic or phenomenon, in a comprehensive manner (Toronto & Remington, 2020).

In this study, three databases were consulted: PubMed®, SciELO, and Medical Literature Analysis and Retrieval System Online (MEDLINE). The keywords chosen were “benzodiazepines”, “indiscriminate use” and “side effects”. The inclusion criteria selected for the selection of articles were: a) Experimental articles in human; b) Published in English, Portuguese or Spanish; c) Published between 1980 and 2024; d) With full text available for access. The following were considered ineligible for this study: a) Duplicates; b) Works that did not address the topic of interest in their title or abstract.

After the search, three studies were found, of which one was excluded because it only

addressed satisfaction/dissatisfaction with medical advice received, without evidencing the quantity, type or period of consumption of the benzodiazepine. In the end, two studies were used to construct this review.

LITERATURE REVIEW

Anxiety and Depression

Anxiety is a vague and unpleasant feeling of fear, apprehension, characterized by tension or discomfort (Allen, 1995). In the anxious state, reactions of defensive behaviors, autonomic reflexes, awakening, alertness, secretion of corticosteroids and negative emotions occur in an anticipatory manner, independent of external events. When these symptoms interfere with normal productive activities, we can distinguish this state of anxiety as “pathological” and not “normal” (Bernstein et al., 1996). Generalized anxiety disorder (a constant state of excessive anxiety that has no clear reason or focus), panic disorder (sudden attacks of uncontrollable fear, associated with sweating, tachycardia, chest pains, tremors and a feeling of suffocation), phobias (fears of specific objects or situations), post-traumatic stress disorder (stress caused by memories of past experiences), obsessive-compulsive disorder (behavior with compulsive rituals, dominated by irrational anxiety), are the clinically recognized anxiety disorders (Bernstein et al., 1996).

Anxiety disorders are clinical conditions in which the symptoms are primary anxiety and are not derived from other psychiatric conditions. Anxiety symptoms, and not the disorder itself, often occur in other psychiatric disorders. It is anxiety that is explained by the symptoms of the primary disorder (e.g., depression and schizophrenic outbreak) and does not constitute a set of symptoms that determines an anxiety disorder (Bernstein et al., 1996).

Depression represents a spectrum of disorders with a variety of severity and a high frequency of comorbidities. Depressive illnesses range from mild, self-limiting illnesses to extremely serious illnesses that may include high suicidal potential, psychosis, and severe functional impairment. Although the likelihood of receiving treatment for depression or anxiety has improved, there are still problems related to duration, dosage, and adherence to treatment. Unfortunately, people with depressive or anxiety disorders continue to suffer considerable delays in diagnosis and appropriate treatment (Brunton, Chabner & Knollmann, 2012).

Pharmacological Treatment of Anxiety

A variety of agents and drug classes provide anxiolytic effects (Brunton, Chabner & Knollmann, 2012). The drug treatment of choice for anxiety is determined by the specific anxiety-related disorders and the clinical need for acute anxiolytic effects (Millan, 2003). When an

immediate anxiolytic effect is desired, benzodiazepines are usually selected (Brunton, Chabner & Knollmann, 2012).

Benzodiazepines are effective anxiolytics as both acute and chronic treatment. There is concern about their use due to their potential for abuse and dependence, as well as negative effects on cognition and memory (Brunton, Chabner & Knollmann, 2012). Benzodiazepines, such as alprazolam, chlordiazepoxide, clonazepam, clorazepate, diazepam, lorazepam and oxazepam, are effective in the treatment of generalized anxiety disorder, panic disorder and situational anxiety. In addition to their anxiolytic effects, benzodiazepines produce sedative, hypnotic, anesthetic, anticonvulsant and muscle relaxation effects. Benzodiazepines also impair cognitive performance and memory, adversely affect motor control and potentiate the effects of other sedatives, including alcohol. The anxiolytic effects of this class of drugs are mediated by allosteric interactions with the pentameric benzodiazepine $GABA_A$ receptor complex, especially those $GABA_A$ receptors composed of □2, □3 and □5 subunits. The main effect of benzodiazepines is to increase the inhibitory effects of the neurotransmitter GABA (Brunton, Chabner & Knollmann, 2012).

Serotonin (5HT) reuptake inhibitors, and 5HT/norepinephrine reuptake inhibitors are effective in treating generalized anxiety, phobias, social anxiety disorder, and post-traumatic stress disorder. Monoamine oxidase inhibitors and tricyclic antidepressants are also effective, but serotonin reuptake inhibitors have fewer adverse effects (Rang, Dale &Ritter, 2015).

Antihistamines, such as hydroxyzine, and several sedative-hypnotic agents have been used as anxiolytics, but are generally not recommended due to their side effect profile. Hydroxyzine, which produces short-term sedation, has been used in patients who cannot use other types of anxiolytics (Brunton, Chabner & Knollmann, 2012).

All barbiturates have central nervous system depressant activity. Barbiturates that continue to be used clinically include phenobarbital, which shares with benzodiazepines the ability to increase GABA action, but binds to a different site on the $GABA_A$ receptor/chloride channel and its action is less specific. They are dangerous in case of overdose, as they induce a high degree of tolerance and dependence (Rang, Dale & Ritter, 2015).

Benzodiazepines

The chemical structure of benzodiazepines consists of a seven-membered ring fused to an aromatic ring that has four major substituent groups, which can be modified without loss of activity. Differences in pharmacokinetic behavior between different benzodiazepines are more important than differences in activity profile. Benzodiazepines act selectively on the

$GABA_A$ receptor, which mediates inhibitory synaptic transmission throughout the central nervous system (Rang, Dale & Ritter, 2015).

GABA (gamma-aminobutyric acid) is the most common neurotransmitter in the central nervous system, found in high concentrations in the cortex and limbic system. GABA is inhibitory in nature and thus reduces the excitability of neurons. GABA produces a calming effect in the brain (Hou et al., 2024). The three GABA receptors are designated A, B, and C. The $GABA_A$ receptor complex is composed of 5 glycoprotein subunits, each with multiple isoforms (Lydiard, 2003). $GABA_A$ receptors contain 2 α subunits, 2 β subunits, and 1 □ subunit. Each receptor complex has 2 GABA binding sites but only 1 BZD binding site. The benzodiazepine binding site is at a specific site at the intersection of the α and β subunits (Chaudhuri & Hosur et al., 2024).

Benzodiazepines enhance the response to GABA by facilitating the opening of GABA-activated chloride channels. They bind specifically to a regulatory site on the receptor, distinct from the GABA binding site, and act allosterically by increasing the affinity of GABA for the receptor (Rang, Dale & Ritter, 2015).

The BZD receptor has been classified based on subunit isoforms and clinical effects related to each type. The BZ1 receptor contains α1 and is highly concentrated in the cortex, thalamus, and cerebellum (Sieghart, 1994; Rudolph et al., 1999). It also has its dimer BZ2, which is held together with BZ1 by a ball-and-socket interaction between the layers. The interaction of BZ1 with BZ2 masks the retention signal, which facilitates targeting to the membrane. The activation of this dimer is the result of GABA binding to the extracellular domain of BZ1 (Rang, Dale & Ritter, 2015).

The BZ1 receptor is responsible for the sedative, anterograde amnesia and anticonvulsant effects (Rang, Dale & Ritter, 2015). Sixty percent of $GABA_A$ receptors contain the α1 subunit. Therefore, amnesia is a common side effect of BZD use because most $GABA_A$ receptors contain BZ1, which is the receptor responsible for amnesia (Mattila-Evenden et al., 2001). Those containing the α2 subunit are responsible for the anxiolytic and muscle relaxant effects (Rang, Dale & Ritter, 2015). Individuals respond differently to the same drug and, often, these different responses reflect the pharmacokinetics and/or pharmacodynamics among different patients. Pharmacokinetics is affected by the route of administration, absorption and volume of distribution. BZDs can be administered intramuscularly, intravenously, orally, sublingually, intranasally or rectally (Kaye et al., 2012).

Benzodiazepines are well absorbed when given orally, usually giving a peak plasma concentration in about 1 hour. Some are absorbed more slowly. They bind strongly to plasma proteins and their high lipid solubility

causes many of them to accumulate gradually in body fat. They are usually administered orally. Intramuscular injection usually results in slow absorption (Rang, Dale & Ritter, 2015).

Benzodiazepines are all metabolized and ultimately eliminated as glucuronide conjugates in the urine. They vary greatly in duration of action and can be roughly divided into short-, medium-, and long-acting compounds. Several are converted to active metabolites, such as N-desmethyldiazepam (nordazepam), which has a half-life of about 60 hours, and this accounts for the tendency of many benzodiazepines to produce cumulative effects and prolonged hangovers when given repeatedly (Rang, Dale & Ritter, 2015). Despite this division, it is now known that the degree of affinity with the receptor can also interfere with the duration of action (Rang, Dale & Ritter, 2015).

According to biotransformation, BZDs can be divided into four groups (Seibel & Toscano-Júnior, 2001):

• Pro-nordiazepam compounds, which are generally formed by N-dealkylation and are metabolized by hydroxylation, such as bromazepam and diazepam;

• Compounds of the oxazepam group, which are metabolized by conjugation with a glucuronic acid, such as oxazepam and lorazepam;

• NO_2-benzodiazepine derivatives, such as clonazepam and flunitrazepam;

• Triazole-benzodiazepines, which have specific metabolic pathways, such as alprazolam.

When selecting a BZD, patients' complaints should be taken into account. Patients who have difficulty initiating sleep but do not have difficulty maintaining it should be treated with BZD with a rapid onset of action and a short half-life, such as triazolam. A BZD with a longer effect, such as flurazepam, can be used for patients who have morning insomnia or who also need an anxiolytic effect during the day. Other BZD, such as diazepam and alprazolam, are used to relieve severe and chronic anxiety, as well as anxiety associated with some forms of depression and schizophrenia. In preparing patients for invasive procedures, midazolam is often used as a rapid onset and short-acting sedative and amnesic. Benzodiazepines facilitate the onset of sleep and also increase overall sleep duration (Golan, 2009; Fuchs & Wannmacher, 2010). Benzodiazepine metabolites are excreted preferentially in the urine, in the form of glucuronides or oxidized metabolites and, in lower concentrations, in the feces. A small percentage is eliminated unchanged in the urine (Oga, 2008; Golan, 2009).

Acute Toxicity

BZDs, in overdose, are considered less dangerous than other anxiolytic-hypnotics. The clinical features of acute sedative intoxication are similar to alcohol intoxication. Psychiatric manifestations include inadequate attention, inappropriate behavior, and impaired mood and

judgment. Physical signs include nystagmus and decreased reflexes, with difficulty performing movements. As the amount consumed increases, especially beyond an individual's tolerance, more impairment occurs in judgment and brain function. Initially, signs include slurred speech, followed by nystagmus, lack of coordination (especially in complex tasks such as driving), ataxia, and memory impairment (blackout) (Weaver et al., 1999; Liu et al., 2020; Brunnauer et al., 2021; Chapoutot et al., 2021; Smid, Mlakar & Stukovnik, 2024). Prolonged use of benzodiazepines can aggravate depression and anxiety (Rickels et al., 1999; Ait-Daoud et al., 2018) and, in the presence of other CNS depressants, particularly alcohol, can cause severe respiratory depression or even life-threatening conditions (Rang, Dale & Ritter, 2015; Ait-Daoud et al., 2018; Smid, Mlakar & Stukovnik, 2024).

Side Effects During Therapeutic Use

Drowsiness, confusion, amnesia and impaired coordination are the main side effects of BDZs. It is important to highlight that the long and unpredictable duration of action of many benzodiazepines is important in relation to side effects. Nitrazepam, a long-acting drug, is no longer used as a hypnotic and even compounds with shorter action, such as lorazepam, can produce impaired performance at work and behind the wheel the following day (Rang, Dale & Ritter, 2015; Ait-Daoud et al., 2018; Smid, Mlakar & Stukovnik, 2024).

Tolerance and Dependence

Tolerance and dependence occur with all benzodiazepines. Tolerance is less pronounced than with barbiturates, which produce pharmacokinetic tolerance due to the induction of liver enzymes that metabolize the drug (Rang, Dale & Ritter, 2015).

The major problem with BDZ is that they produce dependence. When treatment is suspended after weeks or months, in normal individuals and patients, there is an increase in anxiety symptoms, accompanied by tremors and dizziness (Rang, Dale & Ritter, 2015). Symptoms may vary, but most patients present anxiety, irritability, difficulty concentrating, insomnia, nausea, tremors, sweating and headaches. A few days after stopping the drug, the peak of withdrawal symptoms occurs, but they can be observed for months (Wills, 2005; Soyka, 2017; Ait-Daoud et al., 2018).

Specific concerns about long-term use are due to the development of tolerance and dose escalation, dependence, drug abuse and the great difficulty in withdrawal, and increasing risk of death. Prolonged use of benzodiazepines represents a real risk for the development of physiological and psychological dependence, related to the dosage, duration of treatment and potency of the drug (Charlson et al., 2009; Ait-

Daoud et al., 2018; Chapoutot et al., 2021; Lynch et al., 2022).

History of Benzodiazepine Prescriptions

The effectiveness of benzodiazepines is well documented in short-term treatments; however, prolonged use is contraindicated due to the risk of adverse effects, including dependence. Over time, with the popularization of the use of benzodiazepines, new problems have been highlighted, many of them resulting from the misuse of these medications. Chemical dependence on benzodiazepines, with all the implications inherent to these conditions, has become a major concern for public health (Galleguillos et al., 2003). Issues related to the excessive and sometimes unjustified use of benzodiazepines are observed in several countries, regardless of their level of economic development (Auchewski et al.; Poyares et al.; Rancourt et al.; Valenstein et al.; 2004; Dièye et al., 2006; Cook et al., 2007; Alvarenga et al., 2008) in large urban centers (Auchewski et al.; Poyares et al.; 2004) and also in rural populations (Valenstein et al., 2004).

In Brazil, it is estimated that 1.6% of the adult population is a chronic user of benzodiazepines (Laranjeira and Castro, 1999). International organizations, such as the WHO (World Health Organization) and the INCB (International Narcotics Control Board), have warned about the indiscriminate use and insufficient control of psychotropic drugs in developing countries. In Brazil, this warning was reinforced by studies from the 1980s and 1990s, which showed a serious reality related to the use of benzodiazepines (Nappo & Carlini, 1993; Noto et al., 2002). They are used non-medically by people who have problems with alcoholism or abuse of several substances simultaneously, where it can be seen that it is not limited to biological aspects (Gunnar et al., 2004).

Experts have identified the following factors as intervening in the mental health of individuals: working conditions and unemployment, education, poverty, housing conditions, level of urbanization, social discrimination and gender-based violence, early experiences and family interaction, social exclusion and stigma, culture and stressful life events (Alves, 2010).

People's difficulty in tolerating stress may be related to the consumption of benzodiazepines, the emergence of new drugs and the increasing pressure of advertising by the pharmaceutical industry, or even inappropriate prescription habits by doctors (Auchewski et al., 2004).

The prescription and use of BZD continues to grow, believed to be because no superior pharmacotherapeutic alternative has been developed to treat anxiety and insomnia. These drugs act quickly and, at least in the initial prescription, are safe and have predictable effects (Hood et al., 2012).

The importance of medical and/or pharmaceutical guidance in the rational use of benzodiazepines becomes evident with the emergence of research focusing on the development of methodological and monitoring strategies of users of this class of drugs during use or discontinuation (Chapoutot et al., 2021; Lynch et al., 2022; Alberto-Armas et al.; Buzancic et al.; Le et al., 2024).

In this context, the present work aimed to prepare a narrative bibliographic review addressing the indiscriminate use of benzodiazepines, as well as medical and/or pharmaceutical guidance/advice on the risks of the main adverse effects of this family of drugs.

RESULTS

One of the main adverse effects of the use, especially in the long term, of these drugs is dependence, which often makes it difficult to discontinue treatment. Figure 1 shows the main physical and psychological signs and symptoms of benzodiazepine withdrawal.

SIGNS AND SYMPTOMS OF BENZODIAZEPINE WITHDRAWAL	
PHYSICAL	PSYCHICS
• Tremors • Tachycardia • Sweating • Dysphoria • Headache • Nausea • Facial flushing • Sensation of heat and cold • Anorexia • Weakness or general malaise	• Intense anxiety • Hallucinations • Agitation • Panic attacks • Depression • Irritability • Apathy • Dysphoria • Difficulty concentrating • Insomnia

Figure 1: Signs and symptoms of BZD withdrawal. Adapted of Rang, Dale & Ritter, 2015.

The review showed that most patients use benzodiazepines continuously and this is common in different regions of the world. Auchewski et al. (2004) reported that 72% of patients in the city of Curitiba, Brazil, use BZD continuously, while the remaining 28% use the drug intermittently.

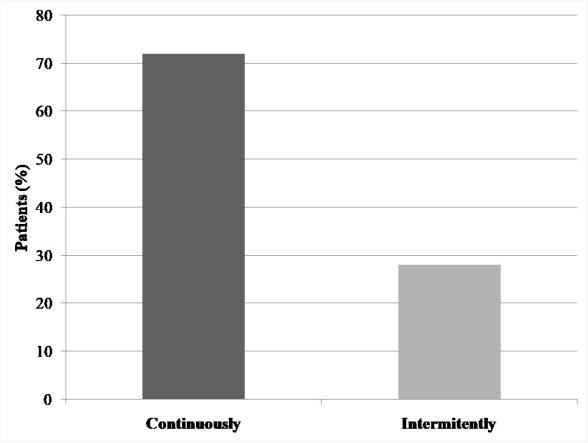

Figure 2: Type of use of BZD in Brazilian patients. Adapted from Auchewski et al., 2004.

In another part of the world, Zahran et al. (2022) showed that 74.2% of Lebanese patients use BZD daily, while the remaining 25.8% use them only occasionally.

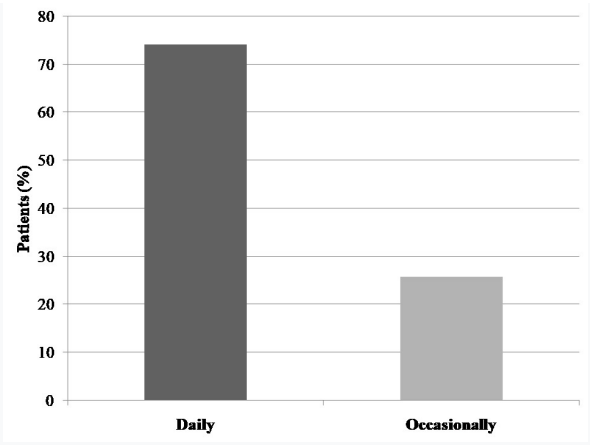

Figure 3: Type of use of BZD in Lebanese patients. Adapted from Zahran et al., 2022.

The prescribed quantity of 60 pills was predominant (61%) in Brazilian patients, followed by the prescription of 20 to 40 pills (32%) and only 7% of patients used another quantity of pills (figure 4).

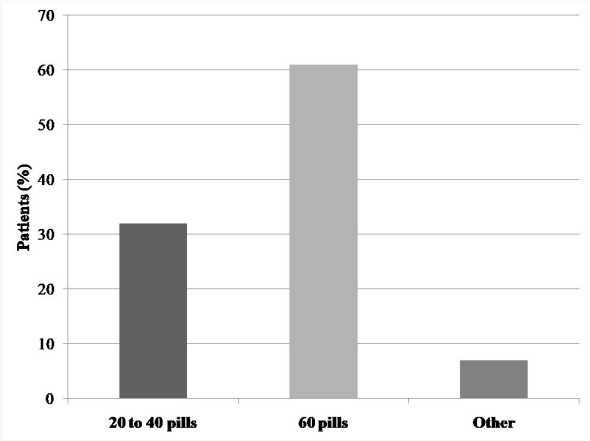

Figure 4: Number of BZD pills prescribed per consultation. Adapted from Auchewski et al., 2004.

The highest frequency of visits of Brazilian patients to the doctor's office was every 2 or 3 months (47%), followed by monthly visits (36%), visits every six months or longer periods (10%) and only 7% of patients go to the office at different times (figure 5).

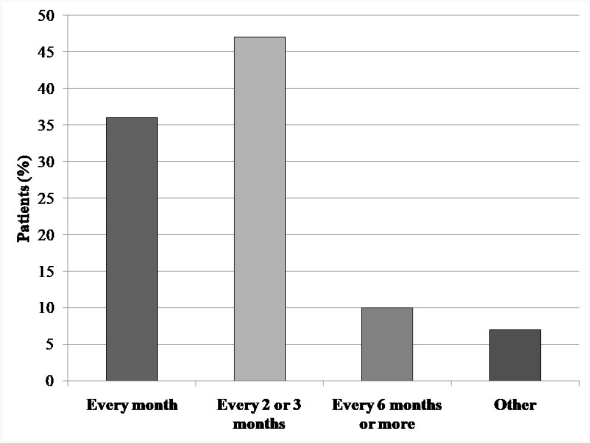

Figure 5: Frequency of consultation of BZD users. Adapted from Auchewski et al., 2004.

Figure 6 shows that, although most Brazilian patients did not attempt to discontinue treatment (58%), twice as many patients who did (28%) received some medical advice, compared to patients who were not advised (14%).

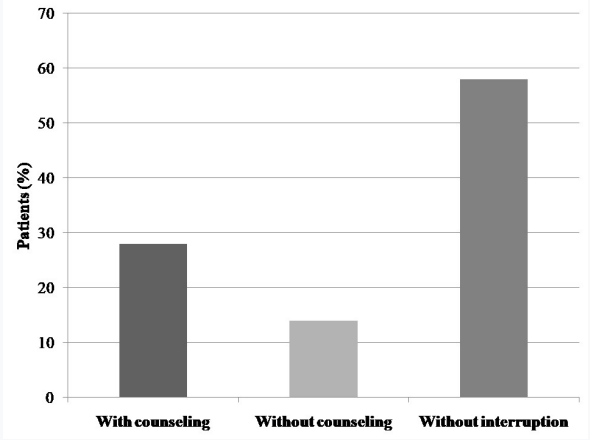

Figure 6: Medical guidance during discontinuation of benzodiazepine treatment. Adapted from Auchewski et al., 2004.

Zahran et al. (2022) showed that, although most Lebanese patients were able to state the purpose of BZD (78.1%), how (74.8%) and when (76.0%) to use the drug, many patients were unable to inform the name of the BZD used (71.9%) and which foods/drinks cannot be consumed together with the medication (69.8%) (figure 7). In addition, 110 patients (46.4%) were dissatisfied with the medical advice received and, of these, only 34.7% were aware of the possible adverse effects and 43.4% of the risk of becoming addicted to BZD (figure 7).

Statement (N = 242)	No	Neutral	Yes
Confident that they know what the benzodiazepines are for	24 (9.9%)	29 (12.0%)	189 (78.1%)
Can confidently describe how to use the benzodiazepines	32 (13.1%)	29 (12.0%)	181 (74.8%)
Can confidently describe when to use the benzodiazepines	33 (13.6%)	25 (10.3%)	194 (76%)
Can name the medications that cannot be taken with benzodiazepines	174 (71.9%)	25 (10.3%)	43 (17.8%)
Can name the foods/beverages that cannot be consumed with benzodiazepines	169 (69.8%)	18 (7.4%)	55 (22.7%)
Satisfied with the overall explanation received from the doctor concerning the benzodiazepines	110 (46.4%)	35 (14.8%)	92 (38.8%)
Understand the possible side effects of benzodiazepines	139 (57.4%)	19 (7.9%)	84 (34.7%)
Aware that there is a chance of becoming addicted to benzodiazepines	101 (41.7%)	36 (14.9%)	105 (43.4%)

Figure 7: The awareness and knowledge of benzodiazepine users about their medication. Adapted from Zahran et al., 2022.

BZD prescriptions for Brazilian patients were mostly for an indefinite period (78%) (figure 8) and 61% of patients had been using BZD for more than 1 year (figure 9).

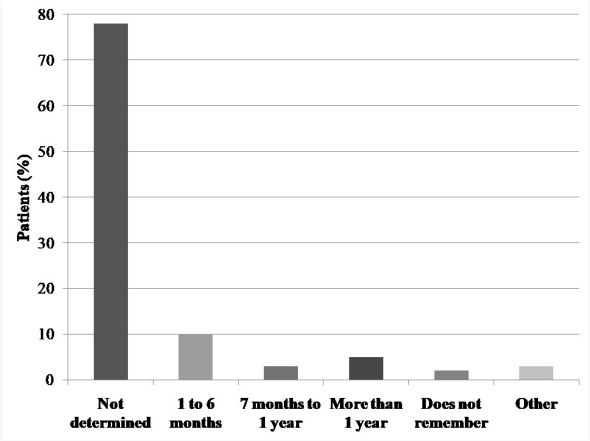

Figure 8: Time to use of BZD recommended by the doctor. Adapted from Auchewski et al., 2004.

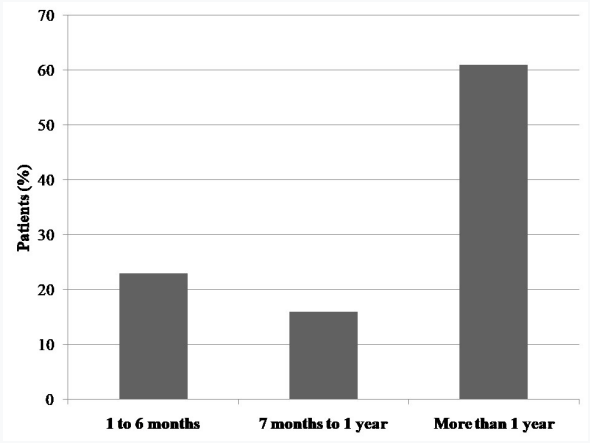

Figure 9: Minimum time of use of BZD. Adapted from Auchewski et al., 2004.

This result, once again, occurred in Lebanese patients, where 42.6% of them used BZD for a period of 1 to 10 years (figure 10).

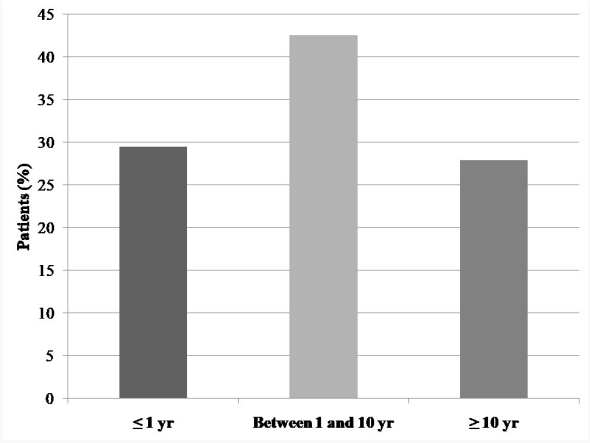

Figure 10: Duration of BZD use in Lebanese patients. Adapted from Zahran et al., 2022.

DISCUSSION

The World Health Organization (WHO) defined rational use of medicines as the need for the patient to receive the appropriate medicine, in the correct dose, for an adequate period of time, at a low cost to him/her and to the community (World Health Organization, 1987). However, in Brazil, the incorrect use of medications is still frequent, mainly in the form of self-medication, which results in high costs in resolving medication-related problems (DRPs) (Gama & Secoli, 2017, 2020).

In Brazil, the consumption of benzodiazepines is controlled through their marketing and prescription, included in Ordinance SVS/MS 344, of May 12, 1998 (Ministério da Saúde), however, they continue to be used incorrectly, based on adulterated, falsified, erased and expired prescriptions (Noto et al., 2002; Ait-Daoud et al., 2018; Liu et al., 2020). The use of benzodiazepines has reached a high and worrying level these days. Azevedo et al. (2016) highlighted the increase in consumption in Brazilian capitals, leading to increasingly indiscriminate use, and Guarda et al. (2024) identified 683 cases of self-medication in Brazil between 2014 and 2020, of which the main class used was benzodiazepine anxiolytics (18%).

It is important to highlight that between 7% and 35% of medicines acquired are obtained through self-medication (Barros, 1995; Zahran et al., 2022). However, if this high rate of self-medication occurs, it is also because the population does not find it easy to access health services, having to wait hours in line and, sometimes, days or even months to be seen by a doctor. The low purchasing power of the population and the precariousness of health services contrast with the ease of obtaining medicines, without paying for consultations and without a prescription, at any drugstore (Zahran et al., 2022).

To better understand the problem of irrational use of medicines, it is necessary to understand society's consumer relations and their interaction with medicines. “Consumption is something inherent to man”, and there is a relationship between the transformations of society and the phenomenon of consumption. Therefore, medicines are not disconnected from this social characteristic. Unlike other historical periods, postmodern capitalism encourages consumption through advertising and the idea of

replacing the “vicarious pleasure of having over being” (Rozenfeld & Porto, 2007). This fact of inadequate consumption of BZD is reinforced by the information that approximately 96% of geriatric patients may be deprescribed these medications (Buzancic et al., 2024).

Azevedo et al. (2016) observed an increase in the consumption of benzodiazepines between 2010 and 2012 in Brazilian capitals. Alprazolam remained at the top, followed by Bromazepam, Clonazepam, Lorazepam and Diazepam. There is a need to improve the control mechanism, given the correlation between acquisition without a prescription and patient misuse, which may explain this increase in consumption by medication.

According to Aquino (2008), drug advertising is a frequent stimulus for the inappropriate use of drugs, because it tends to emphasize the benefits and omit or minimize the risks and possible adverse effects, always giving the impression, especially to the lay public, that these are products without harmful effects, influencing to consume them like any other product. Chronic reports of benefits from users encourage other people to use them inappropriately, thus resulting in exacerbated advertising.

The results found in this study suggest that the Internet has also been used to disseminate advertising to drug consumers, much of it taking a less explicit form since it tries to give the impression that they are educational or informational instruments, aiming to promote health (Barros, 2004). It is important to pay attention to the introduction of public policies that can monitor the increase in the indiscriminate use of BZD, inhibiting advertising, easy access, more severe punishments for illicit sales and raising awareness among the population about the risks of improper use.

According to the literature, chronic use of benzodiazepines, lasting more than six months, can lead to withdrawal symptoms, which usually occur one to eleven days after stopping the medication, making it more difficult for patients to stop treatment. As shown in Figure 1, the most frequent symptoms include: tremors, tachycardia, sweating, dysphoria, headache, intense anxiety, agitation, insomnia and changes in sleep patterns, dizziness, gastrointestinal disorders, anorexia, among others (Rang, Dale & Ritter, 2015).

Symptoms usually worsen between the fifth and sixth day of abstinence and disappear within four weeks. This should be distinguished from rebound symptoms, which are characterized by the return of previous symptoms but in an exacerbated manner (Rang, Dale & Ritter, 2015).

Oga (2008) emphasized that tolerance is the first manifestation of chronic use and that abstinence syndrome is a phenomenon resulting from reversible physiological adaptations, which occur as a natural consequence of exposure to a

drug and which do not imply dependence. It occurs due to mechanisms involving neurologic alterations such as modifications of BZD receptors, in the binding of GABA to its receptor and in changes in the neurotransmission of norepinephrine or serotonin in systems where GABA interacts (Seibel & Toscano-Júnior, 2001).

There are many studies that associate benzodiazepines and dementia. Among them Fastbom, Forsell and Winblad (1998) suggested the protective effect of the use of these medications against Alzheimer's disease. However, Gorenstein et al (1995) had already demonstrated a much greater impairment in cognitive performance in chronic users of these medications. Furthermore, some studies have shown an association between an increased risk of dementia and prolonged use of benzodiazepines (Wu et al., 2009; Gage et al., Gallacher et al., 2012; Gage et al.; Inouye, Westendorp & Saczynski; Steurer, 2014; Rosenberg, 2015; Liu et al., 2020; Smid, Mlakar & Stukovnik; Yamaguchi et al., 2024).

The phenomenon of dependence on benzodiazepines is related to their pharmacokinetics, as they have high lipid solubility and the ability to distribute throughout brain tissue, their biological half-life and their cumulative effects. The greater the lipid solubility and the shorter the half-life, the greater the potential for dependence on the drug. The way in which the withdrawal syndrome manifests itself is also related to the pharmacokinetic properties of benzodiazepines. A slow-acting drug, with slow distribution, with a high rate of binding to plasma proteins and slow biotransformation generally causes less intense withdrawal symptoms. This is probably due to the physiological adaptation of the organism (Oga, 2008; Rang, Dale & Ritter, 2015).

Albertino et al. (2000) characterize that the dependence on BZD can be physical or psychological, and most of the time both are observed. The degree of dependence will vary from one patient to another and can be influenced by factors such as age, personal and/or family problems, work, genetic predisposition, among others.

Auchewski et al. (2004) assessed the guidance provided by physicians to patients in Curitiba, Paraná, regarding the side effects of benzodiazepines, such as the type of use of this class of medications, divided into continuous and intermittent (Figure 2), and the quantity prescribed (Figure 4). Among the various side effects of BZD, the analysis of the guidance received was focused on the effects that had the potential to directly threaten the patient's life and for which medical guidance on them should be essential. The major assessment was the potential for dependence, assessed by the success of treatment interruption, demonstrating that failure is often related to dependence on the drug. This frequent use of BZD was also

reported by Zahran et al. (2022), who studied the consumption of this class of drugs in Lebanese patients (figure 3). The response preserved in these two studies reinforces the need to immediately establish awareness policies on the time and form of BZD use.

It was noted that the vast majority of patients returned to the doctor for a new appointment every two or three months, demonstrating that patient contact with the doctor was frequent (Figure 5). This can be interpreted as a concern on the part of the doctor to monitor the patient's response to benzodiazepines, in addition to promoting a good doctor-patient relationship. However, it is important to emphasize that most patients go to the doctor's office only to obtain a new prescription, since most patients never tried to stop their treatment (Figure 6) and without medical guidance, a common characteristic of people who abuse this type of drug (Auchewski et al., 2004). Although many patients receive guidance on the use of BZDs, it is clear that the information needs to be more comprehensive, since many patients are not able to inform which BZD they are taking and, mainly, what risks of adverse effects/dependence they are exposed to with the long-term use of this type of substance (Figure 7) (Zahran et al., 2022). Most patients reported that doctors did not stipulate a time period for finishing treatment (Figure 8) and that they had been using the same medication for at least more than a year (Figure 9).

One result that emphasizes the need to develop policies to combat misinformation/incomplete information about the use of BZDs is that, like the patients in the city of Curitiba, Brazil, the majority of Lebanese participants in the study by Zahran et al. (2022) consumed the drugs for a period of 1 to 10 years, despite all the known adverse effects to which these individuals are exposed (Figure 10).

Taken together, the results of Lydiard (2003), Auchweski et al. (2004), Gage et al. (2014), Rosenberg (2015), Zahran et al. (2022) and many other publications show the need to strengthen the process of medical and/or pharmaceutical guidance within the scope of the rational use of BZD, with the aim of raising awareness among the general population of the severe adverse effects that can occur with prolonged, or even short-term, use of this family of substances.

There is progress in strategies to encourage the deprescription/discontinuation of BZD use, since the main adverse effects caused by this type of medication can cause serious and irreversible damage to health, reinforcing the need to make the reduction of the dose/prescription of BZD, mainly through medical and/or pharmaceutical advice, a central objective within the scope of the rational use of anxiolytic medications (Chapoutot et al., 2021; Lynch et al., 2022; Alberto-Armas et al.; Buzancic et al.; Le et al., 2024).

CONCLUSION

The growing demand for medications that relieve daily stress and anxiety has brought with it chronic users and with them dependence. Better knowledge about the potential action of these drugs that cause chemical dependence, as well as better participation of pharmacists, together with physicians, can contribute significantly to the prevention of harmful effects and possibilities of pharmacological interactions, developing new therapeutic and diagnostic resources and planning preventive and effective actions, based on the provision of information about the correct way to use these drugs as well as the harm they can cause to health.

The evolution of the consumption of controlled medications requires greater monitoring, given that there is a relationship between acquisition without a prescription and improper use.

However, pharmaceutical care in benzodiazepine therapy can reduce hospitalization costs, improve prescriptions and consequently improve the quality of life of users who need to use these drugs.

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