RCMOS – Multidisciplinary Scientific Journal O Saber. ISSN: 2675-9128.

ADVERSE EFFECTS WITH PROLONGED USE OF ALPRAZOLAM DUE TO LACK OF ADEQUATE GUIDANCE

SIDE EFFECTS IN THE PROLONGED USE OF ALPRAZOLAM DUE TO LACK OF PROPER ORIENTATION

v. 10, p. 01-13, Oct. 2021

Submitted on: 10/27/2021
Approved on: 10/28/2021

DOI: 10.51473/rcmos.v10i10.180

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SUMMARY
Alprazolam is a drug from the benzodiazepine class recognized by ANVISA, and is effective in the treatment of anxiety and panic disorders. However, non-rational use, caused by the lack of adequate professional guidance, can result in the problem of drug dependence. In this study, through qualitative and descriptive analysis of the bibliography of various authors on the harmful effects of the non-rational use of Alprazolam, we sought to present the reader with essential information related to this medication. To this end, Alprazolam was characterized, emphasizing how its pharmacokinetics and pharmacodynamics occur. The dosage of the drug was discussed and it was identified how prolonged use can be problematic. And finally, the importance of the pharmaceutical professional to help promote the rational use of medicine was discussed.
Key words: Alprazolam; anxiolytic; prolonged use.

ABSTRACT
Alprazolam is a drug that belongs to a class of medications called benzodiazepines, recognized by ANVISA and is effective in the treatment of anxiety and panic disorder. However the non-rational use, caused by the lack of proper professional orientation, may result in the drug's addiction. This study, through the qualitative analysis, and descriptive nature, of the bibliography of many authors about the harmful effects of the non-rational use of Alprazolam, sought to present to the reader essential informations related to said drug. For that, Alprazolam was characterized, highlighting how the pharmacokinetics and pharmacodynamics happens. The drug dosage was debated, as well as how prolonged use can be problematic. At last, the importance of the professional pharmacist to help in the promotion of rational use of the drug.

Keyword: Alprazolam; anxiolytic; prolonged use.

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1. INTRODUCTION

The present study discusses the drug Alprazolam, the active ingredient of a medicine better known in Brazil by the trade name Frontal®, manufactured by the multinational pharmaceutical company Pfizer. The active ingredient is registered by the National Health Surveillance Agency (ANVISA) and is part of a class of sedative-hypnotics called benzodiazepines.

Alprazolam is mainly considered a drug for treating anxiety, panic and anxiety disorders caused by depression (ENTRINGER, 2021). The sedation attributes of the medication, caused by its ability to depress the Central Nervous System (CNS), are effective in treating symptoms such as fear, anguish, restlessness, insomnia, difficulty concentrating, inability to relax and discomfort arising from an imaginary situation of danger (PFIZER, 2018).

Anxiety and the high level of stress in today's society mean that the search for medications that alleviate these symptoms is increasing (NUNES*et al.*, 2016). Thus, according to Katzung*et al.*(2014), benzodiazepines are, along with barbiturates, one of the most prominent classes among anxiolytics. However, due to the higher rate of dependence and intoxication of barbiturates, they are the first choice for the treatment of anxiety disorders, and an alternative to treatment with drugs from the phenobarbital class.

On the other hand, it is precisely because it provides this greater security that "its prescription and use occur abusively, even though it is a controlled medicine and dispensed only with the presentation of a prescription" (TELLES FILHO*et al.*, 2011, p.582). Among these effects, the possible tolerance that non-rational use is capable of causing and, consequently, dependence and abstinence stands out.

According to Ordinance No. 3,916/98, from the Ministry of Health, there is rational use of medicines when patients receive medicines appropriate to their clinical conditions, in doses appropriate to their individual needs, for an adequate period and at the lowest cost for themselves and the community. (BRAZIL, 1998). And in the context of Alprazolam, which is an active ingredient that, according to the leaflet for professionals taken from the official website of the company Pfizer (2018, p.4) about Frontal®, "the risk of dependence increases with larger doses and use for a longer period of time." prolonged", it is extremely important that there is effective professional assistance throughout the period of use of the drug. The pharmaceutical professional, as the main

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responsible for dispensing medications, is an important element in this scenario with the practice of Pharmaceutical Assistance, and must assist the patient in order to guarantee the best possible use of the asset.

2. OBJECTIVES

2.1. GENERAL OBJECTIVE

The general objective of the article is to discuss the dangers of prolonged use of the medication Alprazolam caused by the lack of adequate professional guidance on the rational use of the medication.

2.2. SPECIFIC OBJECTIVES

Within the scenario, the text has specific objectives:

• Characterize Alprazolam;

• Identify the main effects caused by prolonged use of the medication;

• Discuss the dangers posed by the lack of adequate professional guidance on the rational use of the medicine.

3. JUSTIFICATION

Due to the challenge of ensuring the rational use of Alprazolam, this research is justified by analyzing the adverse effects caused by prolonged use of the drug, and the danger posed by the lack of professional assistance in treatment, as well as the importance of the pharmacist in ensuring an effective therapy, as recommended by RDC No. 585/2013, the clinical roles of the pharmacist aim to promote the rational use of medicines and optimize pharmacotherapy, to achieve results that improve the patient's quality of life.

4. METHODOLOGY

Detailed readings and research were carried out through articles, books and scientific journals in order to discuss the importance of the rational use of Alprazolam in prevention

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of adverse effects in prolonged drug use. And also about the importance of professional pharmaceutical assistance within this context.

The research methodology in question is descriptive in nature, that is, with the purpose of describing the characteristics of a given population or phenomenon (GIL, 2002). The data were analyzed qualitatively, based on the perception of the phenomenon within its context (TRIVIÑOS,1987).

For the theoretical framework, the basis was the bibliographic and documentary study of magazines, national and international scientific articles, monographs and theses found on sites such as Scientific Electronic Library Online (SciELO), The National Institutes of Health (PubMed), Google Scholar, Revista Academic at the Oswaldo Cruz Foundation (FIOCRUZ), MEDLINE. A total of 24 works from different years and from different perspectives, by authors such as Nassima Ait-Daoud, Michael C. Gerald, Adriana Lopes Latado and Humphfrey P. Rang to build the theoretical foundation.

5. THEORETICAL FRAMEWORK

Through the analysis of several articles and texts referring to the use of Alprazolam, it was possible to notice a high demand for the medicine. According to Brett and Murnion (2015), Alprazolam is one of the most popular medications in the world due to its great anxiolytic effectiveness.

According to Brandão (2021), the drug appeared on the market in 1981. However, in the same decade, after the first cases of abusive use of benzodiazepines (BZDs), development of tolerance, abstinence and dependence by chronic users, the medication began to have restrictions , and the serious reality of the use of BZDs began to be highlighted. In the case of Alprazolam, according to Gerald (2013), problems related to prolonged use, regardless of how they occur with other benzodiazepines, are more pronounced with the medication. Considering, however, the diversity of benzodiazepines on the market today, this article will be limited to a more detailed study of Alprazolam, its characteristics and dangers of prolonged use which, according to Latado *et al.*(2013), are caused by the lack of adequate professional guidance.

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5.1. CHARACTERISTICS OF ALPRAZOLAM

Alprazolam is an active ingredient certified by ANVISA. According to the leaflet for professionals on the Pfizer website (2018), it is indicated for the treatment of anxiety disorders, whether or not they are related to other conditions such as alcohol withdrawal and panic disorders, with or without agoraphobia.

As part of the class of benzodiazepines (BZDs), the drug has similar properties to more than 15 medications such as Diazepam, Clonazepam, Oxazepam, Triazolam, Flurazepam, Lorazepam and Chlordiazepoxide (TELLES FILHO*et al.*, 2011). And these medications differ in terms of their half-life and affinity with the receptor that each one has (AIT-DAOUD*et al.*, 2018).

> Peak plasma concentrations occur within one to two hours after administration. Plasma concentrations are proportional to the doses administered; Within the dose range of 0.5 mg to 3.0 mg, peaks of 8.0 to 37 ng/mL were observed. Using a specific test methodology, it was observed that the mean plasma elimination half-life of Alprazolam is approximately 11.2 hours (ranging between 6.3 and 26.9h) in healthy adults. In healthy elderly individuals, the mean half-life of Alprazolam was observed to be 16.3 hours (range, 9.0 to 26.9h), compared to 11.0 hours (range, 6.6 to 15.8h) in healthy adult individuals. In patients with alcoholic liver disease, the half-life of Alprazolam ranged from 5.8 to 65.3 hours (mean 19.7h); when compared to 6.3 to 26.9 hours in healthy individuals (average: 11.4h). In a group of obese individuals, the half-life of Alprazolam varied between 9.9 and 40.4 hours (average of 21.8h); when compared to healthy individuals, which ranged from 6.3 to 15.8 h (average of 10.6h) (PFIZER, 2018, p.3).

In the context of Alprazolam, the half-life is short compared to other medications in the same class. This is evident in the tests presented, produced by Pfizer and which discuss the half-life of the active ingredient in the body. This difference in benzodiazepines has to do with the structural conformation of the drugs, as despite having common characteristics, they differ in terms of other radicals (PFIZER, 2018).

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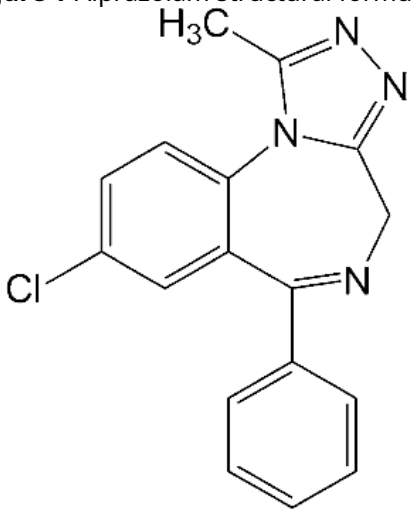
Figure 1-Alprazolam structural formula



Source: Pubchem (2021)

Figure 1 represents the structural formula of Alprazolam – called 8-chloro-1-methyl-6-phenyl-4H-s-triazol[4,3-(alpha)] [1,4] benzodiazepine, according to the Union International Institute of Pure and Applied Chemistry (IUPAC). The classification of BZD is also given by IUPAC because, even with structural differences between the drugs in the class, the benzodiazepine radical, common to all, confers the property of central nervous system depressants (EMS, 2014).

Therefore, it is known that BZDs are anxiolytic drugs that began to be used in the 1960s, with the introduction of Chlordiazepoxide. The class demonstrated high therapeutic efficacy and was soon quickly adopted by the medical profession. The class of drugs is well absorbed orally and most have bioavailability of 80 to 100%. In the case of Alprazolam, however, intramuscular administration is contraindicated, as absorption can be delayed or erratic. (ASSIS, 2018).

According to Rang*et al.*(2016), BZDs are quickly absorbed due to their high solubility, regardless of the route of administration. Furthermore, for the same reason, it has extensive distribution throughout tissues, its metabolites are highly bound to proteins and easily cross the blood-brain and placental barriers.

After administration, the mechanism of action of these drugs occurs in the central nervous system (CNS). They act by enhancing the actions of the neurotransmitter gamma-aminobutyric acid (GABA), the main inhibitor of the CNS. GABA has the function of associating with the active site of the GABA-A receptor, a ligand-dependent ion channel, to promote the opening of the channels. These, once open, allow the influx of chloride ions (Cl-) into the neuron. BZDs, in this context, act as modulators by binding to the site

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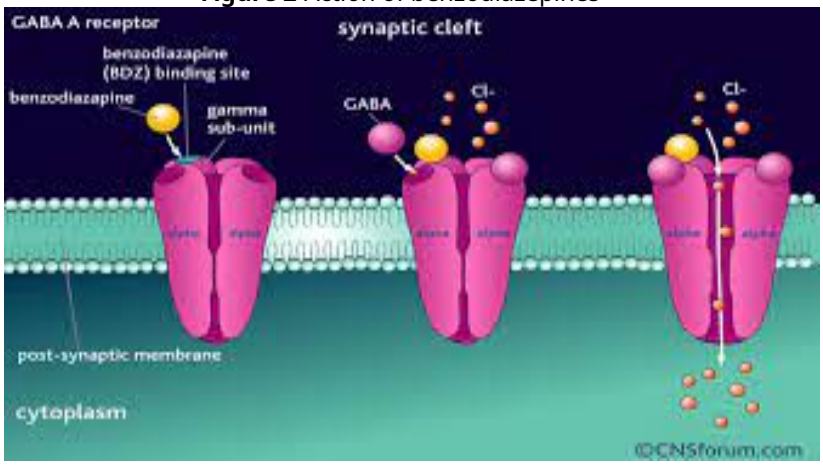
allosteric function of the receptor in order to make the opening of these channels for Cl- entry more likely. There are several subtypes of GABA-A. However, for BZD to bind to the receptor, the presence of 2α, 2β and 1γ is necessary (LATED*et al.*, 2013).

Chloride ions, in turn, being negatively charged, when entering the neuron through the GABA-A receptor on the membrane, results in "a hyperpolarization of these cells, making them less reactive to excitatory neurotransmitters" (MARTINS, 2019, p.10).

Figure 2-Action of benzodiazepines



Source: OLIVEIRA, Mariana,*et al.*, 2016, p.57

In figure 2, the three stages of the pharmacodynamics of benzodiazepines are represented. The first stage represents the binding of the active ingredient to the allosteric site of the GABA-A receptor. This means that, as represented in the second, the channel becomes more likely to open in the third stage. The entry of Cl- into neurons promotes the state of relaxation.

However, despite the positive anxiolytic effects, the importance of rational use of the medication is due to the varied adverse effects it can cause. Especially with prolonged use, there is a lack of adequate guidance on the correct dosage of the medication.

This is because it is a medication that, even in correct therapeutic doses and adequate monitoring, must be given extra attention in relation to possible damage to health. According to the leaflet for professionals on the Pfizer website (2018), it is "contraindicated in patients with known hypersensitivity to benzodiazepines, or any component of the formulation, and in patients with*myasthenia gravis*or acute narrow-angle glaucoma." And, because its metabolites can easily cross the blood-brain and placental barrier, it must

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be avoided during the lactation period and, in cases of pregnancy, the patient must be informed about possible damage to the fetus (RANG*et. al.*, 2016).

In non-rational use, then, the dangers are more significant. According to Ait-Daoud*et al.*(2018), prolonged use can cause tolerance to the medication, requiring constant dose adjustment; dependence, which makes it difficult to withdraw from the medication; and even withdrawal syndrome, when trying to withdraw.

5.2. THE PROLONGED USE OF ALPRAZOLAM AND THE DANGERS OF INADEQUATE PROFESSIONAL ADVICE

In the case of prolonged use of Alprazolam, the potential for withdrawal is greater than in relation to other BZDs. This is because drug pharmacokinetic factors, such as the high affinity with alpha-2 adrenoreceptors and the short half-life concomitant with chronic exposure to the drug, can cause changes in GABAergic neurotransmission. As a consequence, the benefits caused may, due to drug tolerance, decrease over time while the potential for adverse effects continues, and symptoms such as withdrawal may be more severe than with other benzodiazepines (AIT-DAOUD*et al.,*2018).

According to Assis (2018), in the medication withdrawal process, the exchange of short-acting BZDs for long-acting ones is studied. However, it is not a guarantee of success. In cases of low doses or for patients who can easily tolerate withdrawal, the dose is reduced by 50% per week. For moderate to high doses, however, it is done in the following ways:

> Reduce the dose between 10% and 25% every 2 weeks; or reduce the dose by a maximum of the equivalent of 5 mg of Diazepam per week, adjusting the speed of reduction according to the person's tolerance. When the daily dose is below the equivalent of 20 mg of Diazepam, slow down the process, reducing the equivalent of 2 mg of Diazepam per week; or reduce 10% of the original dose every 1 to 2 weeks until a dose of 20% of the original is reached. Then, reduce at a rate of 5% of the original dose every 2 to 4 weeks (BARCELLOS, 2017).

However, the method of withdrawal must be adapted to each patient. This is because, according to Assis (2018), the worse the withdrawal, the slower the withdrawal will be. And it is because of these dangers of dependence, withdrawal, and others that Alprazolam is a special control medication. In this case, the problem of prolonged use is mainly linked to the fact that “a large part of consumers receive prescriptions from general practitioners or other medical specialties,

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and not psychiatrists. This reality leads to the emergence of several complications arising from the long-term use of medication" (TELLES FILHO *et al.,* 2011, p.582).

Corroborating this statement, a study carried out in Teresina on the prescription of BZDs within medical specialties, in 2015, highlighted general practitioners and neurologists as the biggest prescribers of prolonged use of the medication, while psychiatrists and geriatricians seek to limit the use to a safe period of time. in order to avoid dependence (MENDES *et al.*, 2015).

Therefore, the importance of the pharmaceutical professional in promoting the rational use of Alprazolam is easy to observe. This is because, since it interacts with the patient in order to improve medication adherence, it is able to minimize medication-related problems and promotes improvements in medical prescriptions (MELO *et al.*, 2017).

6. RESULTS AND DISCUSSION

As discussed throughout the work, the popularization of Alprazolam has to do with the increasing search for medications that alleviate symptoms of stress and anxiety. Analogous to this, it was observed that this fact, combined with the lack of information and inadequate professional guidance on the use of the medication, was capable of causing the symptom of dependence on the medication, resulting in tolerance, which brings about the need for dosage adjustments. and, finally, abstinence in the attempt to withdraw. (NUNES *et al.*, 2016).

It is a fact that this popularization is related to the increase in cases of anxiety disorders in today's society. The scenario of increasing stress guaranteed an exponential growth in the use of BZDs such as Alprazolam (ASSIS, 2018). The problem with this, however, is the lack of effective professional guidance on its use, since the pharmacodynamic and pharmacokinetic properties of the drug are determined for treatment over a short period (AIT-DAOUD *et al.*, 2018).

As a way to avoid the problem of irrational use of medicines, the Ordinance of the Health Surveillance Secretariat (SVS) No. 344/1998 recommended that Alprazolam, being a drug in class B1 of psychotropics, should only be sold upon notification of a prescription (BRAZIL, 1998). However, the problem is much more in the way the medicine is being prescribed than in clandestine obtaining itself. This is because many doctors

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primary care continue to prescribe it for very long periods, going against the recommendations of addiction experts (AIT-DAOUD*et al.*, 2018).

A study carried out by Alvim*et al.*(2017) on the prolonged use of BZDs with elderly people in a community, a prevalence of Alprazolam was noticed among the most consumed in this population in prolonged use. In the same way as another study, carried out by Romano-Lieber*et al.*(2012) on factors associated with the misuse of psychotropic drugs in the city of São Paulo, the results also pointed to a prevalence of BZDs and, among them, Alprazolam. The two studies corroborate the scenario of dependence on Alprazolam and highlight the need for measures to contain the problem.

The concept of pharmaceutical care, in this sense, emerged to help with the problem, as it seeks to promote rational use by entrusting the pharmaceutical professional with greater responsibilities in treatment (MELO*et al.*, 2017). In Brazil, the concept emerged in 2002 as defined by the Pan American Health Organization (PAHO), the World Health Organization (WHO) and the Ministry of Health (MS). It was conceptualized as:

> A model of pharmaceutical practice, developed in the context of Pharmaceutical Assistance. It comprises attitudes, ethical values, behaviors, skills, commitments and co-responsibilities in disease prevention, health promotion and recovery, in an integrated manner with the healthcare team. It is the direct interaction between the pharmacist and the user, aiming at rational pharmacotherapy and obtaining defined and measurable results, aimed at improving quality of life. This interaction must also involve the conceptions of its subjects, respecting their biopsychosocial specificities, from the perspective of the integrality of health actions (CONSENSO BRASILEIRO DE ATENAÇÃO FARMACÊUTICA, 2002, p.16-17).

With the search for consensus on rational pharmacotherapy, pharmacists became more involved in pharmacological treatments, such as treatment with Alprazolam. In this way, the professional was able to warn and question about therapeutic and adverse effects and, together with the patient and other professionals in the field, seek better effects and avoid the scenario of dependence on the medication.

FINAL CONSIDERATIONS

This bibliographic study demonstrated that, in the same way that anxiety and panic disorders can be a problem, the lack of good guidance from a qualified professional during treatment with anxiolytic drugs, such as Alprazolam, can also be problematic. .

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As presented, Alprazolam is a medicine with truly effective therapeutic effects. However, problematic adverse effects on well-being nonetheless. It is a drug that is known to be safer than some other psychotropic drugs and, therefore, it is important for the pharmacist to warn that this safety does not eliminate existing risks, and to seek, together with the patient, the best treatment for a satisfactory therapeutic effect.

It is concluded, then, that this study is important in both warning about the risk of dependence on the drug, and in highlighting the importance of the pharmaceutical professional in promoting rational use. New research into substances and dosages can also contribute to promoting rational and safe use. As well as the study of more appropriate prescriptions for the medication because, in its current form, it still poses a serious risk to the population.

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