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CHAPTER 3

BENZODIAZEPINES: IMMEDIATE BENEFITS, LONG TERM RISKS

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ABSTRACT

Benzodiazepines are widely used medications for the treatment of anxiety, insomnia, epilepsy, and muscular disorders, primarily due to their efficacy and safety profile. However, prolonged and indiscriminate use of these drugs is associated with numerous side effects, including physical and psychological dependence, cognitive impairment, and increased risk of falls in elderly patients. Literature suggests that chronic use of this pharmacological class may exacerbate symptoms of depression and anxiety, trapping patients in a vicious cycle that hinders medication discontinuation. Dependence occurs in up to 50% of users after six months of continuous use, and abrupt withdrawal can lead to severe withdrawal crises. Studies have shown that retrograde amnesia may become irreversible, particularly in the elderly, raising concerns about the development of dementia. Furthermore, concurrent use with alcohol can result in severe adverse effects, potentially leading to death. Regulation of this drug class is of utmost importance, requiring rigorous monitoring, especially among vulnerable populations. The role of the pharmacist is crucial in ensuring proper adherence to medication, thereby preventing indiscriminate use.

Keywords: Benzodiazepines; Dementia; Cognition; GABA.

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INTRODUCTION

Benzodiazepines are a class of medications that act as central nervous system depressants by enhancing the inhibitory effects of gamma-aminobutyric acid (GABA). They are prescribed for the treatment of anxiety, seizures, sedation, aggression, and muscle relaxation. Introduced in the 1960s, they gained popularity due to their efficacy and safety profile when compared to barbiturates, becoming the most widely prescribed class of psychotropic drugs globally (Forsan, 2010).

The pharmacological action of this class occurs predominantly in the central nervous system (CNS), where benzodiazepines bind to GABA receptors, specifically enhancing the affinity of GABA for GABA-A receptors. This interaction results in decreased neural excitability, producing sedative, muscle relaxant, anticonvulsant, and anxiolytic effects (Katzung; Masters; Trevor, 2014).

Currently, healthcare professionals are increasingly concerned about the abuse of these substances and the long-term consequences of their use beyond the period recommended by prescribers. Although considered relatively safe when used at therapeutic doses under supervision, their combination with other CNS depressants—such as recreational alcohol or opioids—can lead to overdose scenarios (Marques & Marinho, 2023).

One of the primary concerns associated with prolonged benzodiazepine use is the potential for dependence and the development of tolerance to either the dosage or the active compound itself. Over time, the body adapts to the drug's effects, necessitating higher doses to achieve the same therapeutic outcome (Forsan, 2010).

Moreover, abrupt discontinuation after extended use can result in severe withdrawal symptoms, including rebound anxiety, irritability, insomnia, and, in more severe cases, seizures. Therefore, the prescription, monitoring, and use of these medications require caution from both prescribers and patients.

DEVELOPMENT

METHODOLOGY

This research adopts a systematic literature review approach, utilizing the SciELO, PubMed, and Lilacs databases to select scientific articles, citations, and books published between 2010 and 2023, in either Portuguese or English. The descriptors include Benzodiazepines, Long-term use, Chemical dependence, Psychological dependence, and Withdrawal syndrome, combined with Boolean operators (AND, OR) to refine the search. For instance, in PubMed, the strategy will include terms such as (Benzodiazepines [Title/Abstract] OR Benzodiazepínicos [Title/Abstract]) AND (Long-term use [Title/Abstract] OR Uso prolongado [Title/Abstract]), ensuring greater precision.

Studies published prior to 2010, preprints, and non-peer-reviewed works will be excluded. The selected articles will undergo critical analysis and be organized into a synthesis table containing

information such as author, year, objectives, and relevant findings. The discussion will address areas of consensus, divergence, and gaps in the literature, prioritizing evidence on the risks associated with long-term benzodiazepine use, including dependence and withdrawal. This methodology ensures academic rigor and reproducibility and may be supplemented, if necessary, with a PRISMA flowchart to detail the study selection process.

RESULTS AND DISCUSSION

Benzodiazepines are central nervous system depressants widely used in the treatment of anxiety, insomnia, seizures, muscle spasms, and aggression. This pharmacological class is recognized for its high safety profile and therapeutic efficacy, making it one of the most frequently prescribed by healthcare professionals. Their rapid onset of action and versatility have established benzodiazepines as essential tools in managing various neurological and psychiatric disorders (Forsan, 2010).

A significant concern, however, is the impact of long-term benzodiazepine use on mental health. Although commonly prescribed for anxiety disorders, chronic use may paradoxically exacerbate symptoms of anxiety and depression. This phenomenon often leads to a vicious cycle in which patients require increasingly higher doses to achieve the same therapeutic effect, thereby heightening the risk of dependence and tolerance. Furthermore, studies suggest that prolonged use may impair cognition and memory, further complicating the clinical picture. Therefore, benzodiazepine treatment must be rigorously supervised, with gradual discontinuation strategies prioritized when necessary (Campos, Rosa, Gonzaga, 2017).

One of the most alarming effects associated with benzodiazepines (BDZs) is the development of both physical and psychological dependence. Research indicates that the risk of dependence is significant, particularly with extended use. According to a study by Lader and Kyriacou (2016), it is estimated that between 30% and 50% of patients using benzodiazepines for more than six months develop dependence. Abrupt discontinuation can trigger severe withdrawal crises, including intensified anxiety, irritability, aggression, and, in extreme cases, potentially life-threatening seizures. Additionally, withdrawal syndrome may persist for weeks or even months, further complicating the discontinuation process. For this reason, gradual dose reduction under medical supervision is essential to minimize risks and ensure a safe transition to alternative therapies when necessary. Another significant consequence of prolonged and indiscriminate use is cognitive deterioration, particularly among elderly patients. According to Barker et al. (2004), individuals who use BDZs long-term exhibit higher rates of retrograde amnesia and memory impairment, with these effects often proving irreversible even after discontinuation. These outcomes are especially concerning in older adults, where cognitive decline may contribute to the development of dementia (Billioti de Gage et al., 2014).

Due to their sedative effects and interference with motor coordination, long-term BDZ use in elderly patients is significantly associated with increased risk of falls and fractures. One study found that elderly individuals who chronically used benzodiazepines had a 70% higher risk of falls compared to non-users (Leipzig et al., 1999). ANVISA's RDC 66/2022 regulation stipulates that the use of this drug class must be closely monitored, particularly in geriatric patients, recommending short-term prescriptions based on thorough clinical evaluation.

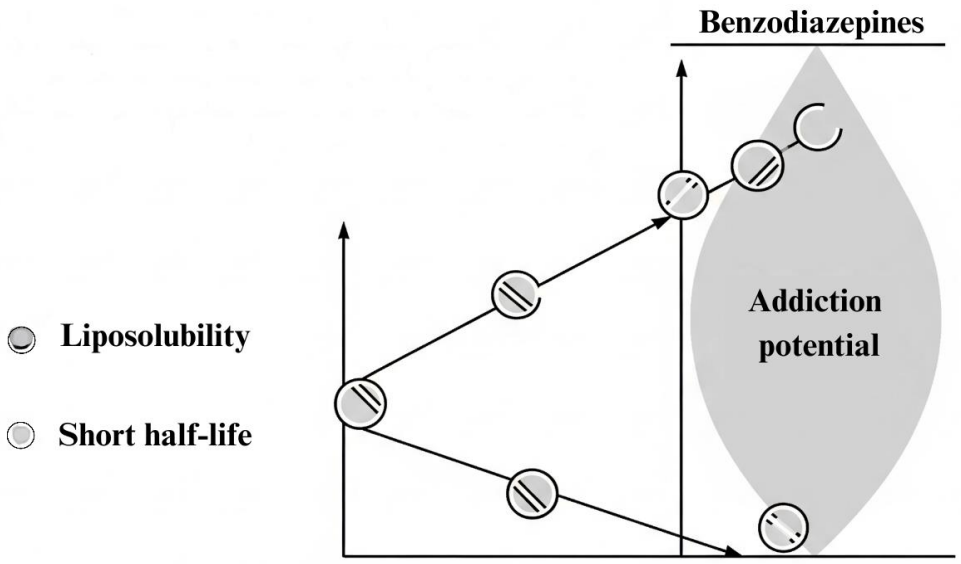
Table 1 - RDC 66/2022 and Its Impacts on Elderly Patients

Aspect	Regulation for Elderly Patients	Specific Risks/Considerations
Prescription	- Requires B1 (blue) prescription with complete patient and physician information. - Validity: 30 days (for benzodiazepines).	- Elderly patients are more susceptible to adverse effects (excessive sedation, falls, mental confusion). - Chronic use may worsen cognitive decline.
Quantity Limit	- Maximum of 60 tablets per prescription (benzodiazepines).	- High risk of physical dependence and drug interactions (e.g., with comorbidities like hypertension/diabetes).
Dispensation	- Pharmacies must retain one copy of the prescription and verify its authenticity.	- Elderly patients may face difficulties returning to the doctor for renewals, leading to self-medication.
Monitoring (SNGPC)	- Mandatory reporting in the SNGPC system.	- Helps track abusive use or repeated prescriptions from multiple physicians
Gradual Reduction	- Recommendation for slow discontinuation to avoid withdrawal.	- Withdrawal in elderly patients may cause severe anxiety, tremors, or worsening of pre-existing conditions.
Restrictions	- Avoid prescribing to elderly individuals with a history of dementia or physical frailty.	- Benzodiazepines increase the risk of falls and fractures (e.g., hip fractures).
Alternatives	- Prioritize non-pharmacological therapies (e.g., psychotherapy for anxiety/insomnia).	- Continuous use may mask symptoms of depression or delirium.

Source: (Adapted / RDC 66/2022). Author, 2025

The liposolubility of benzodiazepines (Figure 1), along with their pharmacological characteristics, also plays a significant role in the development of dependence. Medications within this pharmacological class that have a shorter half-life—such as oxazepam, lorazepam, and alprazolam—are characterized by high liposolubility and present a greater potential for dependence. The longer the duration of use, the higher the likelihood of withdrawal crises. The half-life of benzodiazepine drugs is a relevant factor in characterizing the onset and intensity of withdrawal symptoms. Drugs with a longer half-life, such as diazepam, clonazepam, and flurazepam, are eliminated more slowly from the body, which influences the timing and severity of withdrawal symptoms. In contrast, short- and intermediate-acting benzodiazepines, such as oxazepam and alprazolam, tend to produce fewer side effects due to their rapid elimination (Nunes, 2016).

Figure 1 – Liposobility and dependence on benzodiazepines



Note - (figure 1): The benzodiazepines with high liposolubility, e.g. Lorazepam, oxazepam, shown in the graph, with a long half-life, are associated with greater addiction.

Source: (Adapted). Author, 2025

Clinical practice has shown that dependence on benzodiazepines can develop, with patients often exhibiting a tendency to increase the dosage in order to achieve the same initial therapeutic effect. There is also a notable pattern of indiscriminate use of these drugs (Forsan, 2010). Dependence is an adaptive condition that results from prolonged use of a substance and becomes evident upon abrupt withdrawal, manifesting in the form of withdrawal symptoms.

Before confirming a diagnosis of dependence, it is essential to assess whether the medication was appropriately indicated and whether it was prescribed solely as a palliative measure for an unresolved emotional situation, such as grief. In such cases, discontinuation may bring the patient's underlying distress to the surface, creating a false impression of dependence or withdrawal syndrome (Forsan, 2010).

Events related to dependence, abuse, and toxicity of benzodiazepines most frequently occur after discontinuation of the medication and are typically categorized into three stages: symptom recurrence, rebound symptoms, and withdrawal syndrome.Symptom recurrence refers to the return of the original symptoms that led to the initiation of treatment, such as anxiety and panic attacks. Rebound symptoms involve the reappearance of these initial symptoms, but with greater intensity. Withdrawal syndrome is characterized not only by the resurgence of pre-treatment symptoms but also by the emergence of new symptoms, such as a metallic taste in the mouth. When patients attempt to discontinue the medication, the worsening of withdrawal symptoms may be misinterpreted by some physicians as a deterioration of the

clinical condition, prompting the reinstatement of the drug. During this period, patients often develop tolerance to the medication, requiring increased doses, which further contributes to the cycle of dependence (Foscarini, 2010).

Benzodiazepines are considered drugs of abuse, used both in isolation and in combination with other substances. The drug's receptor selectivity, when combined with individual and environmental factors, contributes to the high abuse potential of these substances (Guebaly et al., 2010).

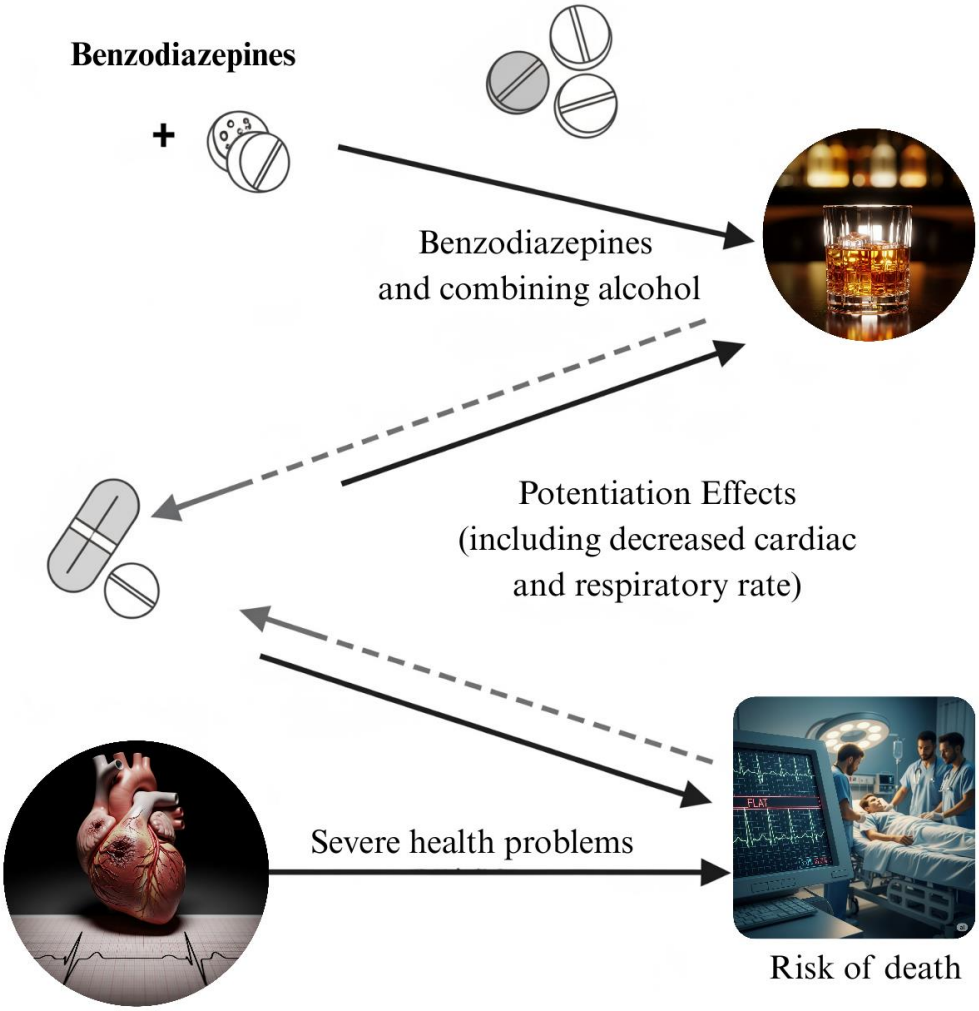
Although there are regulations governing controlled medications—specifically under Ordinance 344/98 of the Brazilian Health Regulatory Agency (ANVISA)—the existence of clandestine markets that distribute these drugs without proper dispensing oversight remains a significant issue. Examples include sales without prescriptions, prescriptions with incomplete information, and altered or forged prescriptions, all of which facilitate unauthorized access to these medications (Foscarini, 2010).

There is also the issue of interaction between benzodiazepines and alcohol consumption (Figure 2), which can either potentiate or diminish the intended therapeutic effects and pose serious health risks, including the potential for fatal outcomes. This highlights the fact that patients are often unaware of the harmful consequences of such combinations and the adverse effects and treatment complications they may face. Therefore, pharmaceutical oversight is vital in cases where patients are being treated with this class of medication (Marques, Marinho, Nunes, 2023).

There are few clinical scenarios in which benzodiazepines are prescribed for chronic use. These include severe anxiety that does not respond to other anxiolytics and refractory epilepsy unresponsive to other antiepileptic drugs. In such cases, patients must be closely monitored by the prescribing professional (Branco, 2013).

It is important to emphasize the pharmacist's role in the dispensing of these medications. There is a constant demand for the sale of benzodiazepines without the required prescription, which must be strictly prevented. Furthermore, pharmacists should provide guidance to patients regarding the correct use of these medications and the risks associated with indiscriminate and prolonged use, as well as the dangers of abrupt discontinuation (Forsan, 2010).

Figure 2 – Risk of alcohol interaction with benzodiazepines



Fonte: Source: (Adapted). Author, 2025

CONCLUSION

Although benzodiazepines are effective in treating conditions such as anxiety, insomnia, and neurological disorders, they pose significant risks when used improperly or over extended periods. Physical and psychological dependence are among the most concerning adverse effects associated with this class of drugs. Evidence indicates that chronic use of benzodiazepines can intensify symptoms of anxiety and depression, leading to a vicious cycle of increasing dosage.

Moreover, adverse cognitive effects such as retrograde amnesia and memory impairment are particularly troubling in elderly patients. These effects may be irreversible even after discontinuation of the medication, increasing the risk of more severe complications such as dementia. The interaction between benzodiazepines and alcohol is also a major concern, as it can potentiate the sedative effects of the medication, increasing the risk of overdose and death.

Therefore, guidance on the rational use of this pharmacological class and awareness of the dangers of self-medication are essential for effective treatment. Additionally, stricter dispensing and regulatory oversight are necessary to prevent easy access to these medications and reduce self-medication, ensuring that the benefits of benzodiazepines are achieved safely while minimizing harm to patient health.

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