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## BENZODIAZEPINES AND Z-DRUGS - BETWEEN TREATMENT EFFECTIVENESS AND THE RISK OF ADDICTION

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### Abstract

Benzodiazepines (BZDs) and Z-drugs are commonly prescribed medications for anxiety and sleep disorders. This review examines their efficacy, associated risks, and alternative treatment options. BZDs enhance the activity of gamma-aminobutyric acid (GABA), reducing anxiety, while Z-drugs selectively target GABA-A receptors' alpha-1 subunits for sedative effects. Despite their effectiveness, both drug classes carry the risk of addiction, physical and psychological dependence, and withdrawal symptoms. Side effects, such as drowsiness, dizziness, and cognitive impairment, are also associated with their use. Recent studies indicate that chronic use of BZDs and Z-drugs may lead to cognitive impairment and an increased risk of dementia in older adults. Furthermore, individual factors, dosage, duration of use, and drug interactions can affect their efficacy. Prescribing trends show a decline in benzodiazepine prescriptions and an increase in Z-drug use due to perceived safety advantages. However, evidence suggests that Z-drugs carry similar risks of adverse effects and addiction potential as benzodiazepines. Healthcare professionals should carefully assess

patients before prescribing these drugs and monitor their use to prevent dependence and addiction. Brief interventions, patient education, drug withdrawal support, and cognitive behavioral therapy have shown effectiveness in reducing long-term benzodiazepine and Z-drug use. Alternative treatments, including cognitive behavioral therapy and relaxation techniques, should be considered, particularly for patients with a history of addiction or those at high risk of addiction. In conclusion, the risk of addiction, withdrawal symptoms, and adverse effects associated with benzodiazepines and Z-drugs necessitates cautious prescribing and the exploration of alternative treatment options.

Keywords : benzodiazepines, Z-drugs, insomnia

## 1. Introduction

Benzodiazepines and Z drugs are a class of drugs that are often used to treat anxiety and sleep disorders [1]. They work by increasing the activity of gamma-aminobutyric acid (GABA), a neurotransmitter that helps regulate brain activity and reduce anxiety [2].

The discovery of chlordiazepoxide and the subsequent introduction of benzodiazepines into clinical practice represented a turning point in the history of anxiolytic drugs. Chlordiazepoxide was discovered in the 1950s by Leo Sternbach. This discovery led to the development of a new class of drugs, the benzodiazepines (BZDs), which quickly became the most widely prescribed anxiolytic drugs in the world. Benzodiazepines have been shown to be effective in the treatment of a wide spectrum of anxiety disorders, including generalized anxiety disorder, panic disorder, and social anxiety disorder. In addition to their anxiolytic properties, benzodiazepines are also frequently prescribed for their sedative, anticonvulsant, and myorelaxant effects. Despite their effectiveness, benzodiazepines are associated with a number of side effects, including drowsiness, impaired coordination, and addictive potential. However, the benefits of using these drugs to treat anxiety disorders make them a valuable tool in the mental health field. Half a century after their introduction, benzodiazepines still remain an important and widely used class of anxiolytic drugs [3].

Z-drugs (non-benzodiazepine sleep aids) such as zolpidem and eszopiclone are a newer class of drugs that are also used to treat insomnia [4]. They work in a similar way to benzodiazepines, but are believed to have fewer side effects and less potential for addiction [5]. However, it may occur with prolonged use. Other potential side effects include: drowsiness, dizziness and cognitive impairment, as well as withdrawal symptoms [6].

The BZD and Z drugs induce sleep by binding to subtype A of the  $\gamma$ -aminobutyric acid receptors [figure 1, 2]. However, Z-drugs show increased selectivity for the  $\alpha 1$  subunits which are responsible for the hypnotic/sedative effect. Due to this more specific pharmacological profile and shorter half-life, it has been hypothesized that Z-drugs will not cause the undesirable side effects associated with BZD, such as impairment of daytime activities due to dizziness and fatigue, and development of addiction [7].

In recent years, the number of prescriptions for benzodiazepines has been steadily declining due to dissatisfaction with their side effect profile. However, interest in non-benzodiazepine derivatives has increased, including the cyclopyrrolone agents zopiclone and eszopiclone, the imidazopyridine derivative zolpidem and the pyrazolopyrimidine compound zaleplon, all of which are currently indicated in the treatment of insomnia [8].

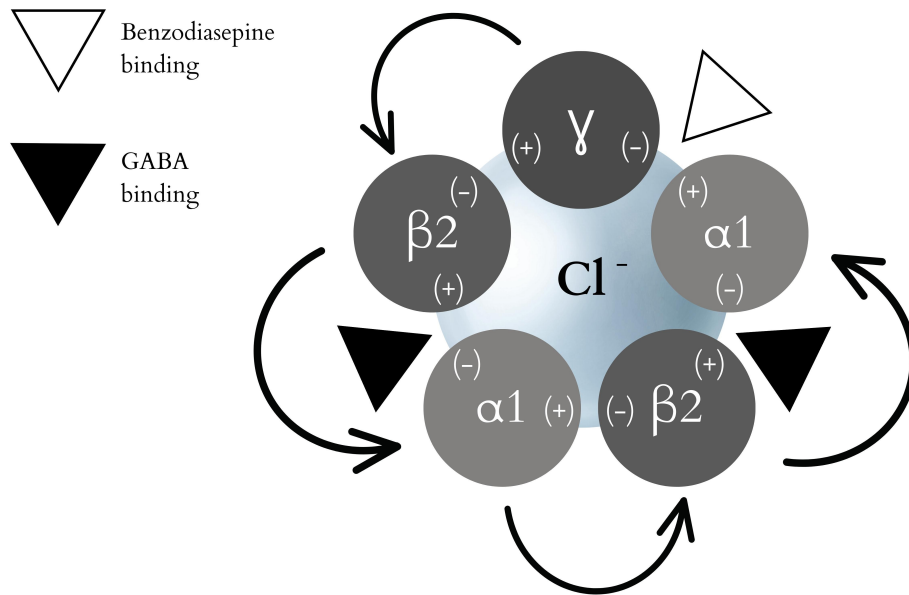


Figure 1: diagram of a pentamer GABA<sub>A</sub> receptor. Five subunits are linked together. The linkers connecting these subunits are represented as arrows. The diagram also highlights two important binding sites: the GABA binding site, indicated by an orange arrowhead, located between the  $\beta 2(+)$  and  $\alpha(-)$  interfaces, and the benzodiazepine binding site, indicated by a gray arrowhead, found between the  $\alpha 1(+)$  and  $\gamma(-)$  interfaces [own elaboration].

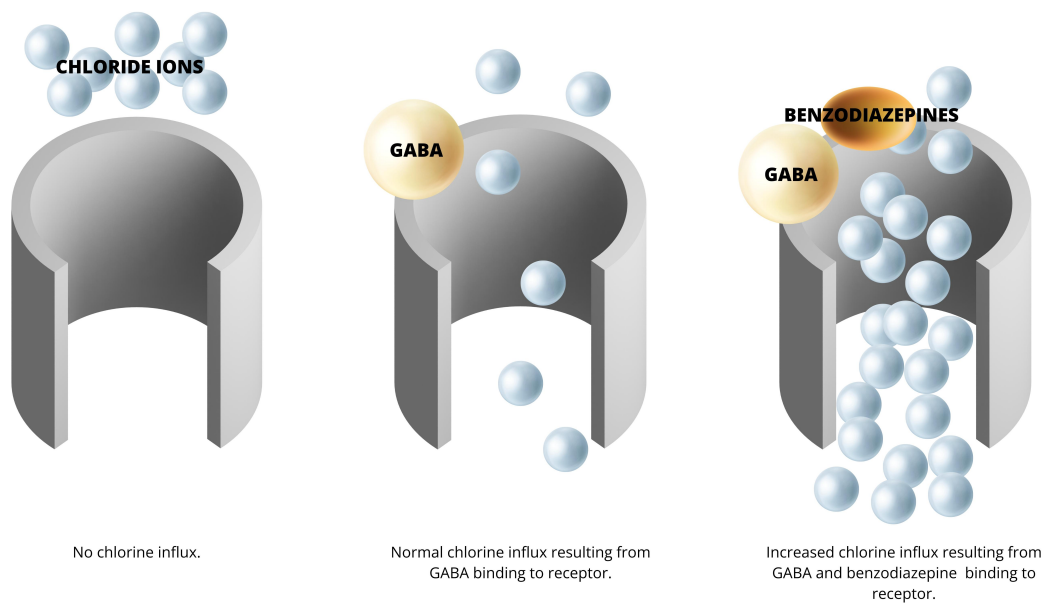


Figure 2: benzodiazepines - mechanism of action [own elaboration]

## 2. Efficacy and risk of benzodiazepines and Z drugs.

Unfortunately, one of the major concerns with the use of benzodiazepines and Z-drugs is their potential for addiction. It is known that long-term use of benzodiazepines can lead to physical and psychological dependence [9]. Z-drugs are also associated with addiction, although to a lesser extent than benzodiazepines [10].

Other potential limitations in the use of benzodiazepines and Z-drugs are their side effects, such as drowsiness, dizziness, and cognitive impairment [11]. In some cases, these drugs can also lead to paradoxical reactions where, instead of reducing anxiety or inducing sleep, they can cause agitation and anxiety. Withdrawal symptoms are also a concern with benzodiazepines and Z-drugs, especially with long-term use. Symptoms may include insomnia, anxiety, and tremors [12]. Discontinuation of these drugs should be done gradually under medical supervision to minimize the risk of complications.

Despite these adverse effects, benzodiazepines and Z-drugs remain important treatment options for patients with anxiety and sleep disorders. The effectiveness of these drugs in relieving symptoms and improving quality of life has been well documented [13]. It is important that each patient's individual situation is carefully assessed before prescribing these medicines and the potential benefits and risks are considered.

Benzodiazepines such as diazepam and lorazepam have been extensively studied and shown to be effective in treating the symptoms of anxiety and panic disorders. They are also effective in treating insomnia, especially in the short term. However, their long-term effectiveness is less clear, and they are usually only recommended for short-term use due to the risk of addiction and withdrawal symptoms [14].

Z-drugs such as zolpidem and zopiclone are effective in promoting sleep and have been shown to improve the onset and duration of sleep in both the short and long term. However, they may not be as effective as benzodiazepines in treating anxiety and other related disorders [15].

More recent research also suggests that the effectiveness of benzodiazepines and Z-drugs may vary depending on individual factors such as age, gender, and comorbidities. Benzodiazepines are less effective in treating anxiety in older adults and are associated with a higher risk of side effects [2]. It turns out that Z-drugs are less effective in promoting sleep in patients with comorbid mental illnesses [16]. In addition, the effectiveness of these drugs may be affected by dosage, duration of use, and drug interactions. For example, benzodiazepines may be less effective when used in combination with certain antidepressants or antipsychotics [17].

Over the past decade, there has been a gradual reduction in prescribing older benzodiazepine hypnotics, while the use of hypnotics continues to increase [18]. This is due to concerns about the use and abuse of benzodiazepines and the increase in prescribing Z drugs, which are generally recognized as safer and less prone to addiction compared to benzodiazepines [19].

Although Z-drugs have been promoted as more effective and safer in terms of side effect and addiction profile compared to benzodiazepines [20], these results are not supported by the study of Siriwarden AN, Quereshi MZ and others. Reported rates of adverse effects of Z drugs were similar in nature and incidence to benzodiazepines [21]. Cognitive problems and psychomotor impairment similar to those associated with benzodiazepines have also been shown in other studies, and recent evidence suggests that Z drugs may also increase the risk of depression [22,23].

### **3. Risk of addiction to benzodiazepines and Z-drugs.**

Although benzodiazepines (BZDs) and Z-drugs are effective in the treatment of anxiety and sleep disorders, they carry a significant risk of addiction [24].

Both BZD and Z-drugs have the potential to cause addiction and withdrawal symptoms and should only be used under medical supervision. It is important to note that BZD and Z-drugs should not be used together or with other drugs that depress the nervous system as this may increase the risk of side effects. In general, although BZDs and Z-drugs can be effective drugs in the treatment of anxiety and insomnia, they should be used with caution and only under medical supervision [24].

BZDs bind to GABA-A receptors and increase the frequency of opening of chloride ion channels, leading to an overall increase in neuronal inhibition. Drugs, in turn, selectively affect the alpha-1 subunit of the GABA-A receptor, which is responsible for the sedative and hypnotic effects. While both types of drugs have similar effects on GABA-A receptors, there are some differences in their pharmacokinetics and pharmacodynamics. For example, Z drugs

have a shorter half-life and faster action compared to BZDs. However, both types of drugs can lead to tolerance, addiction, and withdrawal symptoms with long-term use. In addition, recent studies suggest that chronic use of BZDs and Z drugs may lead to cognitive impairment and an increased risk of dementia in older adults [25].

Benzodiazepines are associated with physical and psychological dependence, withdrawal symptoms, and potential for abuse. The risk of addiction is greater in people with a history of substance dependence, mental health disorders, or those who use benzodiazepines or Z drugs for a long time. A study by Guerlais et al. (2015) showed that long-term use of benzodiazepines and Z drugs was associated with an increased risk of addiction, cognitive impairment and falls in older adults. In addition, withdrawal symptoms associated with these drugs can be serious and potentially life-threatening, including seizures and confusional states. In the case of addiction, gradual discontinuation of drugs and treatment of the addiction may be necessary to prevent further harm to the patient [26].

In conclusion, the risk of addiction to benzodiazepines and Z drugs is a serious problem that cannot be ignored. These medications, while effective in treating a variety of conditions, can lead to addiction, withdrawal symptoms, and even overdose when used incorrectly or overused. It is important that doctors carefully evaluate patients before prescribing these drugs and monitor their use. Patients should also be informed of the potential risks and advised to follow their doctor's instructions carefully. Alternative treatments such as therapy or non-addictive drugs should be considered whenever possible to avoid the potential harm associated with benzodiazepines and Z drugs [27].

Benzodiazepines are classified by the U.S. Drug Control Agency (DEA) as Group IV drugs, indicating their potential for abuse and dependence. Although group Z drugs are not classified as group IV drugs, they still carry the risk of addiction [28].

Long-term use of benzodiazepines and Z drugs can lead to tolerance where higher doses of the drug are required to achieve the same effect. This can lead to a cycle of increasing doses and dependence on the drug [29].

Withdrawal symptoms can occur when someone suddenly stops taking benzodiazepines or Z drugs after long-term use. Withdrawal symptoms may include anxiety, irritability, insomnia, tremors, seizures and in severe cases confusion or hallucinations. Withdrawal should always be done gradually under medical supervision to minimize the risk of complications [29].

It is important for healthcare professionals to monitor patients who receive prescriptions for benzodiazepines and Z drugs for signs of dependence or addiction. For patients with a history of addiction or those who are at high risk of addiction, alternative treatments such as cognitive behavioral therapy or relaxation techniques should also be considered.

Lynch et al. (2020) conducted a comprehensive analysis of studies that examined the effectiveness of brief interventions in reducing long-term use of benzodiazepines and Z drugs in primary care settings. The study found that brief interventions such as patient education, drug withdrawal support, and cognitive behavioral therapy were effective in reducing the use of benzodiazepines and Z drugs over six months to two years. A meta-analysis found that patients who received brief interventions were 2.5 times more likely to be successfully withdrawn than those who received standard care. In addition, the study found that the interventions were cost-effective and acceptable to patients. The results of this study have

important implications for primary care settings, where long-term use of benzodiazepines and Z drugs is common. Primary care providers can use brief interventions to help patients reduce their use of these medications and prevent related side effects such as cognitive impairment, falls, and addiction. This study also highlights the importance of addressing patients' beliefs and attitudes towards these drugs and providing education on alternative treatments for anxiety disorders and insomnia [29].

A comparative study conducted in Brazil looked at the long-term use of BZD and NBZD to determine the differences in their effects. The study found that long-term use of BZD led to a greater risk of addiction and substance dependence compared to NBZD. In addition, cognitive impairment was also more severe in patients using BZD for longer periods. However, the study also found that NBZD use was associated with a higher risk of falls and fractures in older patients. It is therefore essential that healthcare professionals carefully consider the potential benefits and risks of these drugs before prescribing them to patients. In addition, it is important to monitor patients using these drugs long-term to prevent side effects associated with long-term use. According to DF Curado, VV de Barros, AR Noto et al. (2022), long-term use of BZD led to a higher risk of substance dependence compared to NBZD [30]. The publication sheds light on the problem of addiction to sleeping pills. The study provides valuable clues about the differences between benzodiazepine and Z-drug users, highlighting the higher risk of addiction associated with long-term benzodiazepine use. The results of the study underscore the importance of caution when prescribing hypnotics to patients and the need for regular monitoring to ensure safe and responsible use of these drugs [30].

Despite the chemical difference between zolpidem and benzodiazepines, the behavioral effects of zolpidem have been proven to be substantially similar to those of benzodiazepines. Human studies show mixed results, but the variability appears to be related to dosage and the population studied. People with a history of alcohol or drug abuse should be closely monitored while taking zolpidem [31].

Pharmacokinetic factors are believed to be important determinants of drug potency and abuse potential. In many studies, zolpidem was compared with alprazolam, triazolam or diazepam because their peak plasma concentrations occur quickly. Based on these pharmacokinetic data, the potentiating effects and addictive potential of zolpidem cannot be expected to differ significantly from those of benzodiazepines [32].

While the existence of a prior addiction or mental illness has often been reported as a risk factor for abuse, cases of addiction and withdrawal syndrome in patients with no evidence of abuse or mental disorder are also documented. It is likely that the "reward" effect leads predisposed individuals, especially those with personality disorders and a history of substance abuse, to drug-seeking behaviors and subsequent high-dose ingestion. The resulting dependence can then be explained by the loss of specific affinity for the receptor at high dose levels [31].

The number of reported cases of abuse or dependence on zolpidem is low compared to the widespread use of the drug. This low incidence is due to the continued ignorance of clinicians and patients about the potential for abuse of zolpidem [31].

Alternative treatments for anxiety and sleep disorders.

#### **4. Alternative treatment for anxiety and sleep disorders.**

While benzodiazepines and Z-Drugs are effective in treating anxiety and sleep disorders, they carry the risk of addiction. As a result, for patients with a history of addiction or those who are at risk of addiction, alternative treatments should be considered [33].

One alternative treatment for anxiety and sleep disorders is cognitive behavioral therapy (CBT). CBT is a form of talk therapy that aims to change the negative thought patterns and behaviors that contribute to sleep and anxiety problems. It has been proven to be effective in the treatment of anxiety disorders and insomnia, and has a lower risk of side effects compared to medications [33].

Relaxation techniques such as deep breathing exercises, progressive muscle relaxation, and meditation can also help reduce anxiety and improve sleep. These techniques can be done alone or in conjunction with other treatments such as CBT or medication. While relaxation techniques are generally considered safe, they may not work for everyone and may require regular practice to be effective [34].

Lifestyle changes can also have a significant impact on anxiety and sleep. Regular physical activity, a healthy diet and good sleep hygiene can contribute significantly to better mental health and sleep. For example, exercise has been shown to reduce symptoms of anxiety and improve sleep quality. However, lifestyle changes may not be sufficient to completely treat severe anxiety or sleep disorders and may need to be combined with other treatments [35].

It is important that healthcare professionals work with patients to find the best approach to treat their individual needs. While benzodiazepines and Z-drugs can be effective in treating anxiety and sleep disorders, alternative treatments such as CBT, relaxation techniques, and lifestyle changes should also be considered.

Insomnia is a common sleep disorder that affects a significant proportion of the population. The use of complementary medicine as a treatment for insomnia has been gaining popularity in recent years. A systematic review by Sarris and Byrne (2011) assessed the effectiveness of a complementary medicine modality in the treatment of insomnia. The review analyzed 33 randomized controlled trials and found that various complementary medicine modalities, such as acupuncture, relaxation techniques and herbal remedies, showed promising results in improving the quality and length of sleep. Acupuncture has been found to be effective in reducing the time taken to fall asleep and increasing total sleep time. Relaxation techniques such as progressive muscle relaxation, guided visualization, and meditation have also been shown to be beneficial in improving sleep quality. In addition, herbal remedies such as valerian and passion flower have been shown to be effective in improving sleep quality and reducing the time it takes to fall asleep. A systematic review concluded that complementary medicine modalities can be used as adjunct therapy for insomnia, but further research is needed to determine the long-term efficacy and safety of these modalities [36].

Strategies for responsible use of benzodiazepines and Z-drugs.



## **5. Strategies for responsible use of benzodiazepines and Z-drugs.**

One important strategy for responsible use of benzodiazepines and Z-drugs is adherence to recommended dosages. Patients should take their medications exactly as prescribed and not increase the dose without consulting their physician [10].

Another important strategy is appropriate gradual withdrawal from benzodiazepines and Z-drugs after discontinuation of use. Abrupt discontinuation of these medications may cause withdrawal symptoms, including seizures, and should only be done under medical supervision. A gradual withdrawal schedule can help minimize withdrawal symptoms and prevent relapses [25].

Patients should also be aware of potential drug interactions when using benzodiazepines and Z-drugs. These medications may interact with other medications, including alcohol, and increase the risk of side effects and adverse reactions. Patients should inform their physician of all medications, supplements, and herbal products they use before starting benzodiazepines or Z-drugs [37].

In addition, patients should be aware of the potential risks of driving or operating heavy machinery while taking these medicines. Benzodiazepines and Z-drugs can cause drowsiness and affect cognitive function, making certain activities unsafe [38].

Patients should also be aware of the potential risks associated with long-term use of benzodiazepines and Z-drugs. These drugs are associated with cognitive decline and an increased risk of falls, especially in older patients. Therefore, physicians should regularly reassess the need for continued use of these drugs and consider alternative treatments when appropriate [38].

In conclusion, responsible use of benzodiazepines and Z-drugs requires adherence to recommended doses, an appropriate taper protocol, avoidance of potential drug interactions, and awareness of potential risks associated with long-term use. Patients should work closely with their healthcare provider to ensure the safe and effective use of these medications.

## **6. Conclusions.**

Appropriate prescribing practices can help minimize the risk of addiction. Physicians should prescribe benzodiazepines and Z-drugs only after a thorough medical history and medical history, and should regularly monitor the patient's condition while using these drugs.

In the case of anxiety disorders and insomnia, patients and physicians should jointly decide on the use of drugs. Patients should be educated about the risk of addiction and side effects of

drugs and about alternative treatments. Cooperation between the doctor and the patient is crucial to minimizing the risk of addiction and achieving the best treatment results.

### **Author Contributions**

Conceptualization, J.C. and J.B.; methodology, J.C.; validation, E.S; investigation, J.C., J.B. and E.S.; resources, J.C. data curation, J.C.; writing—original draft preparation, J.C.; writing—review and editing, J.B. and E.S.; visualization, J.C.; supervision, E.S.; pfunding acquisition, not applicable.

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### **Data Availability Statement**

Data and material will be available upon completion of this study on request.

### **Conflicts of Interest**

The authors declare no conflict of interest.

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