

## Narrative review

# Physical and mental effects in older adults due to prolonged use of benzodiazepines

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Consuelo Cubero Alpízar<sup>1\*</sup>, Kattia Medina Arias<sup>2</sup>, Beatriz Villalobos Núñez<sup>3</sup>

1-3. University of Costa Rica, San José, Costa Rica.

Correspondence

✉ [consuelo.cubero@ucr.ac.cr](mailto:consuelo.cubero@ucr.ac.cr)

1.  0000-0003-2073-0839

2.  0000-0001-9322-836X

3.  0000-0003-3902-9487

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### Efectos físicos y mentales en adultos mayores por consumo prolongado de benzodiazepinas

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## Abstract

The potential effects and risks of benzodiazepine use have been documented for several decades, with older adults being particularly affected due to the significant changes in pharmacokinetics and pharmacodynamics associated with aging. The objective of this narrative review was to provide answers regarding the effects of benzodiazepine use on the physical and mental health of older adults. A search was conducted in PubMed, Cochrane, Scielo, and LILACS, as well as in the repository of the Library, Documentation, and Information System of the University of Costa Rica. The effects on physical health identified were an increased risk of falls and fractures, while in mental health, an increased risk of dementia and decreased cognitive processing speed were reported. The results emphasize the importance of limiting the prolonged use of benzodiazepines in older adults and promoting non-pharmacological therapeutic alternatives, such as cognitive-behavioral therapy, especially for the management of insomnia and anxiety. Raising awareness among those who prescribe this type of medication is essential so that they seek alternative ways to address conditions such as insomnia and anxiety in this population.

## Keywords

Substance-Related Disorders, Aging, Benzodiazepines, Metabolic Side Effects of Drugs and Substances, Quality of Life.

## Resumen

Los efectos y riesgos potenciales por el consumo de benzodiazepinas han sido documentados durante varias décadas. Las personas adultas mayores tienen un efecto particularmente importante por los cambios relevantes en la farmacocinética y farmacodinamia propios del envejecimiento. El objetivo de esta revisión narrativa fue dar respuesta sobre los efectos por el consumo de benzodiazepinas en la salud física y mental de las personas adultas mayores. Se realizó una búsqueda en PubMed, Cochrane, Scielo y LILACS y en el repositorio del Sistema de Bibliotecas Documentación e Información de la Universidad de Costa Rica. Los efectos en la salud física identificados fueron mayor riesgo de caídas y fracturas; mientras que, en salud mental se reportó mayor riesgo de demencia y disminución de la velocidad del procesamiento cognitivo. Los resultados recalcan la importancia de limitar el uso prolongado de benzodiazepinas en personas adultas mayores, promoviendo alternativas terapéuticas no farmacológicas, como la terapia cognitivo-conductual, especialmente para el manejo del insomnio y ansiedad. La sensibilización dirigida a quienes prescriben este tipo de medicamentos es fundamental, de manera que busquen formas alternativas de abordar los padecimientos de esta población como el insomnio y la ansiedad.

## Palabras clave

Trastornos Relacionados con Sustancias; Envejecimiento; Benzodiazepinas; Efectos Metabólicos Secundarios de Drogas y Sustancias; Calidad de vida.

## Introduction

The effects and potential risks of benzodiazepine use have been documented for several decades<sup>i</sup> and have been identified for different age groups. However, in the elderly, this effect is particularly important, as there are relevant changes in pharmacokinetics and pharmacodynamics that are typical of the physiology of this life cycle.<sup>ii</sup>

The uses of these drugs are broad. However, the literature indicates that in older adults, they are mainly used for anxiety and insomnia.<sup>iii,iv</sup> In addition, prolonged use has been documented, which contravenes the stipulations of the management guide, which indicates that they should not be prescribed for more than four weeks.<sup>v</sup> The aim is to prevent dependence and avoid the development of potentially harmful effects.

On the other hand, improvements in healthcare technologies and overall living conditions have contributed to the increase in life expectancy. This also translates into a challenge for society and health systems as a whole since the population is reaching old age with a series of health problems or multiple pathologies and consequently consumes a large number of drugs, which leads to a decrease in the quality of life.<sup>vi</sup>

In line with the above, an increased consumption of benzodiazepines has been documented in the older adult population, together with adverse effects such as dependence, cognitive impairment, gait disturbances, and increased risk of falls, among others.<sup>vii,viii</sup> All these effects are directly related to basic activities of daily living such as personal hygiene, independence at home, and moving from one room to another within their own home or outside it, affecting, to some extent, the socialization of older adults. In addition, they require a great deal of assistance, which causes dependence on third parties for their care.

Consistent concerns have been documented in the international literature regarding the prolonged use of benzodiazepines in older adults. Studies conducted in countries such as Finland, the United States, France, and the Netherlands have reported adverse cognitive effects associated with their use, which has led to calls for attention to their use in this population.<sup>viii</sup> Nonetheless, its prescription remains a frequent practice. At the same time, it has been shown that a significant proportion of users -particularly older adults- are not fully aware of the potential risks associated with the use of these drugs.<sup>i</sup> On the other hand, recent reviews have addressed relevant pharmacokinetic aspects, as well as the limitations in detecting consumption due to the fact that, in some cases, people do not report their use voluntarily.<sup>x</sup>

Similarly, some authors<sup>ix</sup> propose a change in the approach to caring for various health problems, with the aim of improving the conditions of older adults and, consequently, their quality of life. In addition to the above, the World Health Organization has declared the current decade as the "Decade of Healthy Aging," which increases the need to influence modifiable factors that contribute to favoring this initiative, one of which involves polypharmacy and specifically the prescription of benzodiazepines.<sup>xi,xii</sup>

In this same line, important variables are determined on which actions should be generated to favor healthy aging, among which are independence, autonomy, and

informed consent in health matters. All the aspects mentioned are linked to medications that have effects on these components, such as benzodiazepines.<sup>xi,xiii</sup>

This research design responds to a narrative review of the literature. A search was conducted in PubMed, as well as in the Cochrane, Scielo, and LILACS databases and the repository of the Library Documentation and Information System from the University of Costa Rica. Studies on the effects on physical and mental health of benzodiazepine use in older adults (over 60 years of age) were included. The search strategy included the following keywords: benzodiazepines, aging, adverse effects, adverse effects, long-term adverse effects, mental health, physical health, benzodiazepines, physical and human conditioning, long-term adverse effects, benzodiazepines, and long-term adverse effects, health status and aging. The identified citations were collated and loaded into EndNote 20, a bibliographic software or citation management system (Clarivate Analytics, PA, USA).

This review aimed to provide answers about the effects of benzodiazepine use on the physical and mental health of older adults. Thus, the importance of this research is highlighted, as it adds valuable information to the growing literature and helps to understand better the impact of this type of medication on older adults. Consequently, it provides input for developing better strategies in a comprehensive approach to this issue.

## Discussion

This study aimed to map the physical and mental effects associated with long-term consumption of benzodiazepines in older adults, a particularly vulnerable population due to the physiological and cognitive changes associated with aging. The findings identify specific adverse effects in two major areas: physical health and cognitive health. This also revealed an interrelationship between the two "dimensions" since the effects in one dimension tend to exacerbate those in the other, enhancing the overall negative impact. Given the above, the information obtained from the review provides a comprehensive overview of the potential risks associated with these substances, detailing their documented effects and potential implications for clinical practice and public health.

Given the aforementioned and to contextualize, it should be noted that drugs belonging to the benzodiazepine family comprise a group of substances widely used

in medicine to treat different conditions, some of which are anxiety disorders, insomnia, seizures, and withdrawal syndrome, among others.<sup>xiii</sup> In addition to the above indications, they are being used for all population groups according to their particular condition and need.<sup>vii,xiii,xiv</sup> Despite the above, there are various studies indicating that the population stratum that uses it most or has the greatest number of indications is the elderly.<sup>xiii</sup>

In view of the above, it should be noted that the normal aging process involves natural physical and mental changes, but certain drugs can promote an acceleration in the manifestation of these changes or induce greater deterioration. In addition, it is particularly important to clarify that aging, itself, does not always result in a severe reduction of physical and mental capacities. Nevertheless, it is a stage of life in which some bodily and cognitive functions may gradually diminish and this makes them especially vulnerable or sensitive to the effect of different substances.<sup>ix</sup>

As mentioned above, in older adulthood, the body undergoes physiological changes, some of which can manifest themselves as a decrease in muscle mass, loss of bone density and a decrease in cardiovascular capacity.<sup>xv</sup> Similarly, the brain undergoes modifications, such as a slight decrease in information processing speed and memory, which are considered to be part of normality in this phase.

However, the use of certain medications, especially in inappropriate doses or for prolonged periods, can exacerbate these changes, such as BZDs, commonly used to treat anxiety or insomnia in older adults,<sup>xvii</sup> which can intensify drowsiness, confusion, and affect motor coordination, increasing the risk of falls and fractures.<sup>xiv,xvi-xviii</sup> In addition to the above, age-related changes in liver and kidney function or the distribution of drugs in the body will alter the normal or expected response of the body during older adulthood;<sup>xix</sup> this may result in some drugs interacting with the aging process and generating more pronounced side effects at this stage of life. This is associated with an increased risk of falls and fractures among those who consume these substances as a result of the effects of benzodiazepines, in addition to the changes expected at this stage of life.

In the review conducted by Zhong *et al.*, in addition to the results observed in Table 1, it was found that patients, recent users of BZD, defined according to most of the studies included in the review as less than two years of use, also had an increased risk of dementia (RR 1.55; 95 % CI 1.33 - 1.83;

p 0.32;  $I^2=15.0$ )<sup>20</sup>. An increased risk was also found (RR 1.55; 95 % CI 1.17-2.03; p < 0.01;  $I^2 = 72.6$ ) when evaluating patients with a history of BZD use, with the last dose administered between two and 12 years prior to the start of the studies.<sup>xx</sup>

In the review published by Gómez *et al.*, in addition to the adverse effects described (Table 1), there was also evidence of high BZD consumption in the population > 60 years of age and that the use of BZDs was more frequent in women. However, the limited number of studies in the region does not allow for the generalization of results, which suggests that the exploration of BZD use in MA is in its initial stages and has denoted a need for further and more in-depth study.<sup>xiii</sup>

Although the study by Young *et al.* did not find an increased risk of angle-closure glaucoma in BZD users (Table 1), it was reported that new users (without exposure to BZD 30 days prior to the index date) did present an increased risk (Adjusted OR 1.62; 95 % CI 1.09 - 2.37) of this disease.<sup>xxi</sup>

Now, in response to the objective of this review, it is important to distinguish between the effects of the physical and mental components. However, the fact that they are linked is emphasized, as the effects on the mental component enhance the effects on the physical component, and vice versa.<sup>xxii</sup>

## Effects on physical health

This population group faces changes in muscle mass and strength,<sup>i,xiii-xvi</sup> due to conditions such as sarcopenia,<sup>xxiii</sup> the consumption of BZD aggravates this age-related effect, and, as a result, there are more cases of falls and fractures among users of these drugs.<sup>xvi</sup>

The above reinforces what is reported in the literature when it expresses concern about the indiscriminate prescription and consumption of benzodiazepines among the elderly.

In this same line of argumentation, another group of effects is also found, such as an increase in the risk of acute closed glaucoma and an increased risk of cancer (although it should be clarified that this study included people who were not older adults since age was not a selection criterion), decreased sexual desire, anorgasmia and erectile dysfunction, regarding these the literature mentions that some may be dose-response and others require more research. However, it is worth mentioning, as they should be addressed in greater depth in future research.<sup>xxiv-xxvii</sup> In addition, it is noteworthy to understand that new studies are associating the consumption of these with inflammation processes, which, in turn, are related to the appearance of

certain types of cancer and with the serious and complex behavior of conditions such as asthma or pneumonia; however, more research is required in this regard.<sup>xxviii</sup>

The aforementioned is particularly important in a society with an increasing number of older adults, and the trends of the main health organizations (PAHO and WHO) indicate a decade of healthy aging

and improved quality of life for older adults. The regularization of benzodiazepines, which are used in this age group to treat insomnia and anxiety,<sup>xvi</sup> is fundamental. There are other alternatives for these conditions, including some non pharmacological ones. BDZ consumption is among the modifiable factors that contribute to achieving optimal aging.

**Table 1.** Effects on physical and mental health of long-term benzodiazepine use in the elderly population

Author and year	Description of the study	Time of use	Health effects identified
Zhong, Wang, Zhang, Zhao, 2015 <sup>xx</sup>	<b>Study Type:</b> systematic review and meta-analysis. <b>Objective:</b> quantify the relationship between long-term benzodiazepine use and dementia. <b>Population:</b> six studies were included for a total of 45 391 participants.	Ever use: whether they used BZD during the follow-up time of the studies, maximum follow-up ranged from eight to 25 years.	For the risk of dementia in patients who have ever used BZD compared to those who never used them, significant pooled RRs were obtained (RR 1.49, 95 % CI 1.30- 1.72) with low heterogeneity (p 0.19, I <sup>2</sup> 35.1).
Poly TN, Islam MM, Yang HC, Li YJ 2019 <sup>xvi</sup>	<b>Study type:</b> systematic review and meta-analysis. <b>Objective:</b> assess the magnitude of hip fracture risk with benzodiazepines. <b>Population:</b> 30 studies were included in the review.	Studies in which patients had at least 14 days of exposure to benzodiazepines were included.	In studies that included participants ≥ 60 years, a pooled RR for hip fracture risk of 1.35 (95 % CI 1.24 - 1.47; p < 0.0001) was obtained with a moderate risk of heterogeneity between studies (I <sup>2</sup> 73.37; Q 90.12; r <sup>2</sup> 0.02).
Díaz, Martínez-Cengotitabengoa, Sáez, Cano, Martínez-Cengotitabengoa, et al., 2017 <sup>xviii</sup>	<b>Type of study:</b> systematic review <b>Objective:</b> collect updated data on the relationship between benzodiazepine use and the risk of falls in older adults. <b>Population:</b> 12 articles were included.	The follow-up period of the included studies ranged from five days to ten years.	BZD exposure is associated with the risk of falls in older adults; among the drugs evaluated were lorazepam, alprazolam, clonazepam, and flurazepam.
Gómez, León, Macuer, Alves, Ruiz, 2017 <sup>xiii</sup>	<b>Type of study:</b> systematic review <b>Objective:</b> conduct a review of the available information on the use of benzodiazepines in older adults in Latin America. <b>Population:</b> 21 articles were included.	Not specified	The most frequent adverse effect identified in studies included in this review was the risk of falls and fractures due to falls. Other adverse events identified were chronic headache, insomnia, and dependency.
Young et al., 2019 <sup>xxi</sup>	<b>Type of study:</b> case-control <b>Objective:</b> investigate whether BZDs increase the risk of acute angle-closure glaucoma in a geriatric population. <b>Population:</b> 1117 cases and 4468 controls.	One to 30 days	BZD use did not significantly increase the risk of acute angle-closure glaucoma (adjusted OR, 1.14; 95% CI, 0.94-1.37).
Liu, Jia, Jian, Zhou, Zhou, Wu, Tang, 2020 <sup>viii</sup>	<b>Type of study:</b> systematic review and meta-analysis. <b>Objective</b> explore the following two questions in the elderly: is benzodiazepine use associated with impaired cognitive functions in the elderly? And, which cognitive domains have decreased functionality associated with benzodiazepine use and abuse? <b>Population:</b> 13 articles were included in the review, but only eight could be included in the meta-analysis.	Not specified	Impairment in processing speed was found in BZD users (N 253; SMD -0.61; 95 % CI -0.91 - 0.31; I <sup>2</sup> 0; p < 0.0001). There was no significant cognitive deficit in BZD users (N 9262; SMD -0.18; 95 % CI -0.36 - 0.00; I <sup>2</sup> 87; p 0.05), but there was in those who abused (N 7726 SMD -0.23; 95 % CI -0.44 - -0.03; I <sup>2</sup> 86 p 0.02).

**SMD:** Standardized Mean Difference.

## Effects on cognitive health

Older adults frequently present alterations in their cognitive functions as part of the aging process. Among these changes are difficulties in memory, especially in the short term, and in processing speed, which means that tasks are performed more slowly.<sup>xxiii</sup> Additionally, they experience difficulties with concentration and certain executive functions, including problem-solving and decision-making.

This frames what are considered some of the main psychological changes of aging, which should be considered and confronted with the common effects of benzodiazepines. In this regard, the literature refers to disorientation, confusion, mood changes, and sleep disturbances, among others. This reinforces the evidence found, which details how they affect cognitive processes and slow down learning and memory,<sup>xxix</sup> increasing the risk of dementia, cognitive impairment, and the speed at which information is processed.<sup>viii,xiv,xv</sup>

From the mapping of the evidence compiled in this review, it is observed that, in the context of various national and international policies aimed at promoting active, healthy, and functional aging, with the full participation of older adults in society, the use of benzodiazepines requires special attention. The literature suggests that their prescription should be careful and, preferably, carried out by specialists such as geriatricians, who can assess the changes inherent to aging and adequately weigh the risk-benefit ratio when prescribing these drugs to treat common conditions such as insomnia or anxiety.<sup>xxx</sup>

It is important for health professionals to be aware that cognitive deterioration can lead to long-term physical deterioration and vice versa and to take into account the importance of restrictions in the prescription of this group of drugs.

## Limitations and recommendations of the review

Among the main limitations identified were the time required for the search process and the scarcity of studies with large samples, long follow-up periods, and direct comparisons between benzodiazepine users and non-users. Nevertheless, the information gathered is relevant, especially when considering the projected growth of the older adult population. In addition, it highlights the need for research to investigate the causes of prolonged prescription of these drugs and to explore therapeutic

alternatives to address common problems such as insomnia or anxiety. This allows to identify priority areas for future research.

The similarities between the studies are explained by the nature of the documented adverse effects, such as falls and cognitive impairment. On the other hand, differences in specific findings, such as oncologic risks, can be attributed to variations in methodological designs, population characteristics, and prescribing practices in different geographic regions.

These results underscore the importance of limiting the prolonged use of benzodiazepines in older adults and promoting non-pharmacological therapeutic alternatives, such as cognitive-behavioral therapy, especially for the management of insomnia and anxiety.<sup>xxx</sup>

On the other hand, it is important to recommend the importance of continuing medical education to sensitize prescribers of the risks associated with the use of benzodiazepines, as well as strict prescription and follow-up protocols, prioritizing the intervention of specialists such as geriatricians.

All of the above cannot be overlooked; however, it is recommended that longitudinal research be conducted to compare consumers and non-consumers, evaluating the long-term effects on various health dimensions.

## Conclusion

The main side effects on physical and mental health identified were increased risk of falls, dementia, as well as loss of cognitive abilities. According to the available evidence, it has been found that there is a reduction in the quality of life and the possibility of self-care of older adults associated with the side effects of benzodiazepines. The literature emphasizes the importance of adopting alternative measures to improve the quality of life for the older adult population. Therefore, it is essential to raise awareness among those who prescribe this type of medication so that they seek alternative ways of dealing with the ailments of this population, such as insomnia and anxiety.

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