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MANAGEMENT OF INSOMNIA IN AGING POPULATIONS: COMPARING THE INFLUENCE OF BENZODIAZEPINES AND Z-DRUGS ON COGNITIVE HEALTH AND NEURODEGENERATIVE RISK - A REVIEW OF THE LITERATURE

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ABSTRACT

Background: Insomnia is a prevalent sleep disorder among older adults and is associated with impaired cognitive function and increased risk of neurodegenerative diseases. Pharmacological management commonly involves benzodiazepines and non-benzodiazepine "Z-drugs" (zolpidem, zaleplon, zopiclone), which act as sedative-hypnotics through modulation of GABAA receptors. Although cognitive-behavioral therapy is the first-line treatment, hypnotic medications remain widely prescribed.

Aim: This review evaluates the mechanisms linking benzodiazepines and Z-drugs to neurodegeneration and summarizes the clinical and epidemiological evidence regarding their long-term impact on cognitive function in older adults.

Methods: A literature review was conducted using PubMed, PMC, and Google Scholar databases, focusing on full-text, English-language publications from 2013–2025. Search terms included "benzodiazepines and dementia risk," "Z-drugs and cognitive impairment," and drug-specific names such as zolpidem, zopiclone, zaleplon, and diazepam. Both observational and mechanistic studies were considered.

Results: Long-term benzodiazepine use is consistently associated with an increased risk of cognitive decline and dementia, particularly with higher cumulative doses and long-acting compounds. Evidence for Z-drugs suggests a generally more favorable cognitive profile at low doses or short-term use, although high-dose or long-term exposure may similarly increase dementia risk and adverse events such as falls and fractures. The underlying mechanisms involve modulation of GABAergic neurotransmission, potentially altering hippocampal and cortical network activity, synaptic plasticity and memory consolidation. The interpretation of causality is complicated by potential confounding factors, such as underlying insomnia or anxiety.

Conclusion: Benzodiazepines and Z-drugs are effective for insomnia management in older adults but may carry long-term cognitive risks. Minimizing dose, limiting treatment duration, and prioritizing non-pharmacological interventions such as cognitive-behavioral therapy are essential strategies to mitigate potential neurodegenerative outcomes. Future studies should aim to optimize dose–response regimens, incorporate long-term follow-up assessments, clarify the biological mechanisms through which these drugs affect cognitive function and include randomized controlled trials as well as long-term observational studies to more precisely evaluate the effects on specific cognitive domains, such as memory, attention and executive function.

KEYWORDS

Insomnia, Benzodiazepines, Z-drugs, Cognitive Impairment, Neurodegeneration, Elderly

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Introduction

One of the most common sleep disorders in the older adult population is insomnia, which represents a significant clinical concern in this age group. Difficulties with sleep initiation or maintenance may affect up to approximately 50% of elderly individuals. The prevalence of insomnia symptoms is higher among older adults compared with younger adults, with estimates ranging from 30% to 48%, while full-threshold insomnia disorder affects approximately 12–20% of this population.[1]

Insomnia is a sleep disorder characterized by difficulty initiating or maintaining sleep, or by early morning awakenings, occurring at least three times per week for a minimum of three months, and resulting in daytime functional impairment or reduced well-being.[2]

Older adults are particularly vulnerable to adverse cognitive outcomes due to age-related physiological changes, increased comorbidities, and a high prevalence of polypharmacy, which collectively contribute to a greater susceptibility to drug-induced cognitive impairment and neurodegeneration.[3]

Sleep disturbances have a significant impact on cognitive functions as well as on neurobiological processes related to memory and the integrity of neuronal networks. Sleep mechanisms not only support

physiological restoration but also facilitate the clearance of brain metabolites and regulate neuroplasticity. Disruption of these processes may lead to pathological changes that promote cognitive impairment and increase the risk of developing dementia, including Alzheimer's disease. Sleep disturbances may precede or exacerbate neurodegenerative processes and accelerate cognitive decline, highlighting the importance of early identification and management.[4]

Pharmacological treatment of insomnia primarily relies on the use of sedative-hypnotic medications. This group includes benzodiazepines and non-benzodiazepine $GABA_A$ receptor agonists, known as Z-drugs (e.g., zolpidem, zaleplon, and eszopiclone), which represent one of the most commonly prescribed classes of medications for sleep disorders. Although cognitive-behavioral therapy for insomnia (CBT-I) is recognized as the first-line treatment for chronic insomnia, pharmacotherapy remains widely used in clinical practice, and hypnotic medications are frequently prescribed to patients with sleep disturbances.[5] Recent studies continue to emphasize the widespread use of benzodiazepines in elderly populations for insomnia management, highlighting the need to carefully evaluate both therapeutic benefits and potential cognitive risks. [6]

Epidemiological studies suggest that the use of benzodiazepines and Z-drugs may be associated with an increased risk of developing dementia, particularly at higher doses and with short-acting formulations. This association indicates a potential impact of long-term pharmacotherapy for insomnia on cognitive function, especially in the older adult population.[7]

These medications exert their effects by modulating $GABA_A$ receptors in the central nervous system, enhancing inhibitory processes and facilitating sleep initiation. Prolonged modulation of the GABAergic system may lead to alterations in neuronal network activity, including in structures such as the hippocampus and prefrontal cortex, which play key roles in memory processes and synaptic plasticity. Experimental studies suggest that the influence of these drugs on $GABA_A$ receptors may disrupt mechanisms of neuronal plasticity and memory consolidation, providing a potential explanation for the associations observed in epidemiological studies between long-term hypnotic use and cognitive decline.[8, 9, 10]

Z-drugs were introduced as a more selective and potentially safer alternative to benzodiazepines; however, an increasing number of studies indicate that their adverse effect profile may be comparable, and their long-term safety-particularly regarding cognitive function and neurodegenerative risk remains a subject of ongoing debate.[11]

Understanding the mechanisms of action of these medications and their long-term effects on cognitive function is essential for optimizing the management of sleep disorders. This is particularly important in the context of the aging population, in which both insomnia and neurodegeneration are highly prevalent.[2]

Aim of the publication

This review analyzes the mechanisms of action of hypnotic medications and also examines the potential risk of cognitive impairment and neurodegeneration associated with the use of benzodiazepines and Z-drugs in elderly patients. A primary focus of the review is on the clinical and epidemiological evidence regarding the long-term effects of these medications, which are frequently used to treat insomnia in the geriatric population.

Both drug classes have a pharmacological profile that includes the ability to inhibit neuronal activity, modulate memory processes, and affect cognitive function. In addition, the article reviews the comparative risk of neurodegenerative disease and cognitive decline associated with the use of benzodiazepines or Z-drugs in the management of insomnia in older adults, and discusses the clinical implications for treating insomnia in this population..

Ultimately, the results of this review may help clinicians improve clinical judgement in the pharmacological treatment of insomnia in the elderly population by evaluating the benefits of treatment against the long-term cognitive risks associated with these treatments.

Methodology

A literature review was conducted to analyze current knowledge regarding the mechanisms of action of benzodiazepines and Z-drugs and their potential association with cognitive impairment and neurodegenerative risk in elderly patient populations. In addition, the review aimed to evaluate the long-term cognitive safety profiles of both drug classes when used in the treatment of insomnia.

Relevant articles were searched using PubMed, Google Scholar, and PMC databases. The review included publications released between 2014 and 2026. Only full-text, English-language, open-access articles were considered.

The search strategy was developed using key terms including: "dementia risk in benzodiazepine users," "cognitive impairment associated with Z-drug use," "neurodegenerative effects of hypnotic medications," "mechanism of action of benzodiazepines," and drug-specific names such as zolpidem, zopiclone, zaleplon, and diazepam.

This review synthesizes evidence from systematic reviews, meta-analyses, clinical observational studies, and epidemiological research addressing the cognitive safety and neurodegenerative risks associated with hypnotic medication use in older adult populations.

Mechanism of action: Benzodiazepines

Benzodiazepines are positive allosteric modulators of $GABA_A$ receptors. They act by binding to distinct sites within the $GABA_A$ receptor complex, which includes various α, β, and γ2 subunits. This binding increases the receptor's affinity for endogenous GABA, resulting in enhanced chloride ion influx into neurons and strengthening synaptic inhibition in the central nervous system. The net effect is a reduction in neuronal excitability, which clinically manifests as anxiolytic, sedative-hypnotic, muscle-relaxant, and anticonvulsant effects. A characteristic clinical property of benzodiazepines is their ability to induce anterograde amnesia, mediated by modulation of GABAergic transmission in brain regions involved in memory consolidation. Long-term use is also associated with the development of tolerance and potential dependence.[12]

Mechanism of action: Z drugs

Z-drugs, including zolpidem, zaleplon, and eszopiclone, act as positive allosteric modulators of $GABA_A$ receptors. They bind to the benzodiazepine site located at the interface between the α(+) and γ(−) subunits, most commonly in receptor complexes containing the γ2 subunit. This interaction enhances the effects of endogenous GABA, resulting in increased chloride ion flow through the receptor channel, neuronal hyperpolarization, and strengthened inhibitory signaling in the central nervous system. Consequently, the likelihood of action potential generation is reduced. In contrast to benzodiazepines, Z-drugs exhibit greater selectivity for receptors containing the α1 subunit, which is primarily associated with hypnotic effects and relatively less anxiolytic activity. Consequently, they are among the most commonly used pharmacological therapies for the treatment of insomnia.[11]

Beyond their receptor-level effects, Z-drugs may also influence neuronal network activity during sleep. Studies by Kersanté et al. demonstrated that zolpidem can enhance slow-wave oscillation synchronization and strengthen functional connectivity between the hippocampus and prefrontal cortex during non-REM sleep. This is associated with increased neuronal inhibition and may play a significant role in memory consolidation processes.[13]

Comparison of Neurodegenerative Risk: Benzodiazepines vs. Z-Drugs

Benzodiazepines

Benzodiazepines exhibit a heterogeneous impact on neurodegenerative processes, which may be partly related to their pharmacokinetic properties and duration of action. Studies examining benzodiazepine use in the context of Alzheimer's disease risk indicate that long-term administration of agents such as diazepam is associated with a greater risk of cognitive decline compared with shorter-acting drugs like oxazepam, suggesting that pharmacokinetics may influence potential neurodegenerative outcomes.[12]

In 2023, an Umbrella Review of Meta-Analyses was published summarizing the evidence and assessing the association between benzodiazepine use and dementia risk. The authors analyzed five meta-analyses encompassing sixteen individual studies, which yielded remarkably consistent results. The studies demonstrated a significant increase in dementia risk among benzodiazepine users compared with non-users. Despite the consistent direction of the effect across all meta-analyses, the magnitude of risk increase varied: the lowest risk elevations were reported by Lucchetta et al. and Penninkilampi et al., indicating increases of 38% and 39%, respectively, whereas Zhong et al. and He et al. reported risk increases of approximately 50%. The highest reported increase was observed by Islam et al., showing a 78% higher risk of dementia among benzodiazepine users. The authors of the Umbrella Review also considered whether the elevated dementia risk resulted directly from benzodiazepine use or was influenced by confounding by indication. In studies conducted by Joyce et al., the risk of dementia was higher among patients exposed to higher levels of benzodiazepines (>365 days over a 2-year period). Another question addressed whether anxiety itself constitutes a risk factor for dementia. Research by Brieler et al. demonstrated that both long-term benzodiazepine use and a diagnosis of anxiety disorders were independent risk factors for dementia development in individuals aged 65–75 years. [14]

Z-drugs

In 2015, Hsin-I Shih and colleagues published a population-based case-control study aimed at investigating the impact of zolpidem on the risk of developing dementia and Alzheimer's disease. The study included 8,406 patients aged 65 years and older with newly diagnosed dementia or Alzheimer's disease. The control group (16,812 individuals) was matched using a 2-fold frequency matching method based on sex, age, and year of study entry, allowing for the isolated assessment of zolpidem as a potential risk factor. Patients with dementia, compared to controls, were exposed to zolpidem for longer durations, received higher cumulative doses, and used it more frequently (44.8% vs. 30%). Similar differences were observed for eszopiclone (20.3% vs. 12.9%) and benzodiazepines (91.3% vs. 83.6%). The case group also had a higher prevalence of comorbidities, including hypertension, diabetes, stroke, ischemic heart disease, hyperlipidemia, depression, and anxiety disorders. Despite adjusting for confounding factors using multivariable logistic regression models, zolpidem exposure was associated with a 33% increased odds of developing dementia. This association was primarily observed for non-Alzheimer's dementia. Additionally, a clear dose-response relationship was noted: dementia risk increased by 18% at low cumulative doses (<170 mg/year) and reached 52% at doses exceeding 820 mg/year. Importantly, subgroup analyses revealed that zolpidem remained an independent risk factor even among patients without hypertension, diabetes, or cardiovascular disease. Concomitant use of zolpidem with antidepressants or antipsychotics further increased dementia risk, highlighting the need for particular caution with combination therapy in older adults. These findings provide new insights into the safety profile of Z-drugs. Although these medications have long been promoted as a less neurotoxic alternative to benzodiazepines, epidemiological data indicate that long-term use, especially at higher doses, is associated with a significant and clinically relevant increase in the risk of persistent cognitive decline. [15]

In 2021, Guo and colleagues conducted a clinical observational study involving 120 patients aged 50 to 77 years with chronic insomnia who were using Z-drugs (zolpidem and zopiclone). The study aimed to assess the relationship between exposure to these medications and cognitive function. Participants underwent comprehensive cognitive assessments, including global evaluation using the Montreal Cognitive Assessment (MoCA) and tests of memory, attention, executive function, verbal, and visuospatial abilities. Multivariable regression analyses were subsequently performed, adjusting for potential confounding factors. In the multivariable regression analysis, benzodiazepine exposure density was identified as an independent risk factor for cognitive decline. In contrast, neither the use of Z-drugs nor their exposure density was significantly associated with global cognitive performance. Notably, Z-drug use was positively associated with attention performance. Other variables, including income level, severity of sleep problems, and age, independently influenced overall cognitive function. The authors emphasized that although Z-drugs were not associated with global cognitive decline, their use in older adults should be carefully considered due to the risk of tolerance and dependence. Benzodiazepines, on the other hand, should be prescribed at the lowest effective doses.[16]

Adverse effects associated with hypnotic therapy

Benzodiazepines

The use of benzodiazepines is associated with numerous adverse effects, primarily due to their depressant action on the central nervous system. Long-term use of benzodiazepines, particularly those with prolonged duration of action, may increase the risk of cognitive decline as well as the development of dementia and Alzheimer's disease. The likelihood of adverse effects rises with cumulative dose and duration of therapy. The most commonly observed side effects include drowsiness, dizziness, impaired motor coordination, and reduced psychomotor performance. In older adults, these symptoms can lead to an elevated risk of falls and injuries. Benzodiazepines may also impair memory, including causing anterograde amnesia, by affecting GABAergic transmission in brain regions responsible for memory consolidation. Prolonged use of these agents is additionally associated with the development of tolerance and the risk of dependence.[12,7]

Z-drugs

Z-drugs, such as zolpidem, zopiclone, and zaleplon, may increase the risk of adverse events in older adults, particularly with long-term use and higher drug exposure. These drugs are associated with adverse effects primarily involving the central nervous system, such as impairments in memory, attention, and overall cognitive performance. Additionally, the literature reports the occurrence of complex sleep-related behaviors, including sleepwalking and engagement in activities during partial arousal.[17,18] Notably, there is an elevated risk of falls, fractures(including hip fractures) and ischemic vascular events. At lower doses, the risk of clinical complications appears minimal or inconsistent across available observational studies.[19]

Discussion

This review underscores the complex relationship between hypnotic medications and cognitive outcomes in older adults, particularly focusing on benzodiazepines and Z-drugs. Both are commonly prescribed for insomnia, yet emerging evidence indicates that their long-term use can have important implications for cognitive function and the risk of neurodegeneration.

Benzodiazepines have repeatedly been linked to an increased risk of dementia. The 2023 Umbrella Review of Meta-Analyses, which combined data from five meta-analyses covering sixteen individual studies, found that benzodiazepine use was associated with a 38–78% higher risk of developing dementia compared with non-users. The magnitude of this risk appeared to depend on cumulative exposure and duration of treatment. Additionally, underlying conditions such as anxiety may independently contribute to dementia risk, highlighting the importance of carefully selecting patients and prescribing the lowest effective doses.[14] Furthermore, it is important to acknowledge the possibility of confounding by indication: sleep disturbances and anxiety conditions that often prompt prescription of benzodiazepines or Z-drugs may themselves represent prodromal features or early manifestations of neurodegenerative processes, complicating the interpretation of observed associations between hypnotic use and dementia risk.These findings suggest that the cognitive effects of benzodiazepines may stem from their modulation of $GABA_A$ receptors, which can alter neuronal network activity in brain regions essential for memory, such as the hippocampus and prefrontal cortex, potentially interfering with synaptic plasticity and memory consolidation.

Z-drugs, often marketed as a safer alternative, present a more nuanced picture. Hsin-I Shih and colleagues (2015) found that long-term or high-dose zolpidem use was associated with a significant increase in dementia risk, particularly for non-Alzheimer's types. The study showed a clear dose-response relationship, with risk rising from 18% at low cumulative doses to 52% at high doses. Moreover, combining zolpidem with other central nervous system medications appeared to further increase risk, underscoring the need for caution in older adults receiving multiple therapies.[15] On the other hand, Guo et al. (2021) demonstrated that in patients aged 50–77 using Z-drugs for chronic insomnia, neither overall use nor cumulative exposure was associated with global cognitive decline. Interestingly, Z-drugs were positively associated with attention, suggesting that in some cognitive domains, their impact may even be beneficial. Nevertheless, Guo and colleagues highlighted that long-term use carries risks of tolerance and dependence, which must be considered when prescribing to older adults.[16]

Taken together, these findings suggest that while benzodiazepines generally carry a higher and more consistent risk of cognitive decline, Z-drugs are not entirely risk-free, especially when used long-term or at high doses. The comparison emphasizes the importance of individualizing treatment decisions, carefully weighing the benefits of symptom relief against the potential long-term cognitive consequences. Importantly, non-pharmacological approaches, particularly cognitive-behavioral therapy for insomnia (CBT-I), should remain the first-line treatment for older adults due to their proven efficacy and minimal adverse effects.

It is also important to recognize the limitations of the current evidence. Most data come from observational studies, which cannot establish causality and may be influenced by confounding factors. Insomnia itself might be an early symptom of neurodegenerative disease rather than a completely independent condition, potentially complicating the interpretation of associations. Future research should focus on longitudinal studies with standardized cognitive assessments to better understand dose-response relationships and the mechanisms by which hypnotic medications may affect cognition over time.

Conclusions

Benzodiazepines and Z-drugs are effective for insomnia management in older adults but may carry long-term cognitive risks. Minimizing dose, limiting treatment duration, and prioritizing non-pharmacological interventions such as cognitive-behavioral therapy are essential strategies to mitigate potential neurodegenerative outcomes. Future studies should aim to optimize dose–response regimens, incorporate long-term follow-up assessments, clarify the biological mechanisms through which these drugs affect cognitive function and include randomized controlled trials as well as long-term observational studies to more precisely evaluate the effects on specific cognitive domains, such as memory, attention and executive function.

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