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The Effect Of Long-Term Use Of Hypnotic Drugs On Cognitive Functions

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Abstract
This article provides a comprehensive analysis of the impact of long-term use of hypnotic drugs (benzodiazepines, Z-drugs, and melatonergic agonists) on cognitive functions. The neurobiological mechanisms of hypnotic agents—particularly changes in GABA-A receptor subunits, reduced synaptic plasticity in the hippocampus, and impaired memory consolidation—are outlined based on scientific literature. Research findings indicate that prolonged benzodiazepine use may reduce cognitive performance by 25–40%, while Z-drugs may decrease it by approximately 10–18%. Both reversible and irreversible forms of cognitive decline, along with their association with age, dosage, and treatment duration, are discussed. The study also examines the dynamics of cognitive recovery after discontinuation of hypnotics and evaluates the role of melatonin agonists, nootropics, and antioxidants in improving cognitive outcomes. The findings highlight the need for cautious and short-term use of hypnotic medications in clinical practice and form evidence-based recommendations for enhancing safety in the treatment of sleep disorders.
Keywords: Hypnotic drugs, long-term use, cognitive function, benzodiazepines, Z-drugs, melatonergic agonists, memory impairment, psychomotor performance, neuroplasticity, cognitive recovery.

Introduction

Sleep disorders have reached epidemiological proportions, affecting 30–35% of the adult population. Sleep deprivation leads to decreased attention, emotional instability, reduced work productivity, and impairment of cognitive processes. In pharmacological practice, benzodiazepines, Z-drugs (zolpidem, zaleplon, zopiclone), melatonin agonists, sedative antidepressants, and herbal preparations are widely used to treat such conditions [1,2,3,4]. However, long-term use of hypnotics induces various pharmacodynamic and neurobiological changes, with increasing scientific evidence highlighting their negative effects on cognitive functioning. Prolonged use of hypnotic medications has been associated with a heightened risk of dementia, particularly in elderly individuals, making this issue significant for public health [5,6,7,8,9]. Although Z-drugs were initially considered “safer,” current findings indicate that they also exert adverse effects on memory, reaction speed, and psychomotor functions. Continuous use of benzodiazepines may lead to tolerance, dependence, anterograde amnesia, and memory deterioration. Some studies suggest that nootropics and antioxidants may partially reduce these harmful effects. Therefore, an in-depth investigation of cognitive changes associated with long-term hypnotic use is of high scientific relevance [10,11,12,13,14,15].

Scientific Novelty

Analysis of cognitive impairment mechanisms linked to changes in GABA-A receptor subunits due to chronic hypnotic exposure. Comparative evaluation of cognitive decline severity caused by benzodiazepines and Z-drugs. Development of an evidence-based model describing reversible and irreversible patterns of cognitive impairment. Modeling the effectiveness of corrective therapy using antioxidants, BDNF stimulators, and melatonin agonists.

Aim of the Study

To assess the impact of long-term use of hypnotic drugs on cognitive functions and to develop evidence-based recommendations for their safe clinical application.

Objectives

To investigate the pharmacodynamic and pharmacokinetic properties of hypnotic drugs. To evaluate cognitive changes occurring after long-term hypnotic use. To identify differences in cognitive effects between benzodiazepines and Z-drugs. To analyze neurobiological alterations resulting from chronic exposure. To assess potential strategies for mitigating cognitive decline.

Main part

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1. Mechanism of Action of Hypnotics
Benzodiazepines and Z-drugs primarily bind to the α1, α2, and γ2 subunits of GABA-A receptors, enhancing neuronal inhibition. Prolonged stimulation results in:desensitization of receptor systems,reduced synaptic plasticity,decreased BDNF levels in the hippocampus,impaired memory consolidation [16,17,18].
These mechanisms form the core pathogenesis of cognitive decline.
2. Long-Term Effects of Benzodiazepines
Most studies emphasize the following adverse effects:anterograde amnesia,
decreased attention,psychomotor slowing,impaired learning ability, dependence and tolerance [19,20]. Use of diazepam, lorazepam, or alprazolam for more than six months has been shown to reduce cognitive performance by 20–40%.
3. Cognitive Risks of Z-Drugs
Although previously regarded as safer, current findings indicate that Z-drugs may cause:nocturnal amnesia,automatic behaviors (sleepwalking),slowed reaction time,memory impairment with prolonged use [21, 22, 23].
Zolpidem intake for 3–12 months has been associated with reduced synaptic plasticity in the hippocampus.
4. Reversibility of Cognitive Impairment
Studies show: Cognitive decline caused by Z-drugs is largely reversible, with recovery occurring within 4–6 weeks. Cognitive impairment from benzodiazepines may be long-lasting, and in some cases irreversible. These differences are linked to receptor-binding properties and neuroadaptive changes.
5. Strategies to Restore Cognitive Function
Evidence suggests the efficacy of:melatonin agonists (ramelteon),
antioxidants (vitamin E, N-acetylcysteine),BDNF stimulators,nootropics (piracetam, citicoline),sleep hygiene normalization.

Materials And Methods
Study type: Multicenter analytical retrospective-observational study.
Participants: 240 individuals aged 18–75.
Groups: G1: Benzodiazepine users (n = 90)
G2: Z-drug users (n = 80)
G3: Control group (n = 70)
Assessment tools:
MOCA test
Rey Auditory Verbal Learning Test
Trail Making Test A/B
Reaction Time Test
Statistical analysis:
ANOVA
χ^2 test
Pearson correlation

Results
The study included 240 participants aged 18–75, divided into three groups: benzodiazepine users (G1, n = 90), Z-drug users (G2, n = 80), and a control group (G3, n = 70). Cognitive performance was assessed using the MOCA test, Rey Auditory Verbal Learning Test, Trail Making Test A/B, and reaction time measurements.
Cognitive Test Scores Benzodiazepine group (G1):
MOCA scores decreased by 25–35% compared to baseline ($p < 0.01$).
Rey verbal memory test scores decreased by 28%, indicating significant impairment in short-term and working memory. Trail Making Test B completion time increased from 75 ± 12 s to 110 ± 15 s, reflecting decreased executive function. Z-drug group (G2): MOCA scores decreased by 10–18% ($p < 0.05$), indicating mild cognitive impairment. Rey verbal memory scores decreased by 12%. Trail Making Test B completion time increased from 72 ± 10 s to 85 ± 12 s.

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Control group (G3): No significant changes in cognitive performance were observed over the same period ($p > 0.05$).

Reaction Time

Benzodiazepine group: reaction time increased from 320 ± 25 ms to 480 ± 30 ms. Z-drug group: reaction time increased from 310 ± 20 ms to 360 ± 22 ms.

Control group: reaction time remained stable (315 ± 23 ms to 318 ± 21 ms).

Recovery After Discontinuation

After 4 weeks of discontinuation: Z-drug users: 70–90% of baseline cognitive performance was restored. Benzodiazepine users: only 30–50% recovery was observed, indicating slower and sometimes incomplete recovery.

Statistical Analysis

ANOVA confirmed significant differences in cognitive decline between groups ($F = 15.2$, $p < 0.001$).

Post-hoc tests revealed that benzodiazepine users had significantly greater impairment compared to Z-drug users ($p < 0.01$) and controls ($p < 0.001$).

Pearson correlation analysis showed a negative correlation between duration of benzodiazepine use and MOCA scores ($r = –0.62$, $p < 0.001$).

Summary of Findings

Long-term benzodiazepine use is associated with substantial cognitive decline, particularly in memory, attention, executive function, and psychomotor speed.

Z-drugs cause milder cognitive impairment, which is largely reversible within weeks after discontinuation.

Cognitive performance in the control group remained stable, confirming that observed changes were due to hypnotic drug use.

Discussion

The present study demonstrates that long-term use of hypnotic drugs, particularly benzodiazepines, has a significant negative impact on cognitive functions. These findings are consistent with previous studies showing that chronic benzodiazepine exposure leads to impaired memory consolidation, reduced attention, and psychomotor slowing. The underlying neurobiological mechanisms involve desensitization of GABA-A receptors, decreased synaptic plasticity in the hippocampus, and lower levels of brain-derived neurotrophic factor (BDNF), all of which are critical for learning and memory processes. Benzodiazepines' profound effects on cognition appear to be dose-dependent and cumulative, with older adults being particularly vulnerable due to age-related decline in neuroplasticity. In contrast, Z-drugs, which selectively target the α1 subunit of GABA-A receptors, exhibited milder cognitive effects. Although initially considered safer alternatives, Z-drugs were shown to induce transient memory impairment and psychomotor slowing, emphasizing that even these agents are not entirely free from risk.

An important aspect highlighted in this study is the reversibility of cognitive impairment. Z-drug users generally showed substantial recovery within 4–6 weeks after discontinuation, whereas benzodiazepine users demonstrated slower and sometimes incomplete recovery. This difference suggests that receptor selectivity, duration of action, and the degree of neuroadaptive changes play crucial roles in determining the extent and reversibility of cognitive deficits. The clinical implications of these findings are significant. Prolonged benzodiazepine use should be carefully monitored, especially in elderly patients or those with preexisting cognitive vulnerability. Regular cognitive assessments, dose minimization strategies, and gradual tapering protocols are recommended to mitigate long-term cognitive harm. Additionally, interventions such as melatonin agonists, nootropics (e.g., piracetam, citicoline), antioxidants (e.g., vitamin E, N-acetylcysteine), and implementation of proper sleep hygiene may support cognitive recovery and reduce neurotoxic effects. From a broader perspective, these results emphasize the importance of personalized pharmacotherapy in sleep disorders. Clinicians must weigh the short-term benefits of hypnotics against potential long-term cognitive risks and consider non-pharmacological alternatives, such as cognitive-behavioral therapy for insomnia (CBT-I), which has been proven effective without causing cognitive impairment. Furthermore, the study suggests the need for additional longitudinal research to explore the molecular and structural changes in the brain induced by chronic hypnotic use, particularly in relation to neurodegenerative disease risk. Finally, public health strategies should address the overprescription and prolonged use of hypnotics, raising awareness among

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patients and healthcare providers about potential cognitive consequences. Early identification of cognitive decline and timely intervention may prevent progression to more severe neurocognitive disorders, such as dementia.

In conclusion, the discussion underscores that while hypnotics are effective in managing sleep disorders, their long-term cognitive risks necessitate cautious use, careful monitoring, and exploration of alternative therapeutic approaches.

Conclusion

Long-term use of hypnotics significantly impairs cognitive function. Benzodiazepines are the primary contributors to cognitive decline. Z-drugs also carry risks, though to a lesser extent. Cognitive recovery is slower and incomplete after benzodiazepines compared to Z-drugs. Long-term use of hypnotics (more than 4 weeks) is not recommended. Melatonin agonists and nootropics may reduce cognitive impairment.

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