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Sleepless in Dementia: A Narrative Review and Pragmatic Algorithm for the Pharmacological Management of Insomnia in Patients with Dementia

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Abstract **Review Article**

Insomnia is common in patients with dementia, affecting up to 60% of individuals, and is associated with poorer quality of life, increased caregiver burden, and faster cognitive decline. Managing these symptoms is difficult, given the limited available pharmacological options and their safety concerns. This narrative review summarizes current evidence on pharmacological treatments for insomnia in older adults with dementia, based on a structured search of PubMed, the Cochrane Library, and ScienceDirect (2010–2025). We reviewed available data on orexin receptor antagonists, melatonin, hypnotics, antidepressants, antihistamines, and antipsychotics; with particular attention to their efficacy and safety profiles. We propose a pragmatic, stepwise clinical algorithm to support day-to-day decision-making. The approach favors better-tolerated options such as orexin receptor antagonists and low-dose trazodone, while reserving higher-risk medications for selected, refractory situations.

Keywords: Dementia, Insomnia, Pharmacological treatment, Orexin receptor antagonists, Geriatrics, Neurocognitive disorders.

INTRODUCTION

The geriatric population is increasing worldwide, estimated at 830 million in 2024 and projected to double within thirty years.[1] A key challenge accompanying this demographic shift is the management of neurocognitive decline, which is often accompanied by behavioral and psychiatric symptoms. The number of people living with dementia globally was estimated at 57.4 million cases in 2021, with an expected increase to 152.8 million by 2050.[2] The prevalence of sleep disorders in patients with different subtypes of dementia is relatively high, reported to be between 20% and 60% in various studies. [3-5] Patients with dementia experience various types of sleep disturbances, including early awakening, inversion of the sleep-wake cycle, nighttime sleep fragmentation, and nocturnal wandering or confusion episodes.[6, 7] In Parkinson's disease (PD) and Lewy body disease (LBD), sleep-related breathing disorders, restless legs syndrome (RLS), circadian rhythm disorders, and rapid eye movement (REM) sleep behavior disorder are also frequent.[8, 9] This review, however, will focus exclusively on insomnia subtypes.

MATERIALS AND METHODS

This narrative review of the literature was conducted to synthesize current evidence on the pharmacological management of sleep disorders, particularly insomnia, in patients with dementia and other neurocognitive disorders. Eligible studies included peer-reviewed publications involving elderly populations aged 65 years and older with a confirmed diagnosis of dementia or a related neurocognitive disorder. The review focused on pharmacological interventions for insomnia, including but not limited to benzodiazepines, non-benzodiazepine hypnotics, melatonin and its agonists, and atypical antipsychotics. Accepted study designs comprised randomized controlled trials, cohort studies, case-control studies, and systematic reviews published in English within the last 15 years. Studies were excluded if they primarily addressed non-pharmacological interventions, focused on primary sleep disorders unrelated to neurocognitive impairment, were not openly accessible, or were published in languages other than English. The literature search was performed on 15 October 2025 and covered articles published between 2010 and 2025. Electronic

databases searched included PubMed, the Cochrane Library, and ScienceDirect, using combinations of the free-text keywords and MeSH terms: "insomnia," "sleep disorders," "dementia," "neurocognitive disorders," "pharmacological treatment," and "hypnotics." The screening process involved an initial evaluation of titles and abstracts to assess eligibility according to predefined criteria, followed by a full-text review of potentially relevant articles to confirm inclusion. Based on the synthesized evidence, a clinically oriented treatment algorithm was developed, outlining recommended pharmacological options tailored to patient characteristics, along with posology guidance, monitoring strategies, safety considerations, and potential drug-drug interactions.

The initial database search yielded approximately 250 records. After screening titles and abstracts, 80 articles were selected for full-text review, of which 25 met inclusion criteria and were included in the final synthesis.

Given the narrative design of this review, a formal PRISMA protocol was not applied; however, efforts were made to ensure a comprehensive and balanced inclusion of relevant high-quality studies, including randomized controlled trials, systematic reviews, and meta-analyses. “Narrative literature review”

MECHANISMS

Sleep disturbances in dementia, particularly Alzheimer's disease (AD), arise from an association of neurodegenerative pathology, circadian dysregulation, neurotransmitter imbalance, and impaired neurophysiological clearance systems. The bidirectional relationship between pathological protein accumulation and sleep-wake regulation is central to this mechanism: the accumulation of amyloid-β (Aβ) and tau disrupts normal sleep architecture and quality, while impaired sleep exacerbates the production and reduces the clearance of these proteins, creating a positive feedback loop that accelerates neurodegeneration and worsens sleep fragmentation. Experimental evidence shows that wakefulness increases neuronal release of Aβ and tau, whereas sleep, especially slow-wave sleep, facilitates glymphatic clearance of these toxic proteins from the interstitial space; chronic disruption of this process promotes their accumulation in the brain. [10, 11]

Moreover, degeneration of circadian pacemaker circuits (e.g., in the suprachiasmatic nucleus) and dysregulation of clock gene expression disturb the intrinsic sleep-wake cycle, contributing to altered rest-activity rhythms, sundowning, and fragmented sleep patterns.[12]

At the neurochemical level, changes in orexin/hypocretin signaling have been implicated in AD-associated sleep-wake abnormalities, linking neurotransmitter dysregulation with both increased wakefulness and impaired clearance mechanisms.[13]

Additional contributors include oxidative stress and neuroinflammation driven by chronic sleep loss, glial dysfunction that impairs homeostatic support for neurons, and hypothalamic alterations that disrupt hormonal and autonomic regulation of sleep.

Collectively, these interconnected mechanisms explain the high prevalence of insomnia, circadian rhythm disorders, and sleep fragmentation in dementia patients and underscore the importance of targeting underlying pathophysiology in pharmacological interventions.

Orexin antagonists

Elevation in orexin levels has been associated with disturbed sleep and cognitive impairment in AD patients.[14] The number of trials on orexin receptor antagonists (suvorexant, lemborexant, daridorexant) has been increasing, focused mainly on sleep disorders in adult and geriatric populations. A 2023 review shows a superiority in terms of benefit-risk of orexin receptor antagonists compared to hypnotic and sedative molecules (benzodiazepines, non-benzodiazepine hypnotics).[15] A recent Cochrane review found moderate-certainty evidence for the benefits of orexin antagonists, which could increase nocturnal sleep duration and quality, reduce sleep latency, and decrease time awake after sleep onset.[16] A 4-week RCT of suvorexant 10 mg including patients with AD and using polysomnography concluded that it led to a clinically significant increase in total sleep time.[17] Another 4-week RCT explored the effects of lemborexant at different dosages, concluding that it improved 24-hour circadian rhythm variables and nocturnal sleep variables.[18] Larger studies on this promising pharmacological option are needed to define effective dosages and optimal treatment duration.

Melatonin

The 2020 Cochrane review on the subject found no evidence for melatonin (≥10 mg) having either beneficial or harmful effects on insomnia in patients with moderate to severe AD dementia. Most available studies are limited by small samples, inconsistent doses, open-label designs, or the use of subjective efficacy evaluation methods, leading to inconclusive results. There was no evidence for beneficial effects of the melatonin-receptor agonist ramelteon.[16] The latest NICE recommendations on the management of sleep disorders in patients with dementia discourage the use of melatonin.[19] A meta-analysis of RCTs reported that melatonin treatment significantly improved total sleep time in dementia patients. Melatonin did not improve cognitive abilities assessed by the Mini-Mental State Examination (MMSE) and the Alzheimer's Disease Assessment Cognitive Subscale. The included RCTs had variable treatment durations, ranging from 10 days to 24

weeks.[20] A systematic review and meta-analysis reviewed the neurocognitive effects of melatonin treatment in patients with AD. They reported a significant improvement in global cognitive function in patients with AD who used melatonin long-term (>12 weeks). Based on the severity of the disorder, an MMSE improvement of significant value was reported in mild AD. The study found no improvement when melatonin treatment was short-term (<12 weeks) or when AD was of moderate severity. The Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) scale, however, showed inconsistent results across groups.[21] Larger RCTs using objective measurement methods are needed to assess the efficacy of melatonin in treating insomnia in patients with neurocognitive disorders. Its relative safety profile, however, may explain its frequent clinical use for insomnia in geriatric patients with dementia.

Hypnotics

Benzodiazepines and non-benzodiazepine hypnotics (Z-drugs) have demonstrable effects on sleep and are indicated for the short-term treatment of sleep disorders in the adult population. We found no recent studies that specifically evaluated the use of benzodiazepines for treating sleep disorders in patients with dementia. These molecules are associated with an increased risk of falls in this population; they also have cognitive side effects that may worsen the underlying disorder. [22, 23] An RCT compared the effects of eszopiclone to alprazolam on sleep and cognition in patients with AD and sleep disorders. It found clinically significant effects on sleep quality for both groups, with more significant results for eszopiclone. This study had multiple limitations, rendering the results inconclusive.[24] In an RCT comparing zopiclone 7.5 mg, zolpidem 10 mg/day, and placebo for 14 days, although both medications were clinically efficient in treating insomnia, they further impaired AD patients' cognition.[25] The risks associated with these molecules generally do not justify their use in this population. If their prescription is necessary, it must be for the shortest possible duration and under close monitoring.

Antidepressants and antihistamines

Trazodone:

The 2020 Cochrane review reported with low certainty that a nightly dose of 50 mg of trazodone for weeks may increase the duration and improve the efficiency of nocturnal sleep in patients with AD. The article, however, highlighted the need for larger trials to reach more definitive conclusions.[16]

Mirtazapine:

A double-blind, placebo-controlled study using actigraphy, the MMSE, and the Katz scale concluded that mirtazapine did not improve the efficiency or duration of nocturnal sleep. It did, however, lead to increased daytime sleepiness.[26]

Antihistamines

No recent studies have focused on antihistamines in geriatric patients. Their anticholinergic and sedative side effects are amplified in the elderly, with reports of increased fall risk due to sedation and daytime somnolence, cognitive impairment, and delirium.[27]

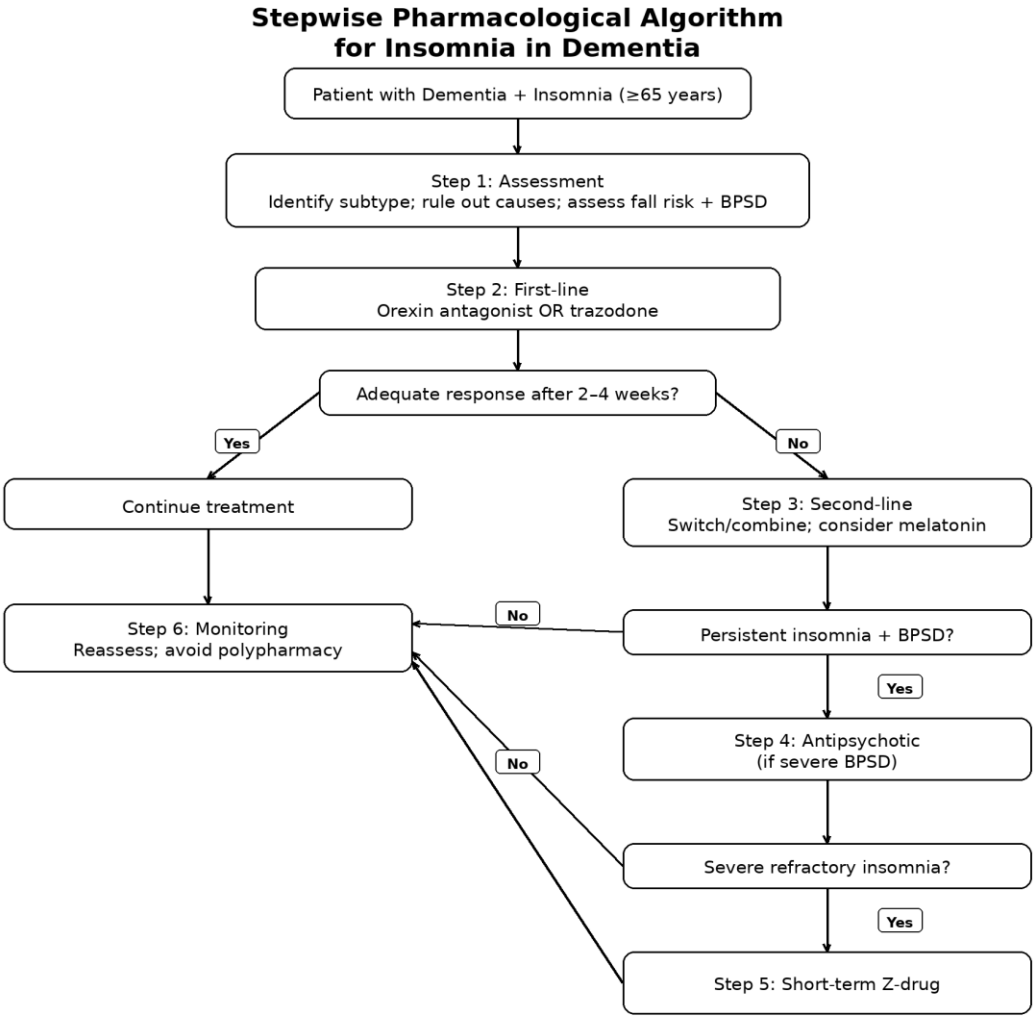
Antipsychotics

The use of antipsychotics in patients with dementia has been linked with a small but increased risk of death.[28] These molecules are often used to treat behavioral and psychiatric symptoms in patients with dementia, including delusions, hallucinations, agitation, aggression, and depression.[29] Their effects on disease progression are not clearly established, with some reports indicating a higher risk of deterioration.[23] A 2015 study reported that a 0.5-1 mg dose of risperidone improved the 5-year outcome in AD patients with insomnia, improving psychotic symptoms and reducing the percentage of patients admitted to special dementia care units. The study compared long-term treatment of sleep disturbances with low-dose risperidone (as an adjuvant to donepezil 5-10 mg) to zolpidem, melatonin, or no drug treatment. Risperidone improved sleep disturbances during the day and nighttime, alleviated the progression of psychiatric symptoms, and reduced the percentage of AD patients who lived in special care dementia units. The treatment did not accelerate the cognitive decline of AD patients.[30] However, these results have not been reproduced, and the sample size was relatively small.

Non-pharmacological treatment

Non-pharmacological interventions, including sleep hygiene optimization, environmental modifications, and cognitive behavioral therapy for insomnia (CBT-I), remain first-line strategies for chronic insomnia in the general adult population.[31,32] In people living with dementia, guidelines recommend personalized multicomponent non-pharmacological approaches; however, their implementation may be more challenging in moderate to severe dementia, where cognitive impairment and functional dependence can limit feasibility, and cautious pharmacological treatment may be considered in selected cases.[16,19]

ALGORITHM



BPSD: behavioral and psychiatric symptoms of dementia

Figure 1: Pharmacological Algorithm for the Management of Sleep Disorders in Patients with Dementia

CONCLUSION

Managing insomnia in patients with dementia remains challenging, as clinicians must constantly weigh modest potential benefits against the risk of adverse effects. Although the evidence base is growing, it is still limited and often inconsistent, which makes treatment decisions difficult in practice.

Among the available options, orexin receptor antagonists appear promising and may be considered early, although their role in this population still needs to be better defined. Low-dose trazodone is another reasonable option, particularly when depressive symptoms are present. In contrast, the benefits of melatonin remain uncertain despite its favorable safety profile. Antipsychotics should be used with great caution and only in cases where insomnia is closely linked to severe behavioral and psychological symptoms. Benzodiazepines and Z-drugs, given their well-known risks in older adults, should be restricted to short-term use in carefully selected cases.

The proposed algorithm is intended as a practical guide rather than a rigid framework. It emphasizes careful initial assessment, stepwise treatment, regular follow-ups, and early consideration of dose reduction or discontinuation. In this context, management should always remain individualized and adapted to each patient's clinical situation.

Further research is clearly needed. Well-designed, andomized trials with objective sleep measures and longer follow-up are essential to better define the effectiveness and safety of these treatments in patients with dementia.

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