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A Focus on The Role of Sleep Disorders in Alzheimer's Disease and Their Pharmacological Treatment Approaches

Yedluri Dimplesriramya[1*], Rahul Akkapeddi[2], Palle Esha Reddy[3*] and Sharon Manoj Oommen[4]

[1]All India Institute of Medical Sciences, Raipur, Chhattisgarh, India
[2]Gandhi Medical College, Secunderabad, Telangana, India
[3]Kurnool Medical College, Kurnool, Andhra Pradesh, India
[4]Adichunchanagiri Institute of Medical Sciences, B.G Nagara, Karnataka, India

Abstract

Sleep disorders are a prevalent and often debilitating symptom in Alzheimer's disease (AD), significantly impacting cognitive function, daily activities, and quality of life (QoL). Current therapeutic options, including pharmacological treatments such as melatonin, benzodiazepines, and sedative antidepressants, offer modest improvements but are limited by side effects and variable efficacy. Non-pharmacological approaches, like cognitive-behavioral therapy and light therapy, show promise in managing sleep-wake cycle disruptions, though their effectiveness may diminish in the later stages of AD. Despite these challenges, advances in understanding the neurobiological mechanisms underlying sleep disorders in AD, such as the roles of neurotransmitters like acetylcholine, serotonin, dopamine, and orexin, have paved the way for more targeted treatment strategies. Looking forward, future treatments for sleep disorders in AD hold great potential. Precision medicine, leveraging neuroimaging and genetic insights, may allow for personalized therapeutic approaches that better address the unique needs of each patient. Additionally, novel pharmacological agents target specific neurotransmitter systems, and the combination of pharmacological and behavioral therapies offer promising solutions. Early intervention and lifestyle-based strategies may further improve patient outcomes by preventing or mitigating sleep disturbances before they significantly affect cognitive decline. With ongoing research and innovation, there is optimism that more effective, well-tolerated treatments will emerge to manage sleep disorders in AD, ultimately enhancing both patient care and QoL.

Keywords: Alzheimer's Disease, Sleep disorders, Neurotransmitters, Pharmacological treatments, Non-pharmacological interventions

Correspondence to: Yedluri Dimplesriramya and Palle Esha Reddy, All India Institute of Medical Sciences, Raipur, Chhattisgarh, India and Kurnool Medical College, Kurnool, Andhra Pradesh, India.

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Introduction

Sleep disorders are prevalent among patients with AD and significantly impact their QoL. These disorders not only exacerbate cognitive decline but also affect the overall health and well-being of both patients and their caregivers. The most common sleep disorders associated with AD include insomnia, sleep apnea, circadian rhythm disturbances, and restless legs syndrome (Figure 1) [1]. These disorders contribute to a decline in cognitive function, increased behavioral issues, and a higher rate of institutionalization [2, 3]. Understanding these disorders and their impact is crucial for improving patient care and QoL.

Insomnia is frequently observed in AD patients and is characterized by difficulty in falling or staying asleep. It is associated with worse cognitive and functional abilities, as well as increased behavioral and neuropsychological problems [4]. Obstructive sleep apnea is prevalent in older adults and is characterized by repeated episodes of airflow cessation during sleep. It is linked to cognitive impairments, particularly in attention and memory, and shares some pathological features with AD, such as hippocampal abnormalities [5]. Circadian rhythm disturbances are common in AD and involve disruptions in the sleep-wake cycle. They can appear early in the disease course and are associated with the progression of AD [6]. Restless legs

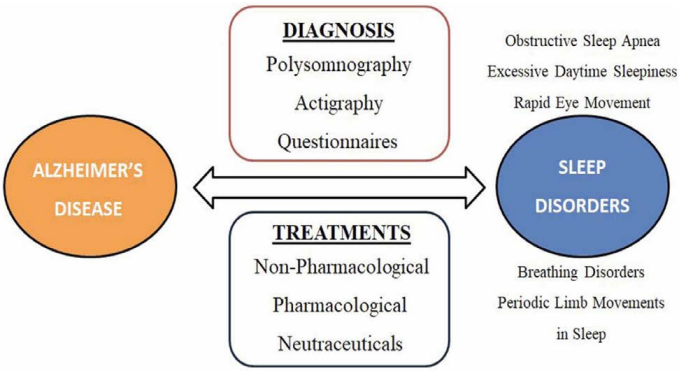

Figure 1: Association between sleep disorder and AD, and possible diagnosis and treatment approaches [2].

syndrome is another common disorder in AD patients, characterized by an uncontrollable urge to move their legs, often accompanied by uncomfortable sensations. It can lead to significant sleep disruption [7].

Sleep disturbances are linked to increased levels of amyloid-beta and tau proteins, which are biomarkers of AD pathology [8]. This contributes to cognitive decline and the progression of AD symptoms. Sleep disorders exacerbate behavioral and psychological symptoms in AD patients, leading to increased caregiver burden and a higher likelihood of institutionalization [9]. Poor sleep quality affects the overall health status of AD patients, reducing their QoL and that of their caregivers. It also increases the risk of other health issues, such as cardiovascular diseases [10].

Statistical Insights

Sleep disorders are prevalent in 50 - 60% of individuals with AD [11]. Studies indicate that up - 40% of AD patients experience sleep apnea or other breathing-related sleep disorders [12]. Insomnia affects around 30 - 40% of patients, with fragmented sleep and frequent nighttime awakenings being the most common issues [13]. Circadian rhythm disturbances, including advanced or delayed sleep-wake cycles, occur in approximately 30% of patients [14]. Excessive daytime sleepiness impacts nearly 20% of those with AD, while parasomnias, such as rapid eye movement (REM) sleep behavior disorder, are reported in about 10 - 15% [15]. Sundowning, characterized by evening agitation, is observed in 20 - 25% of patients [16].

Sleep duration also decreases with disease progression, with severe-stage AD patients experiencing a 40 - 50% reduction in total nighttime sleep compared to healthy individuals of the same age [17]. Studies show that AD patients spend significantly less time in slow-wave sleep (30 - 50% reduction) and REM sleep (up to 25% reduction) [17]. Additionally, caregivers report sleep disruptions in nearly 70% of AD patients, contributing to increased stress and a higher risk of caregiver burnout [18]. These statistics highlight the widespread nature of sleep disorders in AD and their impact on patients and caregivers.

While sleep disorders significantly impact the QoL in AD patients, they remain under-researched and poorly characterized. There is a need for larger, prospective studies to better understand the clinical correlations of these disorders and the effectiveness of various treatment options. Addressing sleep disturbances in AD patients not only has the potential to improve their QoL but may also slow the progression of cognitive decline.

Associated Neurobiological Mechanisms

The neurobiological mechanisms underlying sleep disorders in AD are complex and multifaceted, involving disruptions in circadian rhythms, neurotransmitter systems, and neuroinflammatory processes (Figure 2) [19]. These disturbances not only exacerbate AD pathology but also contribute to cognitive decline. Understanding these mechanisms is crucial for developing therapeutic interventions that target both sleep disorders and AD progression. Circadian rhythm disruptions are a hallmark of sleep disorders in AD, affecting the sleep-wake cycle and contributing to cognitive decline [20]. These disruptions are linked to alterations in neurotransmitter systems, including serotonin and dopamine, which are crucial for maintaining sleep homeostasis. Neurotransmitter imbalances, particularly involving the adenosinergic system, have been implicated in sleep disturbances in AD. Astrocytes play a significant role in modulating these neurotransmitters, influencing both sleep and AD pathology [21].

Neuroinflammation is a critical factor in the relationship between sleep disorders and AD. Microglia and astrocytes contribute to a proinflammatory environment, exacerbating both sleep disturbances and AD progression [22]. Key inflammatory markers include tumor

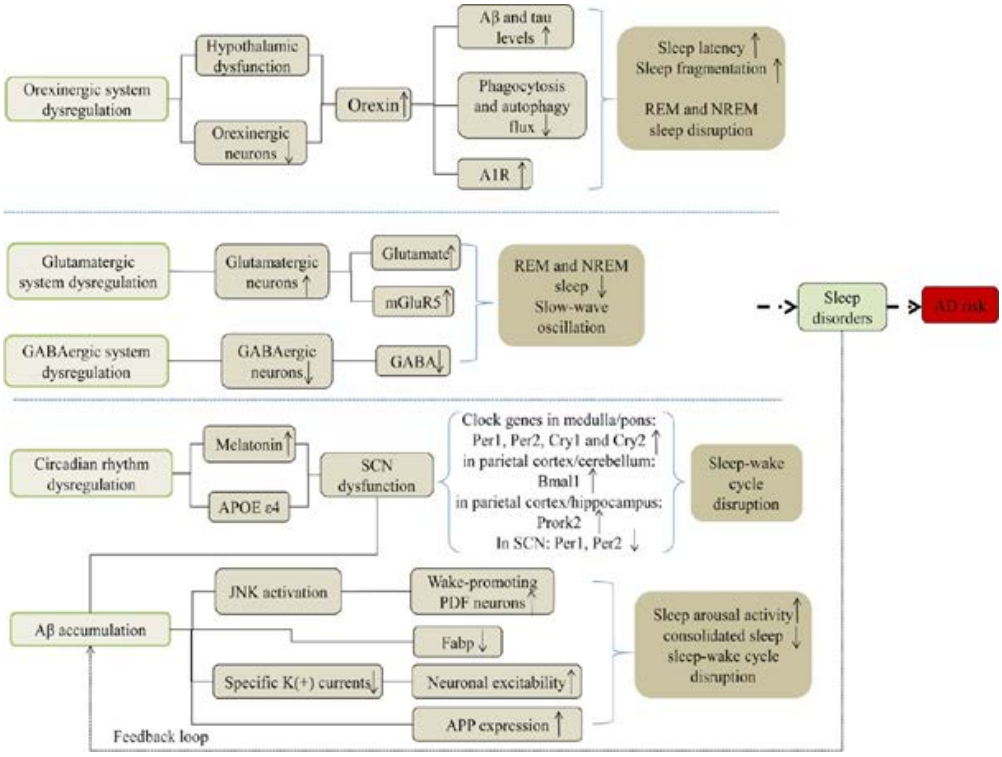

Figure 2: Possible mechanisms associated with sleep disorders in AD [1].

necrosis factor-α, interleukin-1b, and interleukin-6, which are elevated in AD and linked to sleep disruptions [23]. The interaction between amyloid-beta and tau proteins with astrocytes and microglia further promotes neuroinflammation, creating a feedback loop that worsens both sleep disorders and AD pathology [24].

Proteostasis failure, characterized by impaired protein degradation and clearance, is a significant contributor to sleep disorders in AD [25]. This dysfunction affects neuronal circuits regulating the sleep-wake cycle, leading to impaired slow-wave and REM sleep patterns. The glymphatic system, responsible for clearing metabolic waste from the brain during sleep, is disrupted in AD. This disruption impairs the clearance of amyloid-beta and tau, contributing to their accumulation and further sleep disturbances [26].

While the neurobiological mechanisms linking sleep disorders and AD are becoming clearer, the complexity of these interactions presents challenges for therapeutic development. The bidirectional relationship between sleep disturbances and AD suggests that interventions targeting sleep may also influence disease progression. However, further research is needed to fully elucidate these mechanisms and optimize treatment strategies.

Role of Neurotransmitters and Receptors

In AD, disruptions in the sleep-wake cycle are closely linked to alterations in neurotransmitter systems that regulate sleep. Neurotransmitters such as acetylcholine, serotonin, dopamine, gamma-aminobutyric acid (GABA), and orexin play crucial roles in maintaining the balance between wakefulness and sleep stages [27]. In AD, degeneration of neurons and receptor dysfunction in these systems contribute to fragmented sleep, circadian rhythm disturbances, and impaired restorative sleep, which exacerbate both cognitive decline and behavioral symptoms [28].

Acetylcholine and sleep regulation

Acetylcholine is a key neurotransmitter involved in the regulation of the sleep-wake cycle, particularly in maintaining REM sleep. In AD, the cholinergic system is significantly impaired due to the degeneration of cholinergic neurons in regions such as the basal forebrain and hippocampus. This loss of acetylcholine contributes to disrupted sleep patterns, including reduced REM sleep and fragmented sleep-wake cycles. The impairment of cholinergic signaling also exacerbates cognitive deficits, as acetylcholine plays a crucial role in attention, memory, and learning, further complicating the pathophysiology of sleep disturbances in AD [29-31].

GABA and sleep-wake transitions

GABA is the primary inhibitory neurotransmitter in the brain and plays a crucial role in promoting sleep, particularly by facilitating the transition from wakefulness to non-REM sleep. In AD, there is a reduction in GABAergic signaling, particularly in areas such as the cerebral cortex and hippocampus, which contributes to hyperactivity and difficulty in initiating and maintaining sleep. This GABAergic dysfunction leads to sleep fragmentation and the inability to enter deeper stages of restorative sleep. The decreased inhibitory action of GABA also results in heightened neuronal excitability, which may contribute to neuropsychiatric symptoms like agitation and aggression commonly observed in AD patients [32, 33].

Serotonin and the circadian rhythm

Serotonin (5-HT) is another neurotransmitter that plays a central role in regulating the sleep-wake cycle and circadian rhythms. In AD, alterations in serotoninergic pathways, particularly in the dorsal raphe nucleus, disrupt the normal sleep-wake patterns. Serotonin helps modulate sleep onset and transitions between different sleep stages, including deep sleep. In AD, deficits in serotonin availability are associated with poor sleep quality and irregular circadian rhythms. The loss of serotonergic neurons and the reduced ability to synthesize serotonin from its precursor tryptophan contribute to disturbances in the sleep-wake cycle, leading to insomnia and increased daytime sleepiness [31, 34, 35].

Dopamine and sleep cycle dysregulation

Dopamine, a neurotransmitter known for its role in regulating alertness and arousal, also influences sleep-wake transitions. In AD, dopaminergic dysfunction contributes to both motor symptoms, such as bradykinesia and tremor, and sleep disturbances. Dopamine normally promotes wakefulness and inhibits sleep during the daytime. However, in AD, the dysfunction of dopaminergic pathways, particularly in the substantia nigra and striatum, leads to dysregulated sleep patterns, including excessive daytime sleepiness and difficulty staying awake during normal waking hours. Additionally, dopamine dysregulation may contribute to behavioral symptoms like hallucinations and delusions, further complicating the management of sleep disorders in AD [36-38].

Orexin and sleep cycle disruption

Orexins (also known as hypocretins) are neuropeptides involved in regulating wakefulness and promoting arousal. These neuropeptides are synthesized in the hypothalamus and play a crucial role in maintaining alertness and stability in the sleep-wake cycle. In AD, there is a marked reduction in orexin levels, which contributes to the disruption of sleep-wake transitions, leading to fragmented sleep and excessive daytime sleepiness. Orexin deficiency in AD patients is thought to impair the ability to maintain stable wakefulness and contribute to symptoms of hypersomnia. Studies have shown that targeting orexin receptors may hold potential for treating sleep disturbances in AD by restoring the balance between sleep and wakefulness [39-42].

Treatment Approaches

Sleep disorders are common in AD, with patients experiencing difficulties such as insomnia, fragmented sleep, and circadian rhythm disruptions. These disturbances significantly impact the patient's QoL and exacerbate cognitive decline and behavioral symptoms. Treatment approaches for sleep disorders in AD include pharmacological, non-pharmacological, and nutraceutical strategies, each targeting different aspects of sleep regulation to improve overall sleep quality and daytime functioning (Table 1) [2].

Non-pharmacological interventions are generally preferred due to their safety and include behavioral therapies, bright light therapy, and lifestyle modifications. They aim to improve sleep hygiene and stabilize circadian rhythms [43]. Targeting slow-wave sleep has shown promise in mitigating AD pathology. Enhancing slow-wave sleep can improve memory consolidation and reduce amyloid accumulation, offering a potential therapeutic strategy [44]. Melatonin supplementation and light therapy have been explored as interventions to regulate circadian rhythms and improve sleep quality in AD patients [45]. These approaches aim to reduce neuroinflammation and improve cognitive outcomes. Continuous positive airway pressure therapy has been effective in treating obstructive sleep apnea, a common sleep

Table 1: Treatment approaches for sleep disorders [2].

Treatments	Approaches	Uses	Mechanism of action	Evidence/Remarks
Non-pharmacological	Peter Hauri rules	Enhances sleep quantity and quality	Provides structured sleep hygiene techniques	Widely recognized as foundation for managing insomnia
	NITE-AD program	Behavioral techniques reducing nighttime awakenings and improving daily activities	Combines behavioral therapy and structured routines	Demonstrated efficacy in reducing nocturnal awakenings in clinical studies
	Light therapy	Alternative treatment for agitation in AD patients	Regulates circadian rhythms by exposing patients to bright light	Effective for sundowning syndrome and improving circadian rhythm disturbances
Pharmacological	Clonazepam	Provides long-lasting control of REM sleep behavior disorder symptoms	GABA agonist that suppresses motor activity during REM sleep	Effective in controlling motor disturbances linked to REM sleep behavior disorder
	Melatonin	Reduces the frequency and severity of RBD symptoms	Modulates the circadian rhythm and enhances sleep onset	Mixed results in AD; limited efficacy in long-term use
	Nelotanserin	Increases non-REM sleep time and deep sleep (delta-wave)	5-HT2A receptor inverse agonist, promoting deeper stages of sleep	Shown to improve non-REM sleep in clinical trials
	Intepirdine	Enhances attentiveness and memory functions	Acts as a 5-HT6 receptor antagonist to improve cognitive and sleep parameters	Limited trials available; focus on cognitive enhancement
	Antipsychotic agents	Alleviates agitation, sundowning behaviors, and sleep disturbances	Modulates dopamine and serotonin pathways to reduce agitation	Useful in severe cases; risk of side effects such as sedation
Nutraceuticals	Caffeine	Effective for managing excessive sleepiness	Blocks adenosine receptors, promoting wakefulness	Should be used cautiously due to its stimulating properties in AD
	Chamomile	A natural remedy for insomnia	Contains apigenin, which binds to GABA receptors to promote relaxation	Safe for mild insomnia; requires regular use
	Cherries and cherry juice	Supports sleep enhancement and regulates sleep patterns	Natural source of melatonin, aiding sleep regulation	Evidence suggests modest benefits in improving sleep duration
	Kava Kava	Treats anxiety and depression symptoms	Enhances GABAergic activity to reduce stress and improve relaxation	Use with caution due to potential hepatotoxicity
	L-tryptophan	Reduces sleep onset time and increases subjective sleepiness	Precursor to serotonin and melatonin, promoting sleepiness	Shown to improve sleep latency in some clinical studies
	Valerian	Acts as a sedative to promote better sleep	Increases GABA availability in the brain	Effective for mild insomnia, but evidence on efficacy is mixed

disorder in AD, highlighting the potential of sleep-based interventions in managing AD symptoms [46].

When non-pharmacological methods are insufficient, medications such as trazodone, melatonin, and dual orexin receptor antagonists may be used to manage sleep disorders in AD patients [47]. Treatment of sleep disorders in AD often involves pharmacological approaches aimed at addressing the underlying mechanisms of insomnia and circadian rhythm disturbances. Suvorexant, an orexin receptor antagonist, has demonstrated efficacy in improving total sleep time and sleep quality in AD patients [48]. Trazodone, a sedative antidepressant, has shown promising results in enhancing total sleep time and sleep efficiency, particularly in patients with moderate-to-severe AD, though evidence quality is limited [49]. Melatonin, commonly used for sleep regulation, has shown mixed results, with meta-analyses indicating no substantial improvement in major sleep outcomes over an 8 - 10 week period [49]. Thus, pharmacological treatments are carefully selected based on individual patient profiles and symptom severity.

Clinical Relevance to Implications

Clinical studies have extensively examined the relationship between sleep disorders and AD, often reporting statistically significant findings with confidence intervals (CIs) that underscore the strength of these associations. A study by Sabia et al. [50] investigated the impact of sleep duration on dementia risk, indicating that individuals aged 50 and 60 who slept 6 h or less per night had a higher risk of developing dementia compared to those with a normal sleep duration of seven hours. Specifically, the hazard ratio for dementia was 1.22 (95% CI: 1.06 - 1.40) for those aged 50 and 1.37 (95% CI: 1.10 - 1.72) for those aged 60, highlighting a statistically significant increased risk associated with shorter sleep duration.

A study by Zhang et al. [51] reported that individuals with sleep problems had a 3.78 times higher risk of preclinical AD (95% CI: 2.27 - 6.30), indicating a strong and statistically significant association between sleep disturbances and the early stages of AD pathology. A study by Webster et al. [52] the prevalence of sleep disturbances in individuals with AD, the pooled prevalence of clinically significant sleep disturbances was found to be 20% (95% CI: 16% - 24%) based on validated questionnaires, underscoring the commonality of sleep issues among AD patients.

A study by Pase et al. [53] examined whether differences in sleep architecture precedes dementia onset. The study found that certain sleep disturbances are common in dementia, although it remains unclear whether these differences occur before the onset of dementia. A study by Sindi et al. [54] found that individuals with long sleep duration (more than 9 h) had an increased dementia risk (adjusted odds ratio = 3.98, 95% CI = 1.87 - 8.48) compared with those with normal sleep duration. Furthermore, midlife insomnia (fully adjusted hazard ratio = 1.24, 95% CI = 1.02 - 1.50) and late-life terminal insomnia (fully adjusted odds ratio = 1.94, 95% CI = 1.08 - 3.49) were associated with a higher dementia risk.

A study by Wong et al. [55] reported that sleep-initiation insomnia was significantly associated with a 51% increased dementia risk (hazard ratio=1.51, 95% CI: 1.12 - 2.03), highlighting the potential impact of insomnia on cognitive decline.

Clinical Studies

Clinical studies have evaluated various pharmacological treatments for sleep disorders in AD, focusing on their efficacy and safety profiles. Below is a summary of key findings of a few studies.

Suvorexant

A randomized, double-blind, placebo-controlled trial tested the efficacy and safety of suvorexant for treating insomnia in patients with mild-to-moderate AD. The study reported significant improvements in sleep parameters among the treatment group, with CI indicating the reliability of these effects. Out of 285 participants randomized to the study (142 received suvorexant and 143 received a placebo), 277 participants (97%) successfully completed the trial (136 in the suvorexant group and 141 in the placebo group). By week 4, the least squares mean improvement in total sleep time from baseline was 73 min in the suvorexant group compared to 45 min in the placebo group, resulting in a difference of 28 min (95% CI: 11 - 45 min; $p < 0.01$). Somnolence was reported in 4.2% of participants treated with suvorexant and in 1.4% of those in the placebo group [48].

Lemborexant

Lemborexant, another orexin receptor antagonist, has been evaluated for its efficacy in treating sleep disorders in AD patients. A phase 2 randomized clinical trial assessed its safety and efficacy in patients with irregular sleep-wake rhythm disorder and AD dementia. The study found that lemborexant improved sleep efficiency and reduced wake after sleep onset compared to placebo. The least squares mean difference in sleep efficiency from baseline was 3.6% (95% CI: 0.7 - 6.5) for the lemborexant group compared to placebo. 62 participants were randomized and provided data on circadian, daytime, and nighttime parameters across five groups: placebo (n = 12), lemborexant 2.5 mg (n = 12; LEM2.5), lemborexant 5 mg (n = 13; LEM5), lemborexant 10 mg (n = 13; LEM10), and lemborexant 15 mg (n = 12; LEM15). At week 4, the mean L5 (the least active 5 h period) showed a reduction from baseline in the LEM2.5, LEM5, and LEM15 groups, which was significantly greater than that observed in the placebo group ($p < 0.05$), indicating reduced restlessness. For relative amplitude, the least-squares mean change from baseline to week 4 demonstrated improved differentiation between nighttime and daytime activity levels with all lemborexant doses. Significant improvements in relative amplitudes compared to placebo were observed for LEM5 and LEM15 ($p < 0.05$). Additionally, the median percentage change in mean daytime stationary behavior from baseline to week 4 showed a numerical reduction in duration for the LEM5, LEM10, and LEM15 groups. The reductions for LEM5 and LEM15 were significantly greater than placebo ($p < 0.01$ and $p = 0.002$, respectively) [56].

Melatonin

Melatonin, a hormone regulating sleep-wake cycles, has been assessed for sleep disturbances in dementia. A Cochrane review included four randomized controlled trials with 222 participants, but only two studies provided data on primary sleep outcomes. The review concluded that there is insufficient evidence to support the efficacy of melatonin in improving sleep in dementia patients, with studies showing no significant differences between melatonin and placebo groups. A review of studies found no evidence that melatonin, at dozes up to 10 mg, improved significant sleep outcomes over 8 to 10 weeks in patients with AD and sleep disturbances. Data synthesis was possible for two primary sleep outcomes: total nocturnal sleep time showed a mean difference of 10.68 min (95% CI: -16.22 - 37.59; n = 184; two studies), and the ratio of daytime sleep to nighttime sleep had an MD of -0.13 (95% CI: -0.29 - 0.03; n = 184; two studies). Single studies showed no significant differences between melatonin and placebo for sleep efficiency, time awake after sleep onset, or the number of nighttime awakenings. Additionally, two studies reported no effect of melatonin on cognition or activities of daily living. No serious adverse effects of melatonin were identified, but the evidence was considered low quality [49].

Trazodone

Trazodone, an antidepressant with sedative properties, has been studied for its effects on sleep in AD patients. A randomized, double-blind, placebo-controlled study found that trazodone significantly improved sleep parameters. The mean difference in total sleep time between the trazodone and placebo groups was 42.5 min (95% CI: 15.1 - 69.9; $p = 0.003$). For trazodone, a single study of 30 participants with moderate-to-severe AD found low-quality evidence that 50 mg at night over two weeks improved total nocturnal sleep time (MD: 42.46 min; 95% CI: 0.9 - 84.0) and sleep efficiency (MD: 8.53%; 95% CI: 1.9 - 15.1). However, it did not significantly impact the time spent awake after sleep onset (MD: -20.41 min; 95% CI: -60.4 - 19.6) or the number of nighttime awakenings (MD: -3.71; 95% CI: -8.2 - 0.8). No changes were observed in daytime sleep, cognition, or ADL. No serious adverse effects of trazodone were reported [49].

In summary, while some pharmacological treatments show promise in managing sleep disorders associated with AD, the evidence varies, and further research is necessary to establish their efficacy and safety profiles.

Conclusions

Current therapeutic approaches for sleep disorders in AD face significant limitations. Pharmacological treatments, such as benzodiazepines, melatonin, and sedative antidepressants, often provide modest improvements in sleep quality and are associated with side effects like daytime sedation, cognitive impairment, and falls. Non-pharmacological approaches, including cognitive-behavioral therapy and light therapy, have shown some promise but are not universally effective, particularly in advanced stages of AD. Additionally, the variability in patient response and the complex nature of AD-related sleep disturbances make it difficult to identify one-size-fits-all treatments. Therefore, while current treatments can offer some relief, they do not address the underlying neurobiological mechanisms of sleep disruption in AD.

The pathophysiology of sleep disturbances in AD is intricately linked to neurodegenerative processes, including amyloid-beta accumulation, tau pathology, and neuronal loss. These changes disrupt key neurotransmitter systems such as acetylcholine, serotonin, dopamine, GABA, and orexin, which are crucial for regulating the sleep-wake cycle. Despite the recognition of these mechanisms, therapeutic strategies that specifically target these systems remain limited. For example, while cholinesterase inhibitors improve cognition, they have little impact on sleep regulation. Similarly, drugs targeting serotonin or GABA receptors have shown mixed results. The challenge lies in developing treatments that address both cognitive decline and sleep disturbances without exacerbating other symptoms.

Future research into sleep disorders in AD is likely to focus on a more targeted and personalized approach. Advances in neuroimaging and biomarkers may enable clinicians to better understand the individual patient's neurobiological profile and predict which treatments will be most effective. The development of novel pharmacological agents that specifically target disrupted neurotransmitter systems, such as orexin antagonists for promoting sleep without sedation, holds promise. Furthermore, combining pharmacological treatments with non-pharmacological interventions, such as tailored behavioral therapy or

chronotherapy, may offer synergistic effects in improving both sleep quality and daytime function.

Looking ahead, precision medicine may play a key role in treating sleep disorders in AD. By identifying genetic, molecular, and environmental factors that contribute to sleep disturbances, clinicians could offer more personalized treatment regimens. Early intervention, particularly before significant neurodegeneration has occurred, could prevent or mitigate the onset of sleep problems in AD patients. Additionally, developing preventative strategies, such as lifestyle modifications (e.g., exercise, diet, and sleep hygiene) and targeted interventions to improve circadian rhythms, could help delay the progression of both sleep disturbances and cognitive decline in AD. As research advances, these integrated approaches will offer more effective management strategies, ultimately improving the QoL for AD patients.

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None.

Conflict of Interest

None.

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