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Effectiveness of Melatonin Supplementation in Preventing Cognitive Decline Among Older Adults with Sleep Disorders: A Narrative Review

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ABSTRACT

Melatonin, a hormone primarily secreted by the pineal gland, plays a central role in regulating circadian rhythms and sleep-wake cycles. In recent years, its potential neuroprotective properties have garnered increasing attention, particularly in the context of cognitive decline associated with aging and sleep disturbances. Older adults are disproportionately affected by both sleep disorders and neurodegenerative conditions, such as Alzheimer's disease, where disrupted sleep contributes to accelerated cognitive deterioration. Melatonin's antioxidant, anti-inflammatory, and mitochondrial-stabilizing effects, along with its influence on amyloid-beta clearance and synaptic plasticity, make it a promising agent in cognitive health. This narrative review explores the mechanisms through which melatonin supports neuroprotection, highlights the link between sleep disorders and cognitive decline, and evaluates clinical evidence on melatonin supplementation among older adults. Furthermore, it identifies current limitations in the research and provides future directions for clinical application and scientific inquiry. While findings are promising, further high-quality trials are essential to define melatonin's therapeutic role in preventing cognitive impairment in aging populations. Melatonin supplementation shows promise in managing cognitive decline in older adults with sleep disorders. Its ability to regulate circadian rhythms, along with antioxidant and neuroprotective effects, supports its therapeutic potential. Melatonin not only improves sleep quality but may also help preserve cognitive function. Although limitations in existing studies—such as inconsistent dosing and short durations—warrant caution, its safety, affordability, and availability make it a compelling preventive option. Future research through large-scale, long-term studies is essential to confirm its benefits and clarify mechanisms. Melatonin may emerge as a valuable component of strategies for promoting healthy cognitive aging in the elderly.

INTRODUCTION

Cognitive decline in older adults has emerged as a significant public health concern, closely associated with the natural aging process — a physiological phenomenon characterized by decreased muscle strength and heightened susceptibility to oxidative stress [1]. Neurodegenerative conditions such as Mild Cognitive Impairment (MCI), dementia, and Alzheimer's Disease (AD) involve a progressive decline in memory, learning capacity, and attention span, ultimately affecting both short- and long-term cognitive performance [2].

Sleep disturbances, including poor sleep quality and duration, difficulty initiating sleep, and alterations in circadian rhythm with increased daytime sleepiness, have been identified as key contributors to cognitive impairment in aging populations [3]. These disturbances are known to accelerate cortical thinning in brain regions sensitive to age-related degeneration [4]. In addition, sleep disorders such as fragmentation and Obstructive Sleep Apnea (OSA) further intensify cognitive dysfunction and reduce mental acuity in older adults [5]. Given the rising global elderly population and the compounding effects of aging, identifying effective pharmacological and non-pharmacological interventions to preserve cognitive health has become essential.

Melatonin, a neurohormone secreted by the pineal gland, plays a vital role in synchronizing the body's circadian rhythm and regulating sleep patterns. Apart from its role

in sleep-wake regulation, melatonin acts as a powerful antioxidant by scavenging reactive oxygen and nitrogen species at the mitochondrial level, thereby reducing oxidative stress and inflammation in the brain [6]. It has also been shown to optimize mitochondrial enzymes and inhibit the activation of CNS glial and immune cells that drive oxidative imbalance and neural damage [7]. Furthermore, melatonin stimulates SIRT3, leading to the deacetylation and activation of mitochondrial superoxide dismutase (SOD2), thereby initiating an anti-oxidative cascade that reduces mitochondrial damage and neuronal apoptosis [8].

With advancing age, melatonin production declines due to dysfunction of the hypothalamic suprachiasmatic nucleus (SCN), disrupting the circadian rhythm [9]. This reduction in endogenous melatonin is linked to sleep disturbances and neurodegenerative changes that culminate in cognitive decline. Additionally, aging-related inflammation increases the number and activity of microglial cells, which release neurotoxic substances by activating the NF-κB pathway—further exacerbating neuronal damage [10].

Due to its neuroprotective properties and ability to counteract aging-induced oxidative stress, exogenous melatonin supplementation has gained interest as a potential strategy for preserving cognitive function in older adults. Research indicates that melatonin not only helps regulate circadian rhythms [11] but also restores oxidative balance and neutralizes age-related free radicals in the brain [12]. Several randomized controlled trials (RCTs) have investigated melatonin's efficacy in preventing cognitive decline among older individuals with sleep disorders. While many support its positive influence on sleep and cognition [13] others report mixed results—particularly in its role in preventing delirium among hospitalized patients [14].

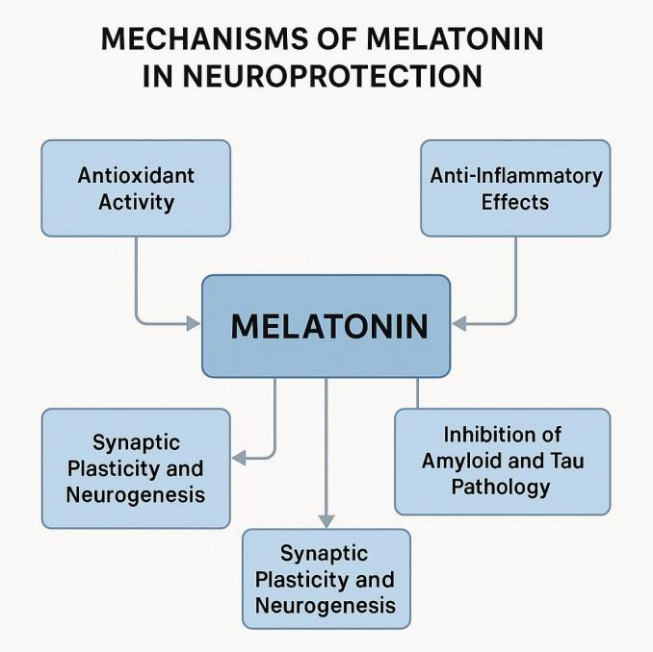
In light of these varying findings, this narrative review aims to comprehensively explore the role of melatonin supplementation in reducing cognitive decline in older adults with sleep disturbances. By highlighting its mechanisms, clinical evidence, and potential limitations, this review seeks to guide future research and clinical practice in geriatric neuroprotection.

Mechanisms of Melatonin in Neuroprotection

Melatonin exhibits multifaceted neuroprotective properties that extend beyond its role in sleep regulation. As a potent endogenous antioxidant and anti-inflammatory agent, melatonin counters the key mechanisms implicated in neurodegeneration, such as oxidative stress, neuroinflammation, mitochondrial dysfunction, and impaired synaptic plasticity.

Melatonin is a powerful free radical scavenger, capable of neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS), which contribute to neuronal damage in aging and neurodegenerative disorders (Reiter et al., 2013). Unlike other antioxidants, melatonin is both lipophilic and hydrophilic, allowing it to cross the blood-brain barrier easily (Hardeland, 2012). It not only neutralizes free radicals directly but also stimulates antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (Tan et al., 2015).

Figure 1



Chronic neuroinflammation, characterized by the sustained activation of microglia and astrocytes, is a hallmark of Alzheimer's disease and other dementias (Heneka et al., 2015). Melatonin suppresses pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α while enhancing anti-inflammatory pathways (Shukla et al., 2021). It modulates the NF-κB pathway, a central regulator of inflammation, thereby attenuating neuroinflammatory responses (Srinivasan et al., 2011).

Aging-related cognitive decline is closely linked to mitochondrial dysfunction and impaired bioenergetics. Melatonin helps maintain mitochondrial homeostasis by preserving mitochondrial membrane potential, enhancing electron transport chain activity, and reducing mitochondrial-generated ROS (Zhou et al., 2020). It also upregulates sirtuins, particularly SIRT1 and SIRT3, which are involved in mitochondrial biogenesis and neuroprotection (Liu et al., 2019).

Melatonin has been shown to interfere with the formation and aggregation of beta-amyloid (Aβ) peptides, a pathological feature of Alzheimer's disease. Studies have demonstrated its ability to reduce Aβ generation and promote Aβ clearance (Pappolla et al., 1998). Furthermore, melatonin inhibits tau hyperphosphorylation by modulating kinases such as GSK-3β and CDK5, thus preventing neurofibrillary tangle formation (Wang et al., 2016).

Melatonin promotes synaptic plasticity by regulating the expression of brain-derived neurotrophic factor (BDNF),

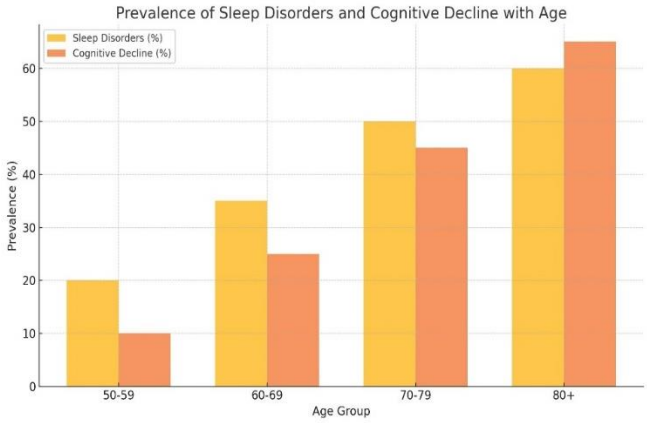
which is essential for learning and memory (Zhang et al., 2017). Animal studies indicate that melatonin enhances neurogenesis in the hippocampus and supports cognitive function, even under stress or aging conditions (Ramírez-Rodríguez et al., 2014).

Sleep Disorders and Cognitive Impairment

Sleep disorders are highly prevalent in older adults, and a growing body of evidence indicates their strong association with cognitive decline and neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Disrupted sleep not only affects memory consolidation and executive function but also interferes with neuronal repair, clearance of neurotoxins, and synaptic plasticity—factors crucial for maintaining cognitive health.

Common sleep disturbances among older adults include insomnia, obstructive sleep apnea (OSA), restless leg syndrome (RLS), circadian rhythm disorders, and reduced slow-wave sleep (SWS) (Crowley, 2011). Age-related alterations in sleep architecture result in decreased sleep efficiency, increased nighttime awakenings, and reduced REM and SWS stages—all of which impair restorative functions of sleep (Mander et al., 2017).

Figure 2



Sleep, especially SWS and REM phases, plays an essential role in memory consolidation. It has been shown that sleep facilitates hippocampus-dependent memory processing and long-term memory formation (Diekelmann & Born, 2010). Disruption of these sleep stages in older adults is associated with deficits in episodic memory, working memory, and attention (Lo et al., 2016).

Poor sleep quality and chronic insomnia are recognized as modifiable risk factors for cognitive impairment. A meta-analysis by Shi et al. (2018) confirmed that individuals with insomnia symptoms had a significantly higher risk of developing dementia. Similarly, OSA has been linked with hypoxemia-induced neuronal injury and increased accumulation of amyloid-beta plaques—a hallmark of AD (Yaffe et al., 2011; Spira et al., 2013).

The glymphatic system—a waste clearance pathway in the brain—relies heavily on sleep to remove neurotoxic proteins, including amyloid-beta and tau (Iliff et al., 2012). Sleep disturbances reduce the efficiency of this system, contributing to the accumulation of these pathological proteins and the progression of neurodegeneration (Xie et al., 2013).

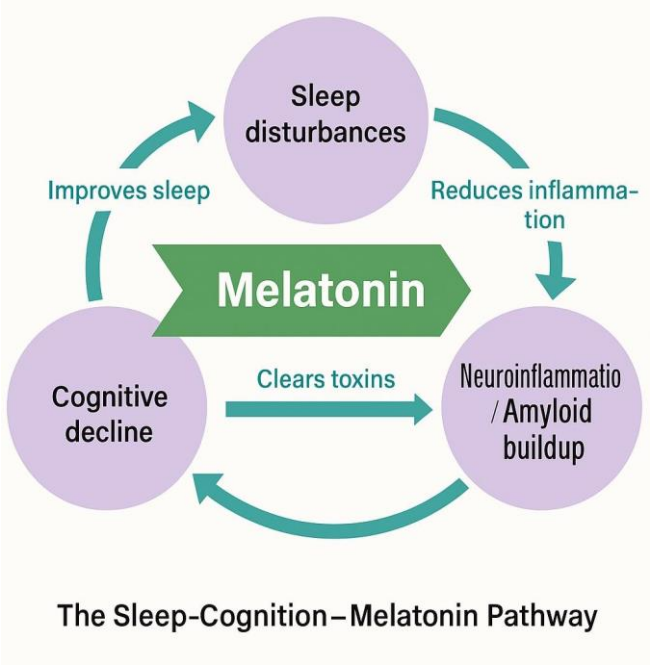
While poor sleep contributes to cognitive decline, early cognitive impairment can also exacerbate sleep disturbances, creating a vicious cycle. For example, individuals in the early stages of Alzheimer's often experience fragmented sleep-wake cycles due to damage to the suprachiasmatic nucleus, the brain's circadian pacemaker (Ju et al., 2014).

Addressing sleep disturbances in older adults could thus represent a critical step in preventing or delaying cognitive decline. Non-pharmacological approaches such as cognitive behavioral therapy for insomnia (CBT-I), lifestyle interventions, and melatonin supplementation have all shown promise in improving sleep and potentially cognitive function.

Clinical Evidence on Melatonin Supplementation

Growing clinical interest has focused on melatonin's potential not only as a sleep aid but also as a neuroprotective agent that may slow or prevent cognitive decline in older adults. While melatonin is widely used for insomnia and circadian rhythm disturbances, increasing evidence from randomized controlled trials (RCTs), meta-analyses, and observational studies supports its efficacy in preserving cognitive function.

Figure 3



Numerous clinical trials have demonstrated the efficacy of melatonin in improving sleep quality, latency, and duration among elderly individuals with insomnia or circadian rhythm disruptions. A meta-analysis by Ferracioli-Oda et al. (2013) reported that melatonin

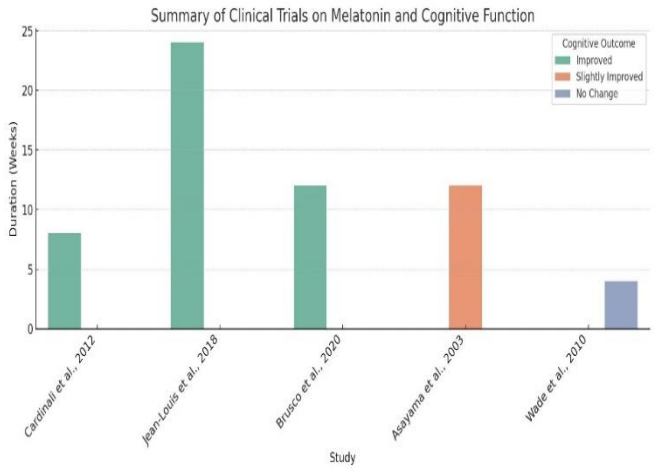
significantly reduced sleep onset latency and increased total sleep time, particularly in older adults and those with sleep disorders. Similarly, Wade et al. (2007) found that prolonged-release melatonin improved sleep quality and morning alertness in elderly patients with primary insomnia.

A growing number of studies suggest that melatonin may have a protective effect on cognitive performance. For example, a double-blind RCT by Cardinali et al. (2012) showed that melatonin supplementation in elderly subjects with mild cognitive impairment (MCI) led to improved Mini-Mental State Examination (MMSE) scores, sleep quality, and mood. Another study by Jean-Louis et al. (2018) found that melatonin supplementation for 24 weeks significantly improved cognitive performance in older African American adults with sleep disturbances.

In a 2020 placebo-controlled trial, Brusco et al. Found that melatonin supplementation in MCI patients led to better performance in memory recall and verbal fluency tasks compared to placebo, suggesting potential disease-modifying effects (Brusco et al., 2020).

Several studies have also explored melatonin's use in populations with Alzheimer's disease (AD) and dementia. Satlin et al. (1992) were among the first to show that melatonin improved sleep-wake rhythms in AD patients. Later studies demonstrated modest cognitive benefits; for example, Asayama et al. (2003) reported improved cognitive function and reduced sundowning symptoms in elderly AD patients after 12 weeks of melatonin treatment.

Figure 4



A 2014 systematic review by Xu et al. Concluded that melatonin supplementation improves sleep in patients with AD and may contribute to stabilization or slight improvement in cognitive function over time, though more large-scale trials are needed.

Doses used in clinical trials range widely—from 0.5 mg to 10 mg per night—with treatment durations varying from 2 weeks to 6 months or more. Long-acting formulations appear to provide sustained effects on both sleep and cognition (Lemoine et al., 2007). While short-term use is generally safe and well-tolerated, long-term data are limited.

Despite promising findings, some studies have yielded mixed results. A randomized study by Wade et al. (2010) found no significant cognitive benefit of melatonin in elderly participants without sleep problems. Variability in study design, melatonin formulations, participant health status, and outcome measures contributes to inconsistencies in results, underlining the need for standardized trials.

Overall, the current clinical evidence indicates that melatonin supplementation can significantly improve sleep and may offer cognitive benefits, particularly in individuals with MCI or AD. However, more rigorous, large-scale studies are required to validate its role as a neuroprotective agent.

Limitations

Despite the promising findings regarding melatonin's role in preserving cognitive function among older adults with sleep disorders, several limitations within the current literature should be acknowledged. One significant challenge lies in the wide variability of clinical study designs, including differences in participant characteristics, dosage, duration of treatment, and the type of melatonin formulation used. This lack of consistency makes it difficult to draw definitive conclusions or generalize findings across diverse populations.

Another common limitation is the small sample sizes and relatively short duration of most trials. Cognitive decline is a gradual process, and short-term studies may not capture the full extent of melatonin's long-term neuroprotective effects. Moreover, many of these studies prioritize sleep outcomes, with cognitive performance assessed as a secondary measure, often using varying and sometimes subjective tools.

Blinding in clinical trials involving melatonin can also be problematic, as its known effects on sleep may inadvertently reveal group assignment to participants and researchers, potentially introducing bias. Furthermore, the absence of standardized cognitive assessment tools across studies makes it difficult to compare or pool data effectively.

There is also no established consensus on optimal dosing regimens for cognitive protection. Some studies use low doses of 0.5 mg, while others go up to 10 mg, with mixed results. Additionally, confounding variables such as coexisting medical conditions, medications, and lifestyle factors are not always adequately controlled, which could influence both sleep quality and cognitive performance.

Lastly, while melatonin is generally considered safe, especially in the short term, there remains a lack of long-term safety data in older populations with comorbid conditions or polypharmacy. Until more large-scale,

long-duration, and standardized trials are conducted, the full clinical potential of melatonin in cognitive preservation remains to be conclusively defined.

Future Directions

As research continues to uncover the intricate links between sleep, aging, and cognitive health, melatonin presents itself as a promising yet underutilized therapeutic agent. To solidify its role in preventing or delaying cognitive decline, future investigations must focus on generating more robust and standardized evidence through large-scale, long-term randomized controlled trials. These studies should prioritize diverse and representative populations, particularly those most vulnerable to both sleep disorders and cognitive deterioration, such as individuals with mild cognitive impairment or early-stage dementia.

There is a pressing need to establish clear clinical guidelines regarding the optimal dosing, timing, and formulation of melatonin for cognitive outcomes. Comparative studies assessing different melatonin formulations (e.g., immediate-release vs. Sustained-release) could provide insights into their differential impact on both sleep architecture and cognitive performance. Additionally, dose-response analyses would help identify the minimum effective dose that balances efficacy with long-term safety.

Future research should also move beyond traditional sleep assessments and incorporate more advanced neuroimaging techniques, biomarkers of neurodegeneration, and digital cognitive tracking to objectively evaluate melatonin's impact on brain health. Understanding the molecular pathways through which melatonin modulates neuroinflammation, amyloid deposition, synaptic plasticity, and glymphatic clearance will be crucial in developing targeted interventions.

Moreover, melatonin's potential role as an adjunct to other therapeutic strategies—including cognitive training, physical activity, and pharmacological treatments—deserves exploration. Integrated care models that combine lifestyle interventions with chronobiotic agents like melatonin could offer more comprehensive neuroprotective benefits for older adults.

Lastly, public health policies should support awareness and education around safe melatonin use, especially in aging populations prone to self-medicating with over-the-counter supplements. Regulatory frameworks ensuring quality control and appropriate labeling of melatonin products will be essential as its use expands from sleep aid to potential cognitive enhancer.

In conclusion, while current findings are promising, the field is ripe for innovation and scientific rigor. With well-structured clinical trials and interdisciplinary approaches, melatonin may emerge as a key tool in the global effort to combat cognitive decline and enhance quality of life in older adults.

CONCLUSION

Melatonin supplementation represents a promising and multifaceted intervention for addressing cognitive decline among older adults with sleep disorders. Its well-established role in regulating circadian rhythms, coupled with emerging evidence of its antioxidant, anti-inflammatory, and neuroprotective properties, makes it a unique therapeutic candidate in the context of age-related cognitive deterioration. While sleep disturbances are increasingly recognized as modifiable risk factors for neurodegeneration, melatonin offers dual benefits by improving sleep quality and potentially preserving cognitive function.

Although current clinical evidence supports its utility, limitations such as heterogeneity in study designs, lack of standardized dosing, and short trial durations constrain the ability to make definitive clinical recommendations. Nonetheless, the generally favorable safety profile of melatonin and its accessibility as a non-prescription agent further enhance its appeal as a preventive strategy.

Future research should aim to address existing gaps through large-scale, longitudinal studies that utilize standardized cognitive assessments and explore underlying mechanisms more deeply. With continued scientific rigor and interdisciplinary collaboration, melatonin could play an important role in integrative approaches to healthy cognitive aging, ultimately contributing to better quality of life and independence in older adults.

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