Acetylcholinesterase Inhibitors and Effects on Sleep in Alzheimer's Disease: A Review

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Alzheimer's Disease (AD) is characterized by the degeneration of cholinergic neurons and reduced synaptic acetylcholine. Acetylcholinesterase inhibitors (AChEIs; donepezil, rivastigmine, galantamine, and benzgalantamine) are a cornerstone of symptomatic treatment of AD. However, due to the role of acetylcholine in sleep regulation, these agents may also influence s leep quality in varying ways. A literature review was conducted to assess the impact of AChEIs on sleep in AD patients. The effects of AChEIs on sleep in patients with AD vary by agent. Donepezil is associated with the most sleep disruption, while galantamine and benzgalantamine appear to be sleep neutral. Rivastigmine, depending on the dosage form, offers an intermediate or mixed profile. Selecting the appropriate AChEI medication may help optimize treatment outcomes for patients with AD and their caregivers.

BACKGROUND

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia globally, affecting millions of individuals.[1] It is characterized by cognitive decline, behavioral changes, and loss of functional independence. A hallmark feature of AD is a significant cholinergic deficit caused by the degeneration of cholinergic neurons, resulting in decreased levels of acetylcholine (ACh), a neurotransmitter essential for learning, memory, and cognition.[1,2]

Sleep problems among patients with AD are highly prevalent and tend to worsen as the disease progresses. Sleep disturbances are associated with both cognitive impairment and AD pathology and are burdensome to nurses and caregivers.[3] Given the long period of asymptomatic preclinical AD, sleep disturbances are hypothesized to be either markers for AD pathology and/or a mechanism mediating increased risk of AD.[4] Improving disturbances in sleep-wake activity could mitigate the onset and progression of AD. Furthermore, the glymphatic system, discovered in the 2010's, is a highly organized cerebrospinal fluid transport system that shares several key functions with the lymphatic vessels of peripheral tissues, including the export of excess interstitial fluid and waste proteins (e.g., amyloid-beta [Aβ]).[5] This astrocyte-regulated mechanism of brain fluid transport ultimately drains into the venous system, where waste proteins are cleared by the liver and kidneys.[6] Fluid flow through the glymphatic system is closely linked with sleep and appears to cease with the onset of wakefulness.[7]

A human study (N=24) compared production and clearance rates of $A\beta_{42}$ and $A\beta_{40}$ in the central nervous system of cognitively normal controls and patients with AD. On average, there were no differences in production rates; however, clearance rates for both $A\beta_{42}$ and $A\beta_{40}$ were impaired in patients with AD compared to controls.[8] Moreover, a growing body of research suggests a bidirectional relationship between sleep disturbances and AD pathology, where poor sleep may contribute to the accumulation of Aβ and tau protein, accelerating neurodegeneration.[4] The glymphatic system is highly active during deep sleep. Impaired glymphatic clearance has been proposed as a potential mechanism linking disrupted sleep with increased AD pathology.[5,7]

The primary pharmacologic treatment strategy for the symptomatic management of AD involves the use of acetylcholinesterase inhibitors (AChEIs), which enhance cholinergic neurotransmission by preventing the breakdown of ACh in the synaptic cleft. This mechanism helps mitigate the cholinergic deficit observed in AD and has been shown to provide benefits in terms of improved cognition, daily functioning, and behavior. Available AChEIs include donepezil, rivastigmine, galantamine and benzgalantamine, an inactive prodrug of galantamine that received FDA-approval in 2024 (marketed under the brand name ZUNVEYL®).[1,2,9] However, as ACh plays a role in sleep regulation, AChEIs, particularly donepezil, have been associated with marked sleep disturbances.[10,11]

OBJECTIVE & METHODS

The objective of this review is to evaluate the impact of AChEIs on sleep in patients with AD.

A targeted literature review (1998-2025) was conducted and included a systematic review and meta-analysis, randomized-controlled trials, open-label investigations, real-world observational studies and data from prescribing information, specifically, donepezil (ARICEPT®), rivastigmine (EXELON®), galantamine (RAZADYNE®), and benzgalantamine (ZUNVEYL®).

RESULTS

Donepezil

Donepezil is frequently associated with sleep disturbances, including insomnia and vivid dreams, primarily due to its 70-hour terminal half-life, which sustains cholinergic stimulation during sleep and can disrupt rapid eye movement (REM) architecture.[10-17]

- Studies indicate a higher risk of insomnia with nighttime administration.[18]

Rivastigmine

Rivastigmine has mixed effects on sleep.

- While some patients report insomnia, the transdermal patch formulation appears to lessen sleep-related side effects, potentially due to more stable drug delivery and lower peak concentrations.[10,19,20]

Galantamine

Galantamine may be the preferable AChEI for patients with sleep disturbances.

- Studies suggest galantamine has a neutral impact on sleep and may even improve sleep quality and hygiene in some cases.[21-24]
- It is hypothesized that these effects may be due to its shorter half-life and dual mechanism of action: reversible competitive inhibition of AChE and positive allosteric modulation of nicotinic acetylcholine receptors.[2,22]

CONCLUSIONS

Evidence suggests that the effects of AChEIs on sleep vary depending on the pharmacodynamic and pharmacokinetic properties. For patients experiencing significant sleep disturbances with donepezil, transitioning to rivastigmine, particularly the transdermal formulation, or galantamine may be a viable strategy. Galantamine has demonstrated a neutral effect on sleep quality in various studies. Benzgalantamine, an enteric-coated prodrug of galantamine, is expected to have similar effects on sleep and may be a suitable choice for patients with AD who are prone to sleep disruptions, as it maintains sleep hygiene and may even improve sleep quality.

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