Insomnia and Alzheimer's Disease

Alzheimer's disease is a progressive neurodegenerative disorder associated with short-term memory loss, cognitive impairment, loss of executive function and language dysfunction. Dementia symptoms gradually worsen over time. Disease pathology is characterized by the accumulation of beta-amyloid in plaques within the extracellular space and hyperphosphorylated tau found in neurofibrillary tangles which leads to neuroinflammation and cell death. The mechanisms underlying the toxic accumulation of these proteins is not well understood; however, it is recognized that disease pathology starts many years before first cognitive symptoms are detected. Alzheimer's disease is also, in some ways, a neuropsychiatric disease since manifestation can change a person's behaviors including sleep. Insomnia is an important aspect of Alzheimer's disease and may be a contributor in the promotion of pathology as well as an outcome of the disease. This discussion explores the bidirectional relationship of insomnia and Alzheimer's disease and highlights clinical management of sleep disturbances in these patients.

Insomnia of Alzheimer's disease

At least half of individuals diagnosed with Alzheimer's disease have some form of sleep disturbance which tends to intensify with disease severity. Patients experience difficulty falling asleep and maintaining sleep. The diagnostic criteria for insomnia should include complaint for at least three nights a week for at least three months. Poor sleep is associated with aging and is dependent on circadian rhythm (sleep-wake cycle), which has a very robust effect on the timing of nighttime sleepiness and daytime alertness. This pattern tends to shift earlier in older individuals and is likely driven by reduction in melatonin or abnormal distribution. The circadian rhythm is also strongly influenced by light exposure and darkness.

Bidirectional relationship

Research indicates that lack of sleep impairs memory and sleep difficulty often precedes other more obvious aspects of cognitive decline with Alzheimer's disease. Current thinking suggests that a bidirectional relationship operates between sleep disturbance and Alzheimer's disease whereby the pathology of Alzheimer's disease causes sleep disruption and lack of adequate sleep promotes the accumulation of neurotoxic proteins. Amyloid-beta deposition is strongly influenced by the sleep-wake cycle. The glymphatic system is the pathway responsible for clearing metabolic waste products produced in the brain during the wakeful state. During deep sleep, amyloid is removed by the glymphatic system, however, inadequate phases or shorter lengths of deep sleep, may contribute to the accumulation of neurotoxic waste. Promotion of sleep through medication or behavioral changes may improve cognitive function and slow Alzheimer's disease progression and support brain health overall.

Sleep architecture

The clinical symptoms of sleep fragmentation in Alzheimer's disease are much more extreme compared to normal ageing individuals. Sleep disturbances include difficulty falling asleep,

maintaining sleep, early waking, daytime sleepiness, wandering behavior and sundowning-agitation during evening hours, all of which may be directly related to the circadian cycle and melatonin rhythms. The vicious cycle of poor sleep leads to less amyloid clearance, and as a result, more amyloid- beta deposition which impairs the functionality of the sleep-wake mechanisms.

Sleep fragmentation is demonstrated by distinct electroencephalogram (EEG) patterns whereby patients display less slow-wave sleep and less slow-wave activity; both in terms of the amount, but also the amplitude of the actual slow-waves. The EEG power spectrum in dementia tends to be shifted towards the higher frequencies representing the fact that there is less slow-wave activity. A higher frequency indicates greater brain activity, which may accelerate deposition of amyloid and limit clearance through the glymphatic pathway. Overall, the structure and organization of sleep stages tends to break down causing patients to experience less rapid eye movement (REM) sleep. Changes in REM sleep stage may invoke vivid dreams, nightmares or experiences of sleep walking or sleep talking in Alzheimer's disease patients.

Insomnia treatment options for Alzheimer's disease patients

Nonpharmacologic treatments

Safe clinical management of insomnia is required to improve patient quality of life and promote clearance of neurotoxic proteins. Caregiver education is key to the success of clinical management. Environmental strategies or nonpharmacologic approaches are important in the promotion of sleep for Alzheimer's disease patients and should be incorporated into the care plan.[1] Strategies such as balancing light and dark periods may improve circadian rhythm. Daily routines should be reinforced and also integrate stimulating music and engaging activities during the day with calming music and quiet activities at nighttime. In addition, studies have shown that cognitive behavioral therapy is beneficial in earliest stages of mild dementia as well as mild cognitive impairment due to Alzheimer's disease.

Nonpharmacologic approaches
Caregiver education
Maintain daily routines
Re-balance light and dark periods to improve circadian rhythm
Re-balance active and quiet periods to the day/night cycle
Cognitive behavioral therapy

Pharmacologic approaches

Traditional sleep-inducing medications should be used with caution since typically, these treatments tend to have a much different effect on patients with cognitive dysfunction. Drug interventions may potentially pose a greater likelihood for fall risk due to sedating side effects.

For both pharmacodynamic and pharmacokinetic reasons, older patients metabolize medications more slowly, and blood levels can build up and continue into the daytime.

Four categories of pharmacologic treatments for insomnia are considered. The first category includes dietary supplements which are unregulated by the FDA. Although, most sleep promoting dietary supplements (valerian, hops) are benign, the FDA has issued consumer warnings for kava kava supplements since usage has been linked to liver toxicity. Melatonin, a hormone which also falls into the supplement category, plays a very important role in the regulation of the circadian system. Melatonin levels rise in the evening, which helps to quiet down arousal and facilitate sleep onset. Since melatonin already rises early in the elderly and Alzheimer's populations, taking more melatonin is not likely to provide a beneficial sleep-inducing effect and may pose possible safety concerns.

The second category is the over-the-counter antihistamines, diphenhydramine and doxylamine, which are regulated by the FDA. Antihistamines are relatively long-acting agents with sedating effects that can linger into the next morning. The major concern regarding antihistamine treatment in the Alzheimer's population and older individuals is the anticholinergic effects that can lead to memory difficulty, confusion and delirium. The third category includes prescription medications that are not approved for treating insomnia but may be sedating such as antidepressants and antipsychotics. Trazodone, an antidepressant, is widely prescribed for insomnia and may be beneficial for some people, however, trazodone should be used with caution in older individuals due to its post-synaptic serotonin blockade and alpha-1 blockade, which can lead to lower blood pressure and orthostatic hypertension, increasing the risk of falls. A large retrospective case-control study assessed the sleep promoting effect of trazodone versus benzodiazepine receptor agonist in Alzheimer's disease patients within a nursing home setting. The study demonstrated that the fall risk was similar in both of these groups and trazodone did not represent a better alternative for treating sleep disturbance.[2]

Finally, the fourth category encompasses prescription medications that are FDA approved for insomnia. The benzodiazepine receptor agonists include structural benzodiazepines and newer generation non-benzodiazepines (zolpidem, zaleplon, eszopiclone). The newer generation agents are somewhat shorter acting, which is beneficial; however, all benzodiazepine receptor agonists can be associated with some memory difficulty, excessive sedation, and ataxia. As a class, these agents are far from ideal for patients with dementia. The melatonin receptor agonist, ramelteon, works in a similar way to melatonin helping to quiet down the circadian arousal in the evening promoting sleep onset. The histamine receptor antagonist doxepin can be beneficial for sleep maintenance. The advantage of low dose doxepin is that is does not show anticholinergic activity as do the other antihistamine products. Finally, the safety and efficacy of the orexin antagonist, suvorexant, has been evaluated in mild to moderate Alzheimer's disease patients. The study showed that suvorexant was well tolerated in these patients and demonstrated significant improvement in sleep duration and a decrease in the wake-after sleep onset.[3]

Dietary supplements	OTC sleep aid - antihistamines	Sedating Rx medications not approved for insomnia	Rx FDA approved for insomnia
melatonin	diphenhydramine	antidepressants	benzodiazepine receptor agonists
	doxylamine	antipsychotics	histamine receptor antagonists
			melatonin receptor agonist
			orexin antagonists

Framework to guide treatment decisions

For optimal patient outcomes, interprofessional collaboration is needed to manage Alzheimer's associated sleep disturbances. This collaborative approach may involve discussions between a cognitive neurologist with a sleep specialist in order to design the best treatment option for the patient. In addition, social workers can provide guidance to caregivers on an ongoing basis for the nonpharmacological interventions. Furthermore, nurse practitioners and physician assistants can educate the patient and caregiver on the pharmacologic and nonpharmacologic approaches to promote sleep and ensure highest quality care.

In summary, restorative sleep is critical to the clearance of neurotoxic waste products which contribute to the pathology and symptoms of Alzheimer's disease. It is recommended that interprofessional collaboration and caregiver education is needed for optimal clinical management of sleep disturbances. Drug treatment strategies must balance the risks and benefits to the patient and future research is needed in this regard. Recognizing the importance of sleep and the prioritization of early treatment for sleep disruption may help slow down the cognitive decline in this population.

References

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