Identification and Management of Insomnia in Alzheimer's Disease

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CONTINUING MEDICAL EDUCATION

LEARNING OBJECTIVES

After reading the review article on insomnia in patients with Alzheimer's disease (AD), participants should be able to:

- Describe the association of insomnia with AD.
- Characterize the burden of insomnia in AD on patients and their family/caregivers.
- Prescribe medication for insomnia in patients with AD based on existing evidence and current recommendations.

TARGET AUDIENCE

Family physicians and clinicians who wish to gain increased knowledge and greater competency regarding primary care management of insomnia in patients with AD.

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THE BURDEN OF ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is the most common cause of dementia, affecting an estimated 5.7 million Americans; nearly two-thirds are women.[1] The vast majority of people with AD are aged ≥65 years.[1] After age 85 years, 34% of people have AD or related dementia.[2] Most people with AD survive an average of 4 to 8 years following diagnosis, although some live as long as 20 years. AD is the only top 10 cause of death

that cannot be prevented or cured.[1] In 2017, AD was the 15th leading cause of disability-adjusted life years worldwide.[3]

Beyond progressive cognitive impairment, people with AD are at increased risk of neuropsychiatric symptoms such as delusions and hallucinations, depressive symptoms, wandering, anxiety, disturbances in diurnal rhythm, and agitation with or without aggression.[4,5] Apathy is more common in those with AD onset before age 65 years.[4] Neuropsychiatric symptoms, particularly delusions, may be associated with a more severe course of AD.[6]

Bodily injury, particularly related to falls, is common in people with AD, often resulting in fractures.[7,8] Falls are often observed during the nighttime hours, in part because individuals with AD commonly suffer from insomnia, sometimes resulting in reversal of their sleep-wake periods.[9,10] Insomnia has been shown to contribute to cognitive decline, as well as early nursing home placement.[1]

The chronic nature of the illness contributes significantly to the public health impact of AD because much of that time is spent in a state of disability and dependence. Thus, the burden is not only the patient's, but is shared with society in general and the family and caregivers in particular. AD rose from the 12th most burdensome disease or injury in 1990 to the 6th in 2016, in part due to its rising mortality rate.[11] In terms of years lived with disability, AD rose from the 23rd to the 19th during the same period. In 2017, caregivers provided an estimated 18.4 billion hours of unpaid care, valued at $232 billion.[12] The total lifetime cost of care for a person with dementia was estimated at $341,840 in 2017, 70% of which is borne by the family, largely through providing unpaid care.[13] Families and caregivers also experience emotional stress and depression, new or exacerbated health problems, including physical difficulties and financial challenges.[14-19] Insomnia often emerges among caregivers when the need to provide nighttime care becomes frequent.[20,21] One-third of family caregivers report that their own health deteriorated since becoming a caregiver.[1]

CASE SCENARIO #1

A 63-year-old woman was seen by her primary care provider for a 1 month follow up visit for her mild obstructive sleep apnea (OSA). While she reports overall better sleep using her continuous positive airway pressure (CPAP) machine, she experiences disrupted sleep and daytime fatigue; she also reports feeling less motivated with her daily routine. Her history reveals frequent difficulty falling asleep as well as falling back to sleep. Her daughter has accompanied her and reports that her mother has increasing difficulty 'finding her words'.

ASSOCIATION OF INSOMNIA WITH ALZHEIMER'S DISEASE

While a person is awake, extracellular levels of metabolites produced by neuronal activity, such as amyloid-β and tau proteins, increase in the brain. During restorative sleep, these metabolites are cleared from the brain through the glymphatic system.[22] When the sleep-wake cycle is disrupted, clearance of these metabolites is diminished.[23,24] Accumulation of amyloid-β and tau proteins hastens the formation of the characteristic amyloid plaques and neurofibrillary tangles observed in people with AD.

Accumulating evidence supports the view that a bidirectional association exists between sleep disorders (eg, insomnia) and AD, beginning before the clinical onset of AD.[24-26] Increased deposition of amyloid-β causes disruption of the sleep-wake cycle,[25] including poorer sleep quality and shorter sleep duration.[27]

Poor sleep quality, as evidenced by decreased non-rapid eye movement (non-REM) sleep slow wave activity, is associated with amyloid-β deposition, as well as intracellular aggregation of tau in the neocortex.[28] Sleep deprivation and sleep fragmentation also increase the accumulation of amyloid-β and tau proteins in the brain.[29] In fact, a positive association between levels of sleep fragmentation at baseline and rate of cognitive decline has been demonstrated (hazard ratio 1.22; 95% confidence interval [CI], 1.03-1.44; *P*=.02 per 1 standard deviation increase in sleep fragmentation).[30]

Disruptions in the circadian system appear to interact with sleep disruption, possibly via orexin and melatonin, to increase progression of AD.[29] Disruption of the sleep-wake cycle is characterized by increased levels of orexin, a wake-promoting neuropeptide. Animal studies in which the orexin gene is knocked out show marked decrease in amyloid-β deposition in the brain and an increase in sleep time.[31,32]

Other factors thought to serve as mediators between sleep deprivation and AD include reactive oxygen species and glymphatic system dysfunction, among others.[25]

Further evidence supporting an association between insomnia and dementia is provided by a meta-analysis of 5 community-based prospective cohort studies. The analysis showed an increased risk (relative risk 1.53; 95% CI, 1.07-2.18) of developing dementia in people with a preexisting diagnosis of insomnia.[33] More recently, a case-control study of 51,734 individuals diagnosed with primary insomnia without a dementia diagnosis at baseline showed a 2.14-fold (95% CI, 2.01-2.29) increase in dementia risk.[34]

THE BURDEN OF INSOMNIA IN ALZHEIMER'S DISEASE

CASE SCENARIO #2

A 71-year-old man is seen for his annual physical. Although he reports that he feels fine and his health has not changed over the past year, his wife reports that 'he doesn't seem like his old self'. He does admit to waking up at night several nights per week, but attributes this to a need to urinate. He further reports difficulty falling back to sleep after these events.

Sleep changes are more common in later stages of AD, although they are observed in early stages.[35] People with AD often experience a shift in their sleep-wake cycle, experiencing insomnia during the night, ie, waking up more often and staying awake longer, while napping during the daytime. In the late stages of AD, people spend about 40% of their time in bed at night awake and a significant part of their day napping. In extreme cases, people may have a complete reversal of the usual daytime wakefulness-nighttime sleep pattern. Restlessness or agitation is common, particularly in late afternoon or early evening, called sundowning. Those who cannot sleep at night may wander, be unable to lie still, or yell or call out. Falling during the night is common and contributes to an increased risk for bodily injury, particularly fractures. The health consequences of insomnia to the person with AD—and the caregiver's inability to provide the needed care—can contribute to early nursing home placement.[36]

Overall, family caregivers generally experience a significant physical and psychological burden, as well as a financial burden.[1] In addition to negatively impacting the family caregiver's sleep,[20,21] the stress of providing dementia care increases the caregiver's susceptibility to disease and health complications.[17] According to the Alzheimer's Association, 74% of caregivers of people with AD or other dementia reported that they were "somewhat concerned" or "very concerned" about their own health.[1] Nearly half of dementia caregivers are in a high-burden situation, which is less than cancer caregivers. However, where cancer caregivers often provide care for short periods of time, dementia caregivers tend to provide care for a long period of time.[37]

ASSESSING COMORBIDITIES IN PEOPLE WITH ALZHEIMER'S DISEASE

The high prevalence and consequences of insomnia in people with AD necessitate a thorough medical examination, including sleep history. It is suggested to include the caregiver or family member so that an accurate history can be obtained. Questions should be asked to identify sleep patterns such as:

- When do you go to sleep?
- When do you arise?
- How many times a night do you awaken?
- When you awaken, how long does it take you to fall asleep?
- What percent of the time you spend in bed intending to sleep do you actually sleep?

In addition, questions should be asked about conditions that may make sleep problems worse, such as:

- Do you snore?
- Has anyone observed that you have episodes where you stop breathing?
- Do you feel a need to move your legs when at rest?
- Do you move around in bed a lot?
- Are you depressed?

Obstructive sleep apnea (OSA) occurs in half of patients with AD, with the OSA severity associated with dementia severity.[38-40] Restless leg syndrome is thought to occur in about 5% of patients with AD[41] and can have a profound impact on sleep. Depression occurs in up to 40% of people with AD, particularly in the early to middle stages of the disease.[1]

Treatment of other conditions that affect sleep should be optimized, including chronic obstructive pulmonary disease, allergies, a pain disorder, and anxiety, as this may reduce the symptoms of insomnia, thereby lessening the disease burden for both patient and caregiver.

TREATMENT OF INSOMNIA

Given the absence of effective disease-modifying treatment options for AD and the long duration of symptoms and disability, safety for the patient, as well as the caregivers, is a consideration for overall patient management. This particularly relates to the management of other conditions, eg, insomnia, so as to avoid the use of medications that might result in complications, such as falls or further cognitive impairment.

As a first step, conditions that may contribute to insomnia should be identified and appropriate action taken.[42] Eating or drinking, particularly alcohol, several hours before sleep should be avoided. A daily schedule with similar daily wake and sleep times and quiet time should be established. Light exposure in the pre-sleep period and during the night needs to be avoided. In contrast, morning sunlight exposure and exercise are important. Bright light therapy is thought to be helpful, but benefits may be affected by treatment

intensity and duration, as well as time of year.[43] Poor sleep habits, such as irregular sleep hours, should be corrected.[35] If possible, medications should be avoided that might impair sleep, eg, alpha-blockers, beta-blockers, corticosteroids, serotonin selective reuptake inhibitors, and angiotensin converting enzyme inhibitors. Diseases that contribute to insomnia should be treated initially with nonpharmacologic options, if possible. For example, acute or subacute low back pain should be managed initially with superficial heat, massage, acupuncture, or spinal manipulation.[44]

When these initial strategies are ineffective in improving sleep, further intervention may be warranted. In patients without AD, cognitive behavioral therapy (CBT) is recommended as the first-line approach for insomnia due to its effectiveness and safety.[42] The major interventions in terms of mediating efficacy, ie, decreasing wake time in bed, are sleep restriction therapy (limiting time in bed) and stimulus control (getting out of bed when not sleeping). Both of these may increase sleepiness while awake, which can further exacerbate compromised alertness in patients with AD. Moreover, stimulus control, getting out of bed repeatedly in patients with AD, may increase the risk of falls. Therefore, while CBT is generally an effective treatment for insomnia, its efficacy and safety in people with AD has not been established and should, therefore, be used with caution in this population.

Pharmacotherapy

When CBT does not achieve its goals, short-term pharmacotherapy should be considered to reestablish a regular sleep pattern. However, there is little evidence from clinical trials to guide the selection of pharmacotherapy for insomnia in people with AD.[42] A 2016 Cochrane Review found only 6 randomized clinical trials that had the primary aim of improving sleep in people with dementia who had insomnia.[45] The reviewers found no evidence to support the use of melatonin ≤10 mg/day or ramelteon 8 mg/day in insomnia associated with AD, with some evidence to support the use of trazodone 50 mg/day. There were no reports of serious adverse effects with melatonin, ramelteon, or trazodone in the trials analyzed. As noted by the reviewers, uncertainty remains about the balance of benefits and risks associated with benzodiazepine and most "non-benzodiazepine" hypnotics such as eszopiclone, zaleplon, and zolpidem, which are commonly used for insomnia in people with dementia, including AD.

In 2012, the American Geriatrics Society sought to provide guidance regarding the use of medications in older adults.[46] To do this, a systematic review of clinical trials, observational studies, and systematic reviews and meta-analyses involving adults aged ≥65 years was conducted. The guidance, called the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults, was updated in 2015[47] and again in 2019.[48] According to the 2019 Beers Criteria, several of the medication classes commonly used to treat insomnia should be avoided in older adults, many because of their anticholinergic properties and/or prolonged sedation. These include first-generation antihistamines, some antidepressants, barbiturates, benzodiazepines, and other benzodiazepine receptor agonists (**TABLE**).[48]

According to the Beers Criteria, these same classes of medications (except barbiturates) should be avoided in older adults with dementia or cognitive impairment. First-generation antihistamines (including those found in OTC sleep aids) and many antidepressants should be avoided due to their anticholinergic and central nervous system effects. Benzodiazepines are to be avoided because they cause dizziness and prolonged sedation. Moreover, their use in people with AD is associated with an increased risk of falling, resulting in fractures.[49-51] There is a black box warning for benzodiazepines regarding the risk of profound sedation, respiratory depression, coma, and death with concomitant opioid therapy. Antipsychotics are associated with greater risk of stroke and mortality in older people with dementia.[48] One case series of 6790 people with at least one prescription for an antipsychotic and a stroke found that the rate ratio for stroke was 3.5 for those with dementia and 1.41 for those without dementia.[52] There is a black box warning of increased mortality in elderly patients with dementia-related psychosis treated with antipsychotics. The benzodiazepine receptor agonists eszopiclone, zaleplon, and zolpidem also should be avoided due to adverse events similar to classical benzodiazepines; in addition, they provide minimal improvement in sleep latency and duration in the AD popultion.[48]

Not included in the Beers list of medications to avoid in older adults, including those with dementia or cognitive impairment, are doxepin ≤6 mg/day, the melatonin receptor agonist ramelteon, and the orexin receptor agonist suvorexant. According to the Beers Criteria, the safety profile of doxepin ≤6 mg/day is comparable to placebo.

Ramelteon has not been prospectively investigated for the treatment of insomnia in patients with AD, but there are 5 case reports in this setting. Each showed improvement in behavioral and psychological symptoms, primarily delirium, with ramelteon 8 mg once daily at bedtime in patients with AD and disrupted sleep-wake cycle.[53-55] Ramelteon is not recommended in people with severe sleep apnea since it has not been studied in this population.[56]

Suvorexant is the first medication to be systematically investigated in a phase 3 randomized, double blind clinical trial for the treatment of insomnia in people with mild-

TABLE Potentially inappropriate medications that are often used for insomnia in older adults[48]

Class/medications		Explanation
Antihistamines, first-generation		Highly anticholinergic; clearance reduced with advanced age, and tolerance develops when used as hypnotic; risk of confusion, dry mouth, constipation, and other anticholinergic effects or toxicity. [Use of diphenhydramine in situations such as acute treatment of severe allergic reaction may be appropriate.]
Brompheniramine	Diphenhydramine (oral)	
Carbinoxamine	Doxylamine	
Chlorpheniramine	Hydroxyzine	
Clemastine	Meclizine	
Cyproheptadine	Promethazine	
Dexbrompheniramine	Pyrilamine	
Dexchlorpheniramine	Triprolidine	
Dimenhydrinate		
Antidepressants		Highly anticholinergic, sedating, and cause orthostatic hypotension; safety profile of low-dose doxepin (≤6 mg/day) comparable with that of placebo.
Amitriptyline	Imipramine	
Amoxapine	Nortriptyline	
Clomipramine	Paroxetine	
Desipramine	Protriptyline	
Doxepin >6 mg/d	Trimipramine	
Antipsychotics, first- and second-generation		Increased risk of cerebrovascular accident (stroke) and greater rate of cognitive decline and mortality in people with dementia. Avoid antipsychotics for behavioral problems of dementia or delirium unless nonpharmacological options (eg, behavioral interventions) have failed or are not possible and the older adult is threatening substantial harm to self or others.
Barbiturates		High rate of physical dependence, tolerance to sleep benefits, greater risk of overdose at low dosages.
Amobarbital	Pentobarbital	
Butabarbital	Phenobarbital	
Butalbital	Secobarbital	
Mephobarbital		
Benzodiazepines, short- and intermediate-acting		Older adults have increased sensitivity to benzodiazepines and decreased metabolism of long-acting agents; in general, all benzodiazepines increase risk of cognitive impairment, delirium, falls, fractures, and motor vehicle crashes in older adults. May be appropriate for seizure disorders, rapid eye movement sleep behavior disorder, benzodiazepine withdrawal, ethanol withdrawal, severe generalized anxiety disorder, and periprocedural anesthesia.
Alprazolam	Oxazepam	
Estazolam	Temazepam	
Lorazepam	Triazolam	
Benzodiazepines, long-acting		
Chlordiazepoxide	Flurazepam	
Clonazepam	Quazepam	
Clorazepate		
Diazepam		
Non-benzodiazepine, benzodiazepine receptor agonists		Have adverse events similar to benzodiazepines in older adults (eg, delirium, falls, fractures); increased emergency room visits/hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration.
Eszopiclone		
Zaleplon		
Zolpidem		

Source: Fick DM, Semla TP, Steinman M, et al. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *J Am Geriatr Soc*. 2019;67(4):674-694; John Wiley & Sons Inc. © 2019 The American Geriatrics Society.

to-moderate AD (N=284).[57] Following screening and run-in periods, patients were randomized to suvorexant 10 mg or placebo daily for 4 weeks. Suvorexant could be increased to 20 mg daily based on clinical response. From a mean baseline of 278 minutes and 274 minutes, mean total sleep time increased 73.4 minutes and 45.2 minutes in patients treated

with suvorexant and placebo, respectively (*P*<.005). The mean wake after persistent sleep onset time decreased 41.8 minutes with suvorexant and 32.5 minutes with placebo (*P*=.01). An adverse event was experienced by 22.5% of patients treated with suvorexant and 16.1% of patients treated with placebo. One patient in each group discontinued treatment due to an adverse event. Mild-to-moderate somnolence was the most common adverse event and was observed in 4.2% and 1.4% of suvorexant and placebo patients, respectively. Other adverse events included headache (3.5% vs 4.2%), dry mouth (2.1% vs 0.7%), and falls (2.1% vs 0%). Prior to initiating suvorexant, the effect on respiratory function should be considered in those with compromised respiratory function.[58]

SUMMARY

Alzheimer's disease is an increasingly common, highly burdensome, and ultimately fatal disease. In addition to neuropsychiatric disorders, disruption of the sleep-wake cycle is common in people with AD, and may be caused by as well as contribute to AD itself. Assessing for the presence and consequences of insomnia and other sleep-related disorders is important. Little investigation in clinical trials has been undertaken to evaluate the safety and efficacy of medications for insomnia in people with AD, although the results of a trial of suvorexant in this setting have recently been reported at a national meeting but not yet published. The Beers Criteria for Potentially Inappropriate Medication Use in Older Adults recommends that many classes of medications used to treat insomnia not be used in older adults with dementia or cognitive impairment. These are first-generation antihistamines (including OTC sleep aids), some antidepressants, benzodiazepines, and "non-benzodiazepines." ●

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