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REVIEW

Clinical management of sleep disturbances in Alzheimer's disease: current and emerging strategies

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Abstract: Sleep and circadian disorders in Alzheimer's disease (AD) are more frequent than in the general population and appear early in the course of the disease. Quality of sleep and quality of life are parallel in these patients, and such disorders also represent a heavy burden for caregivers. Although alterations in melatonin and hypocretins (orexins) seem to play a key role in the origin of these disturbances, the etiology of these disorders is multifactorial, including many factors such as environment, behavior, treatments, and comorbidities, among others. A comprehensive evaluation of sleep in each patient is essential in the design of the treatment that includes nonpharmacological and pharmacological approaches. One particularly interesting point is the possibility of a role of sleep disorders in the pathogenesis of AD, raising the possibility that treating the sleep disorder may alter the course of the disease. In this review, we present an update on the role of sleep disorders in AD, the bidirectional influence of sleep problems and AD, and treatment options. Behavioral measures, bright light therapy (BLT), melatonin, and other drugs are likely well known and correctly managed by the physicians in charge of these patients. In spite of the multiple treatments used, evidence of efficacy is scarce and more randomized double-blind placebo-controlled studies are needed. Future directions for treatment are the establishment of BLT protocols and the development of drugs with new mechanisms of action, especially hypocretin receptor antagonists, melatonin receptor agonists, and molecules that modulate the circadian clock.

Keywords: Alzheimer disease, sleep disorders, melatonin, circadian rhythm

Introduction

Alzheimer's disease (AD) is the most frequent cause of dementia in the elderly. It has been estimated that in 2013, AD affected 4.7 million individuals aged 65 years or older in the United States, a number that is projected to increase to approximately 14 million by 2050.[1] The classic hallmarks are progressive deterioration of memory, language, and intellect. Sleep and circadian rhythm disorders are very frequent in AD, and it has been reported that up to 45% of patients may have sleep problems.[2–4] The most frequent disturbances are excessive awakenings (23%), early morning awakening (11%), excessive daytime sleepiness (10%), and napping for more than 1 hour during the day (14%).[5] Such disturbances can appear early in the course of the disease, although they tend to be correlated with the severity of the cognitive decline.[3] Sleep-related breathing disorders (SRBDs) are also very frequent in AD patients and in this group are clearly more prevalent than in the general population.[6,7]

At least three issues highlight the relevance of the treatment of sleep disorders in patients with AD:

1. Sleep disturbances are associated with increased memory and cognitive impairment.[8]

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2. Sleep and nighttime behavioral disturbances such as wandering, day/night confusion, getting up repeatedly during the night, and nightmares or hallucinations cause significant caregiver burden and are a primary cause of patient institutionalization.[5,9]
3. There is increasing evidence of the role of sleep disturbances in the pathophysiology of AD and a bidirectional relationship has been proposed.[10–12]

This article reviews the main sleep problems in these patients and the interactions between sleep disorders and AD. The clinical evaluation of sleep disturbances, the current treatments for sleep disturbances, and the new perspectives are also addressed.

Architectural disturbances of sleep in AD patients

Normal aging is accompanied by sleep architecture changes, such as increased sleep latency, difficulty in sleep maintenance, decrease in slow-wave sleep (SWS), early morning awakenings, and increased daytime somnolence.[13]

The sleep disturbances present in patients with AD are similar, but more severe than would be expected by the patient's age.[14] Sometimes sleep disturbances in AD are so prominent that should be classified as a primary comorbid sleep disorder, such as chronic insomnia. The change that seems most specific to AD is a quantitative decrease in the rapid eye movement (REM) stage.[15,16] In particular, electroencephalogram (EEG) slowing during REM sleep has been proposed as a biological marker of AD.[16]

The architectural changes present in AD patients are probably related to cognition impairment.[17,18] The cognitive impairment could be different depending on the sleep stage that is altered. For example, Rauchs et al[19,20] found that the mean intensity of fast spindles was positively correlated, in AD patients, with immediate recall performance, while the amount of SWS was positively correlated with the ability to retrieve recent autobiographical memories.

Circadian disturbances in AD patients

Abnormalities in sleep–wake patterns and circadian-related disorders are also common in AD patients.[21] In extreme cases, a complete day/night sleep pattern reversal can be observed.[22] Some authors have proposed that the sundowning phenomenon could be also due to a disorder of the circadian rhythm.[23–25] This phenomenon corresponds to an exacerbation of behavioral symptoms of dementia in the late afternoon.[26] The abnormalities in the circadian timing system in AD patients are also manifested in other circadian systems such as body temperature and hormone concentrations.[24,27–29] Stranahan[30] found that disturbances in the circadian timing system also affect the activity of the hippocampus, worsening learning capacities.

SRBDs in AD patients

SRBDs are also more frequent in patients with AD than in the general population and are present in 40%–70% of these patients.[6,7] In a longitudinal cohort study of sleep disorders using polysomnography (PSG), it was found that the probability of moderate-to-severe sleep-disordered breathing was significantly higher in healthy participants with the APOE E4 allele, independent of age, sex, body mass index, or race.[31] It has been suggested that SRBD could cause AD.[32] Recently, it has been reported that the presence of SRBD was associated with cognitive decline at an earlier age.[33] Once the dementia is established, the severity of the sleep disturbances seems to be correlated with the severity of the dementia.[34] Apneas alter sleep architecture and lead to a decreased amount of REM sleep and SWS, which causes more frequent awakenings than in patients without apneas.[35] However, Yaffe et al[36] found that the oxygen desaturation index and the percentage of time in apnea or hypopnea were associated with cognitive decline but not with sleep fragmentation or sleep duration. These disturbances and the daytime sleepiness could be responsible for additional cognitive symptoms in AD patients that would be reversible.[37,38]

Interactions between sleep disturbances and AD

A bidirectional relationship between sleep disturbances and AD has been proposed (Figure 1). A poor quality of sleep and daytime somnolence seems to increase the risk of developing AD.[11,39–44] However, as pointed out by Ju et al,[10] since the pathological changes occur 10–15 years before the clinical onset of AD, some patients in these studies could already have preclinical AD and could not be considered as incidental cases. In fact, some authors have suggested the change of sleep pattern may predict AD.[45] The physiopathological mechanism is not completely understood, but an association between sleep disturbances and amyloid-β accumulation has been demonstrated in mice[10,11,40] and humans.[46,47] In healthy older adults, Spira et al[46] found a correlation between self-reported shorter sleep duration or poorer sleep quality and larger amyloid-β burden as assessed by positron emission tomography. Conversely, in a prospective

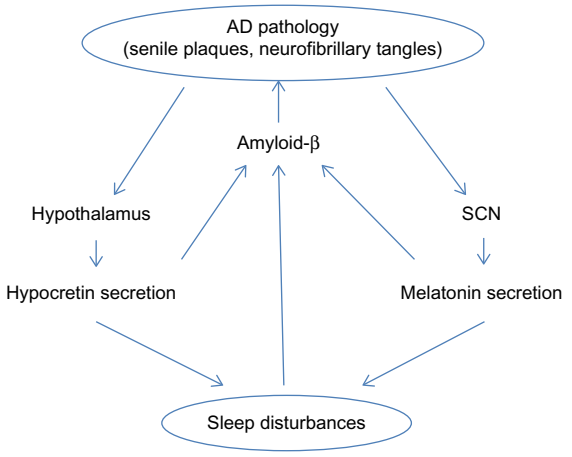

Figure 1 Bidirectional relationship between sleep and AD pathology.
Abbreviations: SCN, suprachiasmatic nucleus; AD, Alzheimer's disease.

longitudinal cohort study, Lim et al[47] found that a better sleep consolidation, measured by actigraphy, reduced the incidence of AD, cognitive decline, and neurofibrillary tangle density (determined by autopsy) in those subjects with the APOE E4 allele. The amount of SWS could explain, at least in part, these findings because the level of cerebrospinal fluid (CSF) amyloid-β is lower during this sleep stage and much higher during wakefulness and the REM stage.[48] Therefore, patients with sleep fragmentation and decreased SWS would have higher CSF amyloid-β levels, leading to the formation of amyloid plaques.

On the other hand, AD also influences sleep, especially the sleep–wake cycle.[49] Patients with AD suffer some disturbances in the secretion of neurotransmitters related to sleep–wake systems, mainly hypocretins (orexins) and melatonin secretion.[29,50] Hypocretin-1 and -2 are produced by a small cluster of neurons in the posterior hypothalamus.[51,52] The hypocretin system acts a stabilizing factor in the sleep–wake flip-flop, keeping it in the waking state.[53,54] The disturbances in the secretion of neurotransmitters not only influence the quality of sleep, but also play a role in the pathogenesis of the AD itself through changes in amyloid-β, originating a complex circle. In fact, it has been reported in mice that physiologic circadian fluctuations of CSF amyloid-β levels are related to the hypocretin system.[55] In AD patients Fronczek et al[56] found low levels of hypocretin-1 levels in ventricular CSF portmortem. However, in humans the relationships between specific AD biomarkers and hypocretin-1 remain unclear. Most studies have found normal levels of CSF hypocretins.[57–61] However, a continuous CSF sampling study via indwelling intrathecal catheter collecting hourly CSF samples found that lower mean amyloid-β42 was related to lower levels of hypocretin-1,[62] even though these were within the normal range. In 2013, after a review of the literature, Slats et al[50] concluded that, although in AD patients hypocretin neurons are decreased, the levels and the circadian rhythm of CSF hypocretins do not differ from those of healthy volunteers. More recently, Dauvilliers et al,[63] in a study of patients with cognitive impairment of different origins, surprisingly found that CSF hypocretin-1 concentrations were significantly higher in early stage AD, suggesting that this finding could contribute to AD diagnosis. Therefore, further studies are needed to clarify the complete role of the hypocretin system in the pathophysiology of AD.

Melatonin plays a key role not only in sleep disturbances but also in the pathogenesis of AD. Melatonin is a tryptophan metabolite that is synthesized in the pineal gland and has several physiological functions including the regulation of circadian rhythms, clearance of free radicals, improvement of immunity, and inhibition of the oxidation of biomolecules.[64] CSF melatonin levels are already decreased in the preclinical stages of AD[65,66] and continue decreasing further as AD progresses.[67] Some irregularities in the pattern of the melatonin rhythm also occur.[65] The defect in the secretion of melatonin is not due to the lesion of the pineal gland but to the involvement of the suprachiasmatic nucleus (SCN), the master clock of the circadian rhythm, which would lead to a decrease in the expression of clock genes and to a loss of the noradrenergic control in the pineal gland.[24,68] The reduced optical transmission in elderly people also influences the activity of SCN. The presence of the ApoE4 allele, a known genetic risk factor for AD, has been linked to a lower level of CSF melatonin[69] and to the presence of sleep alterations (eg, REM sleep reduction and obstructive sleep apnea syndrome).[69–71] On the other hand, melatonin has several antiamyloidogenic and antioxidant effects[72] and its deficit could influence the progression of the disease. It has the ability to regulate APP metabolism, reducing amyloid-β levels and preventing its aggregation. It also influences hyperphosphorylation, but has no effect once deposition has started.[72]

There is some evidence that other neurotransmitters related to sleep, such as melanin-concentrating hormone, are also altered in AD, but more studies are needed to clarify their role.[60]

Clinical evaluation of sleep disturbances in AD

The evaluation of a patient with sleep complaints must begin with the characterization of the pattern of the sleep

disruption and the identification of possible factors that affect or worsen the quality of sleep. As shown in Figure 2, these may include behavioral and environmental factors, comorbidities, and medications.[4] The identification of primary sleep disorders in demented patients may be difficult because the manifestations of the sleep disorders can be atypical. For example, restless legs syndrome (RLS) may be expressed only by nocturnal agitation.[73] A specific guideline to establish the diagnosis of probable RLS has been developed.[74] It emphasizes the behavioral indicators and supportive features. Studies assessing the prevalence of RLS with the usual criteria report a prevalence of 4%–6%.[75,76] However, Rose et al,[73] using the new criteria, reported a prevalence of 24%.

Bedtime ritual and habits, time spent in bed, amount of day-time activity, ambient light, and nocturnal noise may affect sleep quality.[5] Physicians must always bear in mind that they are dealing with an elderly patient, who is at risk for many common sleep disorders typical in this age group, especially congestive heart failure with nocturnal respiratory distress and nocturia, chronic obstructive pulmonary disease, gastroesophageal reflux, arthritis, and nocturia.[57–82] Psychiatric diseases cannot be forgotten since about 50% of AD patients have symptoms of dysthymia or depression.[83] In relation to medications, it is important to evaluate both prescription and over-the-counter medications, and the use of social drugs such as caffeine, nicotine, and alcohol.[84]

The information about the sleep and other health problems obtained from demented patients is not always reliable because they are not aware of the presence or severity of their problems. Sleep questionnaires are also of limited value because AD patients tend to underscore sleep disturbances.[85] Therefore, the clinical evaluation usually requires information from the caregivers who suffer the burden of the behavioral alterations, both the nighttime and daytime consequences. When the origin of the sleep problems is not identified during the clinical interview, a structured evaluation must be used. In 2003 Tractenberg et al[86] proposed an instrument to assess symptoms of sleep disturbances and disorders in AD patients – the Sleep Disorders Inventory. Yesavage et al proposed new criteria to identify sleep disturbances related to AD to facilitate future research.[87]

When the clinical involvement of sleep disturbances is severe, when there is no good response to the usual treatments or when there is a reason to suspect that a patient has a comorbid primary sleep disorder, the most appropriate course of action is to refer the patient to a sleep unit for further investigations. The gold standard to record sleep is PSG. However, it can be difficult or impossible to perform this procedure due to the need for minimum patient cooperation. Moreover, the stage scoring may be complicated due to the diffuse slowing of the EEG.[14] Wrist actigraphy has been used as a more feasible alternative.[88] Ancoli-Israel et al,[89]

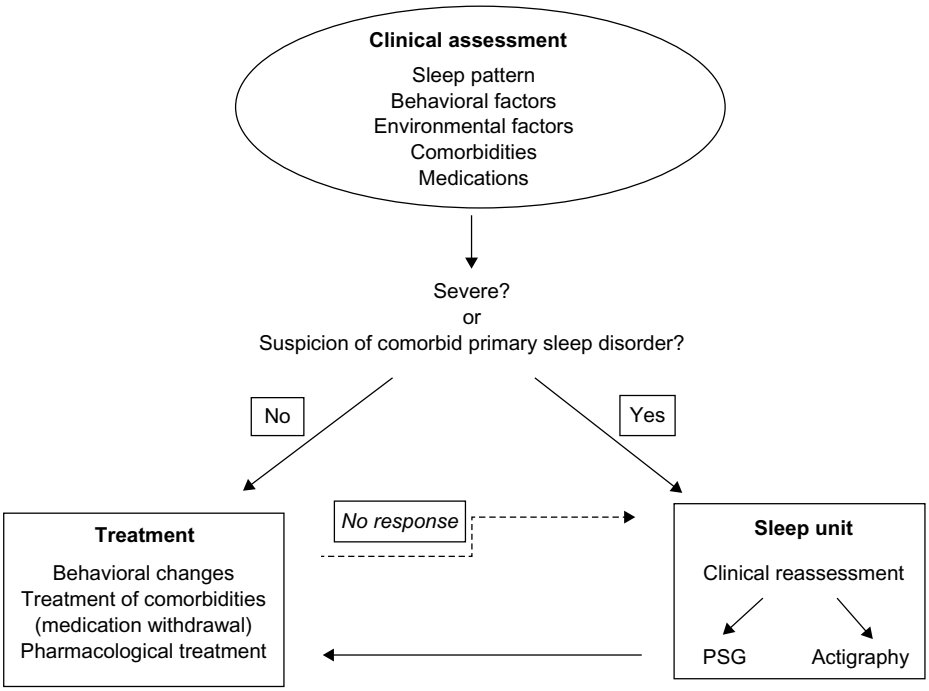

Figure 2 Diagram with the clinical evaluation of the sleep disorders in AD patients.
Abbreviations: AD, Alzheimer's disease; PSG, polysomnography.

using EEG recordings and actigraphy, found a significant correlation between total sleep and wake time, and a high sensitivity and specificity for actigraphy as compared to behavioral observations.

Treatment of sleep disturbances in AD

The aim of the treatment is to improve the quality of life of patients and caregivers. Because of the impact of sleep disorders on cognition, it seems logical to think that the treatment would also improve some cognitive domains. Some authors have even suggested a possible preventive effect for the progression of the AD.[10,41,50,72]

As mentioned in the previous section, a thorough evaluation, including habits, comorbidities, and treatments, is critical to choosing the most appropriate treatment for each patient. The treatment of comorbidities or the withdrawal of a medication might be the first step when we are faced with sleep disturbances in a patient with AD. In the following section, we discuss treatment differentiating between nonpharmacological and pharmacological approaches (Table 1). The treatment of primary sleep disorders is discussed separately.

Nonpharmacological treatment

The nonpharmacological approach tends to be considered the first-line treatment in AD patients, although scientific evidence of its effectiveness is limited. In 2013, after a structured critical literature review, Brown et al[90] concluded that there was a paucity of conclusive research for nonpharmacological sleep interventions in people with dementia, with the evidence being conclusive only for the use of light therapy (LT).

During daytime, AD patients should be encouraged to exercise regularly for at least 30 minutes and walk outdoors. Intake of stimulants such as caffeine or tea should be limited, and naps longer than half an hour or after 1 pm should be avoided. Time in bed should be reduced. The schedule for going to sleep and getting up must be regular and the bedroom should be reserved only for sleeping. Nighttime noise and light exposure and sleep disruptions should be reduced. The last point is especially difficult but important in nursing homes.[91] The efficacy of these measures is well established in demented elderly and in AD.[92–95]

Bright light therapy (BLT) is a chronotherapeutic intervention used to treat circadian disturbances in AD patients.[93] Several classic studies have shown that BLT improves night-time sleep, decreases nocturnal awakenings, increases daytime wakefulness, reduces evening agitational behavior, consolidates rest/activity patterns,[96–99] and also improves cognition.[98–101] Ancoli-Israel et al[102] compared bright light during morning versus dim light during morning and bright light during evening for 10 days. They found a lengthening of the maximum sleep bouts during night only in the first condition, with no significant changes in total sleep time or awakenings. Dowling et al[103] found improvement in the sleep parameters exclusively in the group with more severe involvement of the sleep–wake rhythm. They used a light intensity of 2,500 lux during only 1 hour, Monday through Friday during 10 weeks. The same group in 2008 published the results in 50 patients using the same method of luminotherapy combined or not with melatonin, and they found no changes in sleep parameters using bright therapy alone, but there were changes when it was combined with melatonin.[104] The season could have an effect on the response to BLT. Burns et al,[105] applying bright light at 1,000 lux from 10 am to 12 noon, found that the benefit was higher during winter than during summer. A limitation for BLT in the demented population is that the patient must be calm during that time. Riemersma-van der Lek et al,[101] in a placebo-controlled double-blind study, found that unattended exposure to bright light during daytime (from 9 am to 6 pm) slightly improved sleep and slowed down cognitive

Table 1 Treatments for sleep disturbances in AD patients

Treatment of the sleep disorders			Treatment for AD	
Nonpharmacological	**Pharmacological**	**Others**	**Improve sleep**	**Aggravate sleep**
Behavioral measures	Melatonin[a]	CPAP	Galantamine	Donepezil
Stimulus control	Z-hypnotics		Donepezil	Rivastigmine
BLT[b]	Sedating antidepressant (trazodone[a])		Rivastigmine	
	Antipsychotics			
	Melatonin receptor agonists[c]			
	Hypocretin receptor antagonist[c]			
	Circadian clock modification[c]			

Notes: [a]Therapies with scientific evidence of effectiveness; [b]discordant results; [c]drugs under development.
Abbreviations: AD, Alzheimer disease; CPAP, continuous pressure airway pressure; BLT, bright light therapy.

decline (follow-up: 6 months–5 years). The improvement was greater when the therapy was given in combination with melatonin. Figueiro et al[106] also obtained an improvement in sleep parameters using a tailored lighting with bright light from 6 or 8 am to 6 pm. As Hanford et al[107] underlined, it is important to note that the short-term history of light exposure affects the sensitivity of the circadian system to light. The higher the exposure to light during the day, the lower the sensitivity of the circadian system to light, as measured by nocturnal melatonin suppression and phase shifting. In spite of these positive reports, the Cochrane systematic review carried out by Forbes et al[108] concluded that there is insufficient evidence of its effectiveness. They found only ten studies that fulfilled their search criteria[93,101–105,109–112] and the authors concluded that the lack of evidence could well have been due to the heterogeneity of the studies (light intensity, duration of the exposition per day, treatment duration, etc).

Pharmacological treatment

The most commonly used drugs are melatonin, z-hypnotics such as zolpidem, sedating antidepressants, and antipsychotics. Usually benzodiazepines are avoided because they may worsen cognitive function. Cholinesterase inhibitors, the first-line treatment for AD, can also improve sleep quality. However, there are few studies assessing the efficacy of these drugs. In the critical review of the evidence for current treatments, McCleery et al[113] found eligible randomized controlled trials for only three drugs: melatonin, trazodone, and ramelteon.

Melatonin

Melatonin is considered not only a chronobiotic treatment, but is also used to treat insomnia.[114] The relationship between alterations in the melatonin system and the pathogenesis of AD makes melatonin a particularly interesting target. Furthermore, it has cytoprotective, antioxidant, and antiamyloidogenic effects.[72,115–117] Research has focused not only on the improvement of sleep domains but also on the effect on cognition and AD progression.

We found eight randomized placebo-controlled studies.[101,104,118–123] All but one[123] used actigraphy to objectively measure the changes in sleep parameters. There were no relevant side effects. The results in efficacy were equivocal. Five studies found improvement in nocturnal sleep.[101,104,118,122,123] Two of these studies combined melatonin and BLT.[101,104] In a multicenter, double-blind, randomized placebo-controlled trial that has been previously cited in our discussion of BLT, the researchers found that melatonin by itself improved sleep onset latency and total sleep time, but that it had adverse effects on mood and aggravated withdrawn behavior.[101] The authors evaluated the effects of daily supplementation of light and/or melatonin in a diverse population with dementia and reported that the combination of BLT and melatonin avoided these adverse effects. Dowling et al[104] studied a group treated with BLT and melatonin and a group treated with BLT and placebo and found that only the group with melatonin showed improved sleep parameters. The authors had no group on melatonin without BLT and they concluded that further studies were needed to determine whether the effect was due to the melatonin itself or the two zeitgebers. The largest multicenter, randomized, placebo-controlled trial included 157 subjects.[120] In this study, melatonin facilitated sleep in some subjects but collectively there was only a trend toward increased nocturnal sleep time and decreased awakenings after sleep onset as determined by actigraphy. However, the improvement in subjective measures (caregiver ratings of quality of sleep) was significant. Finally, there are two trials that failed to prove efficacy.[119,121] The discrepancy could be due to several facts such as the dosage, the release form, or the study duration. Interindividual differences, not uncommon in patients suffering neurodegenerative diseases, could also explain part of the inconsistent results. Neuropsychological assessment was performed in only two of these trials[118,123] and both found improvement in cognitive functions.

The effect of melatonin on AD progression has been tested in patients with mild cognitive impairment (MCI). Approximately 12% of MCI patients convert to AD or another dementia every year, and it has been suggested that MCI is a prodromal AD.[124] In a retrospective analysis of 25 MCI patients, Furio et al[125] found that melatonin significantly improved cognitive and emotional performance and daily sleep–wake cycles. In a follow-up study, the same group obtained similar results in a larger sample of patients.[126]

Hypnotics

Hypnotics are classified into benzodiazepines and nonbenzodiazepines. The side effects of benzodiazepines include daytime sedation, anterograde amnesia, daytime sleepiness, confusion, and risk of falls. Given these risks, they are not recommended for AD patients. They also have a deleterious effect on cognition.[127] Furthermore, several studies suggest that the long-term use of benzodiazepines increases the risk of AD.[128–131] However, other studies have found no such association.[132]

The side effects profile of nonbenzodiazepines such as zolpidem and zaleplon makes them more suitable for short-term use in patients with AD, but they must be used with caution.[133,134] In fact, an increased risk of reversible dementia has been described associated with the use of zolpidem.[135]

Antidepressants

Sedating antidepressants are used when there is concomitant depression. However, tricyclic antidepressants have anticholinergic activity and may exacerbate the cholinergic disturbances inherent in AD, and should be avoided.[5] They also have other side effects such as somnolence, sedation, and dizziness, which are of great concern in the demented population.[14]

Serotonin reuptake inhibitors with a sedating profile, especially mirtazapine, are also used to treat insomnia. It has been reported that mirtazapine was useful in the treatment of insomnia in three depressed patients with AD.[136] However, the risk of undesirable side effects is also high.[137]

Trazodone is a triazolopyridine antidepressant that offers a dual action on serotonergic receptors by blocking the 2A receptor and inhibiting serotonin reuptake. It improves sleep in patients with depression, but there is insufficient evidence for its use in patients with insomnia without depression.[138] However, its usefulness in treating sleep disturbances in patients with AD has been demonstrated. In a double-blind, randomized, controlled trial in 30 patients with AD, trazodone (50 mg during 2 weeks) increased total nocturnal sleep time without significant daytime somnolence or negative effects on cognition or functionality.[139] There were no serious adverse effects.

Antipsychotics

Antipsychotics are frequently administered to control behavioral and neuropsychiatric manifestations of AD. Sometimes, when the first-line treatments have failed, they are also used to treat insomnia. However, they are associated with sedation, increased risk of falls, and might also have serious cardiac side effects.[140,141] Furthermore, they can aggravate sleep–wake cycle disturbances.[142]

Antihistaminic drugs

Antihistaminic drugs are included as an option to treat insomnia.[143] They have a wide range of side effects including sedation, cognitive impairment, increased daytime somnolence, and anticholinergic responses. Therefore, they do not seem appropriate to be used in AD patients.

Treatment of AD: effect on sleep

Acetylcholinesterase inhibitors are a common treatment for AD. Acetylcholine not only plays a key role in memory functions but also is related to vigilance states. Levels increase during wakefulness, decrease in non-REM sleep, and rise again in REM sleep. Polysomnographic studies in patients taking acetylcholinesterase inhibitors have shown an increase in the percentage of REM sleep, reduced REM latency, and a decrease in REM sleep slow band power.[144–146] However, disagreement exists surrounding the effects of acetylcholinesterase inhibitors on sleep, although such discrepancies could be due to the time of administration.[147] For example, insomnia and nightmares are frequent side effects of donezepil[148] when it is administered at night but produces a slight improvement in sleep quality when administered in the morning.[149] Galantamine has the best profile regarding sleep and may be the first choice of cholinesterase inhibitor in mild-to-moderate dementia patients in terms of improving sleep quality.[149–151] One case of rivastigmine induced REM behavior disorder (RBD) has been reported.[152] However, it seems that donezepil and rivastigmine might be effective to treat RBD.[153,154]

Treatment of primary sleep disorders

Sleep-related breathing disorders

As mentioned earlier, SRBDs[6] have been identified as an independent risk factor for cognitive decline,[36] although the mechanism remains unknown. Obstructive sleep apnea syndrome (OSAS) produces intermittent hypoxia, sleep disturbances, and daytime sleepiness that lead to cognitive impairment that could be reversible with the treatment of the breathing disorders.[38]

Nocturnal continuous pressure airway pressure (CPAP) is the most effective treatment for OSAS. It restores respiratory function and consolidated sleep, increasing SWS and REM sleep.[155] Despite inconsistencies, there is some evidence for the effectiveness of CPAP in improving cognition in patients with OSAS.[37] In a CPAP treatment versus placebo-CPAP randomized study, CPAP decreased subjective sleepiness and improved a composite neuropsychological score in mild-to-moderate AD patients with an apnea–hypopnea index (AHI) >10.[156,157] Osorio et al[33] analyzing data from patients of the AD Neuroimaging Initiative cohort on CPAP treatment suggested that CPAP treatment might delay progression of cognitive impairment. However, the tolerance to CPAP is a limiting factor in patients with dementia.

Interestingly, there are some data supporting a possible positive effect of donezepil on OSAS. In 2008, Moraes et al[158]

published the results of a randomized, double-blind, placebo-controlled trial including 23 patients with mild-moderate AD patients with an AHI >5/h. They found that donepezil improved AHI and oxygen saturation in patients with AD. This treatment also increased REM sleep duration and reduced ADAS-cog scores. In 2012 another randomized, double-blind, placebo-controlled trial found similar results with improvement on obstructive sleep apnea index, oxygen saturation, and sleepiness.[159]

RLS/periodic limb movement disorders

Nocturnal agitation could be the clinical manifestation of the RLS in some patients with AD. RLS may also cause an inability to fall asleep or to remain asleep. These sleep disturbances might exacerbate cognitive symptoms or even accelerate neurocognitive degeneration.[160,161] Thus, a correct diagnosis will probably lead to appropriate treatment. However, the impact of the treatment of RLS, especially dopaminergic agents, on nocturnal agitation and cognitive function in AD patients is not known.[14] On the other hand, according to Peter-Derex et al, the pharmacological treatment of periodic limb movements in sleep not associated with RLS is not recommended.

Future directions

There is increasing research interest in the treatment of insomnia and circadian disturbances to modulate the receptors of the neurotransmitters directly involved in the control of sleep and the sleep–wake cycle. The most widely studied molecules are the agonists of melatonin receptors and the antagonists of orexin receptors. Both mechanisms are of special interest in AD due to the role that these neurotransmitters seem to play in sleep disturbances and in the pathogenesis of the disease. Interestingly, currently several groups are designing agents that directly target the circadian clock itself.

Melatonin receptor agonists

Ramelteon is a melatonin receptor agonist with high affinity for the melatonin receptors MT1 and MT2 used to treat insomnia.[162] It is well tolerated and appears to lack significant adverse effects.[163] The subjective efficacy of ramelteon was evaluated in clinical trials that included 829 elderly outpatients with chronic insomnia. Significant reductions in sleep onset latency and increases in total sleep time were obtained over 5 weeks of treatment.[164]

Agomelatine is a melatonin MT1 and MT2 receptor agonist and a weak 5-HT2C antagonist.[165] It has been approved for the treatment of depression.[166] Agomelatine appears to improve sleep quality and reduce wakefulness after sleep onset in depressive patients without causing daytime sedation.[167–169] Although it seems well tolerated, there are concerns over its risks because it appears to have the potential to cause severe hepatotoxicity.[170,171]

Tasimelteon is also a specific MT1 and MT2 agonist, and is the only drug approved by the US Food and Drug Administration (FDA) for the treatment of non-24-hour sleep–wake disorder. Physiologic monitoring revealed that tasimelteon resulted in a higher proportion of individuals becoming entrained to the 24-hour cycle compared with placebo.[172] Safety assessments indicated that tasimelteon is well tolerated, with the most common adverse events being headache, elevated alanine aminotransferase levels, nightmares or unusual dreams, and upper respiratory or urinary tract infections.

To our knowledge, no study on the efficacy of ramelteon, agomelatine, and tasimelteon in the treatment of comorbid insomnia in patients suffering from AD has been published to date.

Orexin receptor antagonists

Currently a new generation of hypnotics is emerging. The orexin receptor antagonists include the single orexin receptor antagonists and the dual orexin receptor antagonists (DORAs).[173–179]

Suvorexant is the first orexin receptor antagonist (DORA) that has been shown to be effective in treating insomnia. It appears to be suitable as a chronic therapy for insomnia given the minimal risk of physical dependence.[180] Suvorexant has fewer adverse effects than the classical hypnotics, and it has been found to be generally safe and well tolerated.[181] At the recommended therapeutic dose of less than 20 mg, the most common adverse effect reported was somnolence. However, the FDA and the sponsor disagreed over the effective versus safe doses (November 2012). The FDA considered that 5–15 mg were efficient and probably safe, whereas the sponsors had proposed 15–40 mg. The final approved doses are 5, 10, 15, and 20 mg. The major issues are next-morning somnolence and safety, as seen in driving tests. However, signs of muscle weakness, weird dreams, sleep walking, other nighttime behaviors, and suicidal ideation were also reported. On the other hand, it has been found that suvorexant does not aggravate apneas or oxygen desaturations in patients with mild-to-moderate obstructive sleep apnea using twice the approved dose.[182] However, all these data were obtained in studies with healthy volunteers and the efficacy and side effects in patients with AD remain unknown.

Modulators of the circadian clock

At present several researchers are focusing on the identification of molecules and receptors that can alter the expression of clock genes.[183–189] Although such research is in a preliminary phase, these molecules could be the target to develop drugs that modulate the circadian clock.

Conclusion

Sleep and circadian disturbances are very frequent in AD patients and appear early in the course of the disease. They include a wide range of problems that severely affect the quality of life of the patient, family, and caregivers. In recent years, increasing evidence for the role of melatonin and hypocretins in the cause and mechanism of these disturbances has been found. There is a bidirectional relationship between these disorders and AD pathophysiology, a fact that raises the possibility of modifying the course of AD itself by treating the sleep disorders. The current treatments include nonpharmacological and pharmacological approaches. However, overall these are still unsatisfactory. Evidence of efficacy is scarce and contradictory results are common, with the only exceptions being the use of BLT and melatonin. Future directions for treatment include the establishment of protocols for effective BLT, the development of melatonin receptor agonists, hypocretin (orexin) receptor antagonists, and, although as yet in a very preliminary phase, the modulation of the circadian clock.

Disclosure

The authors report no conflicts of interest in this work.

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