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CLINICAL REVIEW

Sleep and Alzheimer's disease

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SUMMARY

Sleep disorders are frequent in Alzheimer's disease (AD), with a significant impact on patients and caregivers and a major risk factor for early institutionalization. Micro-architectural sleep alterations, nocturnal sleep fragmentation, decrease in nocturnal sleep duration, diurnal napping and even inversion of the sleep–wake cycle are the main disorders observed in patients with AD. Experimental and epidemiological evidence for a close reciprocal interaction between cognitive decline and sleep alterations is growing. Management of sleep disorders in AD is pre-eminently behavioral. Association of melatonin and bright light treatment seems to be promising as well. The presence of sleep complaints, especially excessive somnolence in demented patients, should draw attention to possible associated sleep pathologies such as sleep apnea syndrome or restless legs syndrome.

Introduction

Changes in sleep are part of the normal aging process, with increasing sleep fragmentation, nighttime awakenings and greater tendency for daytime sleep. Dementia causes further degeneration of sleep patterns [1]. While there are various types of dementia, Alzheimer's disease (AD) is the most common form. The prevalence of AD is rapidly increasing and will probably further rise dramatically within the next decades as growing numbers of people are living older.

Although progressive deterioration of memory, language, and intellect are the classic hallmarks of AD, sleep disturbance is a common and often highly disruptive behavioral symptom associated with AD. Epidemiological studies have reported that up to 45% of patients with AD have sleep disturbances [2,3]. These neurobehavioral symptoms may appear at an early stage of the AD process but seem to be usually correlated to a more severe cognitive decline [3,4]. Sleep disturbances can be as stressful for patients and caregivers as the dementia itself and are a major risk factor for early institutionalization [5,6].

The origin of sleep disturbances in AD is thought to be multifactorial. Degeneration of neural pathways that regulate sleep–wake patterns and sleep architecture as well as somatic or psychiatric co-morbidities may contribute to sleep alterations [3,7]. In return, sleep disorders may exacerbate cognitive symptoms through impairment of sleep-dependent memory consolidation processes [8,9]. Recently, a link between sleep characteristics and cognitive decline in the elderly has been suggested, emphasizing the fact that sleep and cognition are closely related [10–12].

This article will review sleep changes with normal aging and AD, common pathologies of sleep and their relation with AD, and the influence of AD treatment on sleep. The consequences of sleep disturbances in AD and their management will be discussed thereafter. Finally, recommendations as to areas in which future research is needed will be proposed.

Sleep and normal aging

Age-related changes in sleep

There are age-related, normal changes that occur in sleep architecture and sleep patterns. Decrease in sleep quality during the

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Abbreviations

AD	Alzheimer's disease
aMCI	amnestic mild cognitive impairment
ApoE	apolipoprotein epsilon
BLT	bright light therapy
CPAP	continuous positive airway pressure
CSF	cerebrospinal fluid
EEG	electroencephalography
MCI	mild cognitive impairment
NREM	non-rapid-eye-movement
OSAH	obstructive sleep apnea and hypopnea
PLMS	periodic limb movements in sleep
PSG	polysomnography
RBD	REM sleep behavior disorder
REM	rapid-eye-movement
RLS	restless legs syndrome
SRBD	sleep-related breathing disorders
SWS	slow wave sleep

aging process is well documented. The frequent complaints of "poor sleep" in elderly include increased sleep latency, difficulty with sleep maintenance, frequent nighttime and early morning awakenings [13]. Objective modifications of sleep architecture on polysomnographic studies are represented by a reduction of total sleep time and sleep efficiency. The number of sleep stage shifts is increased with more frequent nighttime awakenings and sleep fragmentation. All of these changes can lead to excessive daytime sleepiness and increase in diurnal sleep. Amounts of the different sleep stages also show alterations: a reduction in slow wave sleep (SWS) and a compensatory increase in the lighter stages of sleep (stage 1 and 2) are observed. Changes concerning rapid-eye-movement (REM) sleep are less pronounced and seem to appear later with age [13,14]. Sleep latency may show equivocal changes with age. Microstructural alterations are also observed, such as decrease in K complexes and sleep spindles [1]. Apart from these structural alterations of sleep, sleep–wake rhythm disturbances have also been described in the elderly. An increase in daytime sleep and a tendency to phase advancing are frequently observed [13]. Circadian sleep–wake rhythm disorders result not only from behavioral factors but also from neuro-hormonal modifications, especially melatonin whose plasma concentration declines with age [15]. Of great importance in this population is the impact of somatic and psychiatric pathologies, pharmacological treatments, decrease in physical activity and exposure to light in the genesis of sleep disturbances. The incidence of specific sleep disorders such as sleep-related breathing disorders (SRBD), restless legs syndrome (RLS) and periodic limb movements in sleep (PLMS) also increase significantly with age [13].

Sleep alteration and cognition in healthy aging

In the non-demented elderly, subjective sleep complaints and objective sleep alteration may predict cognitive decline. Cross-sectional and longitudinal studies have reported an association between poor sleep quality and cognitive decline [16,17]. Moreover, objective actigraphic-assessed sleep fragmentation and circadian rhythm disruption have been shown to increase the risk of mild cognitive impairment (MCI)/dementia in elderly healthy subjects [11,12]. Recently, Westerberg et al. pointed out sleep disturbances such as reduction of stage 2 sleep spindles and decrease in delta and theta power in amnestic mild cognitive impairment (aMCI) patients [18]. They also reported a correlation between a lower subjective sleep quality and a lower recognition of items learned the previous day in aMCI patients [19]. Whether sleep disorders may represent early symptoms of a neurodegenerative process, or may induce cognitive impairment through an increase of depressive symptoms or through alterations in sleep-dependent memory consolidation is still a matter of debate [10,20]. Indeed, many studies have provided evidence that sleep optimizes consolidation of different forms of memories [21]. Hippocampus-dependent memories (declarative/episodic memories) have been shown to benefit primarily from SWS, whereas memories not depending on the hippocampus (procedural learning related to fronto-striatal circuits) show greater gains over periods containing high amounts of REM sleep [22]. Most of these studies about sleep and memory have been performed in young healthy subjects. However, given that older people are at higher risk for both sleep alteration and cognitive decline, the question of the relationship between sleep and memory consolidation in non-demented and demented elderly is of great interest. Recent studies have suggested an age-related change in the cognitive function of sleep [23,24]. Some authors have shown that impairment of attention following sleep deprivation is greater in younger than in older adults [25]. The "aging effect" on sleep-dependent consolidation has mainly been reported for procedural motor sequence learning, which appears less dependent on sleep period in older than in younger subjects [26]. Regarding declarative memories, results are more conflicting: similar sleep-dependent performance changes in different age groups on episodic/declarative learning have been reported [27,28]. In contrast, Scullin et al. reported that episodic memory is less related to SWS in healthy elderly than in younger adults [29].

Thus, sleep-related memory processes partly change with aging but some learning functions still remain improved by sleep, which suggests a physiological link between aging, sleep (and sleep disorders), and cognition.

Sleep disturbances associated with Alzheimer's disease

Sleep disturbances represent an early component of AD and the severity of this sleep disruption appears to parallel the severity of dementia [4,30].

Sleep evaluation methods

Identification of sleep disturbances in AD requires tools to detect, characterize, and quantify changes in patients' sleep. Even though polysomnography (PSG) is the recognized gold standard for recording sleep, this exploration is often difficult to perform, since it requires patient cooperation. Most AD patients, especially at advanced stages of the illness, are unable to tolerate such laboratory procedures. Moreover, sleep stage scoring may be difficult, due to diffuse slow activity on electroencephalography (EEG) during sleep and wakefulness. Subjective sleep questionnaires (Pittsburgh sleep quality index, sleep disorders questionnaire, Athens insomnia scale) seem to be of limited value in AD patients who tend to underscore sleep disturbances even in early and moderate stage [31]. Wrist actigraphy, providing a way to quantify inactivity versus activity, or sleep versus wake for consecutive 24-h periods, appears as an alternative, less intrusive and equally reliable, procedure. Ancoli-Israel et al. have evaluated wrist activity for sleep and wake monitoring in demented nursing-home patients. They observed: 1) a significant correlation between EEG recording and actigraphy for total sleep and wake time; and 2) a high sensitivity (87%, ability to detect wake)

and specificity (90%, ability to detect sleep) of actigraphy, compared to behavioral observations [32]. Thus, even if studies on sleep characteristics in AD patients are most often derived from PSG recordings, actigraphy seems to be a more suitable method in clinical practice.

Sleep architecture alterations

Sleep disturbances in patients with AD are qualitatively similar to those seen in the normal elderly, but much more severe, except for REM sleep which shows specific alterations probably related to dysfunction in cholinergic neurotransmission. Patients with AD often have more disrupted nocturnal sleep than age matched controls [4,33]. Wakefulness after sleep onset increases as AD progresses and, together with an increase in sleep latency, may be responsible for a total sleep time reduction [1,34]. Clinically, this disorder corresponds to agitation during the night and/or somnolence during the day. Discrimination among non-rapid-eye-movement (NREM) sleep stages, and identification of waveforms characterizing SWS in particular, can be difficult in the AD patient because of the topographically diffuse and low-amplitude slow-wave (0.5–2 Hz) activity characterizing both the sleeping and waking EEGs in these patients. This delta activity, called frontal intermittent rhythmic delta activity, has prompted some researchers to characterize NREM sleep in AD patients as "indeterminate" [34]. However, despite some discrepancies, most studies attest a decrease in SWS and alterations in spindles and K complexes [35,36]. REM sleep is quantitatively reduced in AD, while it is relatively preserved in normal aging. While mean REM sleep episode duration is decreased, the total number of REM sleep episodes and REM sleep latency remain intact [36]. EEG slowing during REM sleep has been proposed to be a biological marker of AD [35]. Hassainia et al. observed an increase in absolute delta and theta activities, and a decrease in absolute alpha and beta activities during REM sleep in AD, those alterations affecting particularly the parieto-temporal and frontal regions [37]. These specific REM sleep abnormalities may be related to the degeneration of the cholinergic structures in the brainstem and forebrain [38]. REM sleep behavior disorder (RBD), characterized by the loss of REM sleep atonia and responsible for "acting out dreams", is a clinically suggestive feature for the diagnosis of synucleinopathies such as Lewy body dementia, but not of AD even if a few cases have been reported. Schenck et al. reported RBD in a patient with autopsy-confirmed AD and suggested that cell loss of monoaminergic neurons in locus coeruleus could disinhibit cholinergic mesopontine neuron and promote RBD [39]. However, it is to note that, one year later, in a letter to the editor, Schenck revealed that Lewy body variant of Alzheimer's disease was identified by postmortem ubiquitin staining in this patient [40]. This observation may suggest that the presence of RBD in AD (as does the absence of RBD in Lewy body dementia) could be suggestive of particular neuropathologic borderline or mixed subtypes of dementia [41]. From a clinical and practical point of view, it is important to note that abnormal nocturnal behaviors (assessed by the Neuropsychiatric Inventory Questionnaire) during sleep are significantly more frequent and appear earlier in dementia with Lewy bodies than in AD [42].

Finally, specific task-induced modifications of sleep have been reported in AD patients. Faster mean theta frequency in both REM sleep and SWS during post-learning sleep has been reported in AD patients versus elderly controls. As this change in theta rhythm was associated with better delayed episodic recall, the authors suggested that this electrophysiological feature could reflect compensatory mechanisms to maintain memory performances [43]. In the same vein, a correlation between specific decrease in fast spindles and learning abilities has also been reported [9].

Sleep–wake cycle alteration

Circadian related disorders and alterations in sleep–wake patterns are common complaints in the elderly, especially those diagnosed with AD. These patients experience difficulties in falling asleep, maintaining nocturnal sleep and excessive sleepiness during daytime hours. In extreme cases, one can observe complete day/night sleep pattern reversal with the main sleep period occurring during daytime [34]. Sleep–wake cycle alterations participate in the emergence of the sundowning syndrome, a particularly stressful phenomenon for the patient and caregivers. Sundowning syndrome is characterized by the emergence or an increment of neuropsychiatric symptoms such as agitation, confusion, anxiety, and aggressiveness in the late afternoon, evening, or at night. The severity of cognitive impairment may be one of the important predisposing factors in the development of sundown syndrome [44]. Circadian rhythm disturbances in AD not only concern sleep/wake cycle but also other circadian rhythms such as body core temperature, motor activity and several hormone secretions. They are represented by a reduction in the amplitude of circadian rhythm and a delayed temperature acrophase [45]. These alterations are supposed to be partly mediated by degeneration of the suprachiasmatic nucleus of the hypothalamus where neuropathological changes (neuronal loss, with increase of the astrocyte/neuron ratio, and neurofibrillary tangle formation) have been observed, particularly in presenile AD women [46,47]. Although the pineal gland does not seem to be affected by AD pathology, a decrease in cerebrospinal fluid (CSF) melatonin level has been reported in these patients, potentially reflecting alteration of the suprachiasmatic nucleus output [48]. Alteration in the melatonin secretion rhythm has been observed too [49]. These findings suggest impairment in the endogenous pacemaker, which may lead to a reduced capacity to synchronize physiological rhythms, including the sleep/wake cycle [45]. Also of great importance are exogenous factors in the determinism of sleep/wake rhythm disturbance. External zeitgebers are responsible for the maintenance of circadian rhythmicity in humans by interacting with the central clock. Decreased input to the suprachiasmatic nucleus during AD and thus reduced zeitgebers (such as light, diurnal activities…) due to the cognitive decline and associated neurosensory dysfunctions, particularly visual ones (cataracts, retinopathies…), probably play an important role in disrupting the sleep–wake cycle [50].

Risk factors for sleep disorders in AD

Severity of the illness

Even if sleep disorders may be present early in the course of the illness, many studies suggest that they worsen over time. In a behavioral observation study among residents in a special care unit, Bliwise et al. showed that profound dementia was associated with more sleep disturbance [51]. Yesavage et al. reported significant deterioration of nocturnal sleep parameters assessed by longitudinal actigraphic measure over the course of approximately 1.5 y follow-up [52]. A correlation between daytime napping and the severity of cognitive decline has been described in AD patients and objective polysomnographic recordings confirmed the relationship between mini-mental state

examination and mean daytime sleep latency in mild/moderate AD patients [53,54]. Nevertheless, some studies show discrepancies with those results. Fernandez-Martinez et al. recently reported an absence of correlation between sleep score (Neuropsychiatric Inventory) and disease severity [55]. Moreover, sleep disturbance does not affect all patients with AD and the stage of the cognitive impairment seems to explain only a small part of the variance regarding the presence of sleep/wake disorders [56]. This may suggest an individual and potentially genetically determined susceptibility.

Genetic susceptibility

A relation between the presence of sleep disturbance and apolipoprotein epsilon (ApoE, a protein involved in maintenance and remodeling of neuronal membranes) isoform is suspected. The ApoE4 allele is a known risk factor for developing AD, especially in homozygous cases [57]. Most studies associate the ApoE4 allele to sleep alterations (e.g., reduction of REM sleep) in MCI or demented patients [58]. Increased sleep disturbances in ApoE4 patients could result from alterations in the production of melatonin: Liu et al. have set evidence of a lower CSF melatonin rate in homozygous 4/4 than in heterozygote patients [59]. In addition, studies have associated genotype 4/4 with an increased risk of obstructive sleep apnea and hypopnea (OSAH), and with sleep alterations and cognitive impairment in patients with OSAH [60–63]. Nevertheless, some authors have reported opposite results: Yesavage et al. have described a protective effect of ApoE4 allele on sleep in AD patients, and Craig et al. reported no effect of ApoE genotype [64,65]. It is possible that a more complex relationship between apoE4 status and sleep could explain these contradictory observations. Indeed, a better sleep consolidation could attenuate the increased risk conferred by the ApoE genotype on the development of AD [66].

Apart from ApoE studies, Craig et al. investigated the monoamine A oxidase promoter polymorphism which may influence sleep/wake regulation by modulating the availability of serotonin, a precursor of melatonin; they found that the high-activity 4-repeat allele of the monoamine A oxidase variable number tandem repeat promoter polymorphism conferred increased susceptibility to sleep disturbance [65]. Nevertheless, it is worth noting that allelic variations in this gene have been associated with behavioral and personality traits in other contexts, which may explain this association [67].

Co-morbidities and environmental factors [68]

Exogenous factors that may be responsible for sleep disturbances in patients with AD should not be underestimated especially regarding long-term care residents. They include environmental conditions, lifestyle habits, medical and psychiatric illness and medications. Nocturnal sleep may be disrupted by noise and light produced in long-term care facilities. Additionally, circadian dysregulation is enhanced by frequent naps, favored by low daytime indoor illumination, physical inactivity and bedridden. Elderly including AD patients suffer from medical as well as psychiatric morbidities, which can disrupt the sleep–wake cycle. This includes pain (e.g., from arthritis), nighttime cough, dyspnea (from cardiac or pulmonary illness), gastro-esophageal reflux, incontinence/frequent nighttime urination and depression. Drug combination therapy may affect sleep quality either by disrupting nighttime sleep as do diuretics and stimulating agents (e.g., sympathomimetics, bronchodilators) or by sedating effect (e.g., antihistamines, anticholinergics, sedating antidepressants) which add to daytime sleepiness. All these exogenous factors, which require non-pharmacological measures to reverse their harmful effects, can easily be managed by the medical staff.

Sleep disorders and Alzheimer disease

Sleep-related breathing disorders

Interactions between SRBD and dementia are complex. Obstructive sleep apnea and hypopnea (OSAH) has been shown to be associated not only with impairment of many cognitive functions, including attention and executive tasks, but also memory, even if some authors argue that the relationship between SRBD and cognitive function may only be mediated by the effect of SRBD on daytime sleepiness [69–71]. Recently, SRBD have also been highlighted as an independent risk factor for cognitive decline in a large longitudinal cohort study of older women [72]. The direction and mechanism of this relation remain hypothetical; SRBD could directly contribute to neuronal dysfunction through hypoxia or sleep disruption or may be secondary to vascular and/or neurodegenerative brainstem lesions. SRBD could also act as an independent factor, precipitating the emergence of clinical cognitive symptoms in patients with pre or subclinical AD [73,74]. The prevalence of obstructive sleep apnea increases with aging, but it seems that patients with AD are at even higher risks, with 40%–70% of patients having five or more apneas–hypopneas per hour of sleep [75–77]. A correlation between the severity of SRBD and the severity of the dementia has been suggested [75,77]. Sleep in AD patients with OSAH is characterized by decreased amount of REM sleep and slow wave sleep and more frequent awakenings compared to AD patients without OSAH [78]. The relationship between sleep apneas and AD might involve neurodegenerative lesions in the respiratory centers in the brainstem. Conversely, sleep apnea syndrome could intensify the cerebro-vascular component of cerebral lesions in mixed dementia and thereby worsen neurological symptoms. OSAH is associated with increased nocturnal awakenings sometimes associated with confusion, increased rates of nocturia, and higher risks of cardio- and cerebro-vascular accidents [74]. It is worth noting that SRBD related cognitive symptoms might be secondary to sleep disruption and associated with daytime sleepiness; such symptoms might be reversible with the treatment of the sleep apnea syndrome. Nocturnal continuous positive airway pressure (CPAP) is the most effective treatment for OSAH, restoring consolidated sleep and increasing SWS and REM sleep and respiratory function [79,80]. In mild-moderate AD patients with apnea–hypopnea index >10, significant reduction of subjective daytime sleepiness and improvement in a composite neuropsychological score have been noted after three weeks of treatment versus placebo CPAP in randomized placebo controlled trials [81,82]. The issue of the tolerance of CPAP treatment often appears as a limiting factor in patients with cognitive impairment. In the Chong et al. and Ancoli-Israel et al. reports, compliance was considered as high, but it is worth mentioning that both studies excluded severe demented patients, and that 25% of patient dropped out after randomization [81,82].

Restless legs syndrome/periodic limb movement disorder in sleep

Restless legs syndrome may cause an inability to fall asleep or to remain asleep. The incidence of RLS has been reported to increase with age and is higher in women [83]. Risk factors for RLS, such as depression, antidepressant drug intake, renal failure, and peripheral neuropathy, also increase with age. In mild cognitive impairment (MCI) and demented (AD and non-AD) patients, Guarnieri et al. reported a prevalence of 6% for RLS

assessed by questionnaires [84]. Nevertheless, in patients with cognitive decline, diagnosis based on questionnaires may be difficult and RLS may only be expressed by nocturnal agitation [85,86]. Specific guidelines for the diagnosis of probable RLS in cognitively impaired elderly have been established, emphasizing behavioral indicators and supportive features such as dopaminergic responsiveness, patient's past history, and presence of periodic limb movements [87]. Using such criteria, Rose et al. reported up to 24% of RLS in 59 demented patients. RLS was associated with nocturnal agitation. A possible association between RLS and cognitive impairment has been reported but some discrepancies appear in the literature, probably depending on the characteristic of the control group [88,89]. Sleep reduction secondary to RLS may enhance cognitive symptoms or even accelerate neurocognitive degeneration [87]. The impact of RLS treatment, especially dopaminergic drugs, on nocturnal agitation and cognitive function in AD patients remains unknown. PLMS are present in up to 80% of patients with RLS. PLMS index has been shown to increase after 65 y [90]. Few studies have objectively assessed the prevalence of PLMS in demented patients but an increase of twitches or jerks in sleep reported by the patient or his family has been described [85,91]. The role of PLMS in sleep disruption is equivocal and a recent study demonstrates a dissociation of periodic leg movements from arousals in restless legs syndrome [92]. Presently, pharmacologic treatment of PLMS is not recommended if not associated with RLS, but PLMS triggered by sleep respiratory events may decrease after CPAP treatment [93].

Cholinesterase inhibitor treatments and sleep

Degeneration of the cholinergic system including the subsystems involved in cognitive functions is thought to participate in the symptomatic expression of AD [94]. Acetylcholine plays a key role in memory functions and its concentration is closely related to vigilance states, as it increases during wakefulness and REM sleep, and decreases during SWS. Acetylcholinesterase inhibitors, by replenishing acetylcholine in the central nervous system of AD patients should have beneficial effects on both sleep pattern and memory [95]. Indeed, despite some discrepancies, studies argue for a REM sleep (and sometimes REM sleep associated parasomnia) promoting effect of acetylcholinestrerase inhibitors [96–98]. Polysomnographic studies in patients taking donepezil have shown an increase in REM sleep percentage and REM density, and a reduced REM latency [99]. These studies also demonstrated that donepezil treatment decreases EEG slowing ratio (ratio between slow and fast EEG frequency bands) and REM sleep slow band power in patients with AD. This latter effect is especially noticed in AD patients with moderate disease [100]. Donezepil could also increase light sleep stage 2, total sleep time, and even reduce sleep apnea/hypopnea index in mild OSAH AD patients [78,101]. The improvement of both REM sleep and cognitive function with donepezil treatment may suggest that REM sleep reduction is involved in the cognitive deterioration of patients with Alzheimer disease [97]. REM sleep behavior disorders and nightmares have been described as side effects of the cholinesterase inhibitor rivastigmine [98]. In contrast, donepezil has been reported as an effective treatment for RBDs in three cases [102]. Time of administration of cholinergic treatment seems important: morning administration should allow to avoid side effects like nightmares and to respect the physiological decrease of acetylcholine levels during SWS compared with wakefulness, which may be required for the consolidation of declarative memory [95].

Cognitive consequences of sleep disturbances in AD

Sleep and cognition in AD patients

Sleep disorders are often considered as clinical neuropsychiatric symptoms of AD. Nevertheless given the critical role of sleep in memory consolidation, alterations of sleep in AD patients may represent in itself an aggravating factor for amnestic symptoms [8]. Indeed, even if age-related changes in the cognitive function of sleep have been reported, many learning abilities seem to be improved with specific sleep stages in the elderly (cf Section Sleep and normal aging). The mechanisms by which sleep is supposed to enhance memories involve information reactivation and hippocampo-neocortical transfer, associated with specific sleep brain oscillations such as slow oscillations, thalamo-cortical spindles and hippocampal ripples during SWS [22]. During REM sleep, a high level of acetylcholine appears to be a critical factor for the consolidation of procedural memories [103]. In AD patients, sleep alterations are more pronounced than in healthy elderly and an association between sleep architectural modifications and learning abilities has been reported. Rauchs et al. observed that in AD patients the decrease in fast sleep spindles during post-learning sleep was correlated with poorer immediate recall performance in an episodic memory task, and that the ability to retrieve recent autobiographical memories was positively associated with the amount of SWS [9,104]. As mentioned in Section Cholinesterase inhibitor treatments and sleep, the alteration of REM sleep, associated with a decrease of acetylcholine levels, could also play a role in memory deficits in AD patients. Indeed, experimental pharmacological REM sleep augmentation with cholinesterase inhibitors has shown positive effects on procedural memory consolidation [105].

Cognitive disturbances in AD patients initially involve short-term memory. However, other cognitive functions, such as language, motor skills, and attention are also impaired. An impact of sleep loss or sleep disruption on almost all behavioral and neurocognitive domains has been reported in non-demented humans [106]. In AD, most studies about sleep and cognition have evaluated learning and memory, but emotional reactivity and executive function might also be weakened by sleep disturbances.

AD patients also experiment circadian rhythm disruption, which could in itself induce cognitive impairment. This hypothesis is supported by several studies. Experimental procedures in animals allow dissociating age-related from disrupted rhythms-related cognitive alterations. In hamsters, Antoniadis et al. demonstrated that circadian rhythm fragmentation impairs ability to form cognitive associations [107]. In rats, a deleterious effect of repeated phase shifts on hippocampal (spatial) memory has been observed [108]. In humans, circadian rhythm sleep disorders are often associated with impairments of selective attention and executive function [109].

Impact of sleep disturbances on pathophysiology of AD

Beyond the short-term impact of sleep disorders on memory processes, interest is growing on the potential impact of sleep disturbances on pathophysiological processes involved in AD. The accumulation of neurotoxic amyloid-β plaques (which is associated with brain interstitial fluid levels of amyloid-β) plays a central role in the pathogenesis of AD [110]. Orexin, also called

hypocretin, is a neurotransmitter that regulates arousal and wakefulness. A very interesting experimental work using in vivo microdialysis in mice showed a correlation between interstitial fluid amyloid-β amount and wakefulness (sleep deprivation) or orexin infusion. Conversely, infusion of a dual orexin receptor antagonist was associated with a decrease of interstitial fluid amyloid-β amount. Thus, chronic sleep deprivation may play a role in the pathogenesis of AD [111]. Nevertheless, results in humans suggest an equivocal (or even indirect) link between hypocretin and amyloid-β accumulation. Indeed, patients with Alzheimer's disease usually exhibit low levels of CSF amyloid-β42 [112]. Slats et al. found a correlation between CSF levels of hypocretin-1 and amyloid-β42 in AD patients, low level of hypocretin-1 being associated with low levels of amyloid-β42 in AD patients [113]. Moreover, patients with narcolepsy-cataplexy (in whom hypocretin is lacking) do not seem to be protected against AD [114,115]. It is worth noting that CSF (especially obtained by lumbar puncture) and brain concentration of neuropeptides may differ, which can explain some conflicting results. A functional imaging study has recently reported a correlation between shorter sleep duration or poorer sleep quality and greater amyloid-β burden assessed by positron emission tomography in 70 healthy older adults [116]. Finally, recent data suggest that other transmitters involved in wakefulness regulation, such as the melanin-concentrating hormone could be altered in AD [117]. Further studies will certainly clarify the intriguing role of arousal, hypocretin and melanin-concentrating hormone in the pathogenesis of AD.

Thus, the link between AD and sleep disorders is complex and bi-directional. It probably involves associated factors, namely vascular, which contribute to the emergence of dementia (see Fig. 1).

Management of sleep disorders in AD

Management of sleep disorders in patients with AD consists in pharmacological and/or non-pharmacological measures, aims to ameliorate the quality of life of patients and caregivers and so may result in postponing institutionalization [2].

Pharmacological measures

Melatonin

The secretion of melatonin by the pineal gland is closely associated with the light–dark cycle. The nocturnal rise in melatonin is associated both with increased sleep propensity and synchronization of the circadian clock [118]. Moreover, cytoprotective, antioxidant and even anti-amyloid effects of melatonin have been suggested [119,120]. The demonstration of alterations of melatonin secretion in patients with AD gave great hopes regarding the usefulness of exogenous melatonin in the treatment of both insomnia and daytime sleepiness in these patients. Evidence regarding the effectiveness of melatonin supplementation on sleep in patients with AD is limited. Six double blind randomized placebo controlled trials, mostly of limited sample size except for Singer et al.'s study (n = 157) have been published [5,121–125]. These studies used actigraphy, subjective reports, sleep logs, and nursing observation for measuring outcome, but none performed PSG. Although it is clear that melatonin has no significant side effect, even at high doses, the results of its efficiency are equivocal. Indeed, some studies showed beneficial effects, mainly improvement of day/nighttime sleep ratio, and decrease of nocturnal activity [121,124,125]. Others studies failed to demonstrate objective effectiveness [5,122,123].

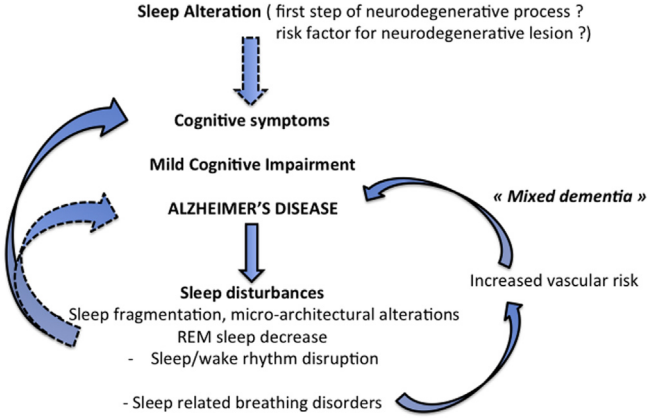

Fig. 1. Possible interactions between sleep disorders and Alzheimer's disease.

Antipsychotics

Antipsychotics are usually administrated to control the behavioral and neuropsychiatric manifestations of AD and sometimes for insomnia treatment after failure of all other measures. They are associated with an increased risk of falls secondary to sedation and may have serious cardiac side effects especially with second-generation antipsychotics [126–128].

Hypnotics

Hypnotics form a large group consisting of either benzodiazepines or non-benzodiazepines. They decrease sleep latency by promoting sedation at the expense of alterations in the sleep architecture. There are limited published data on their effectiveness in the management of sleep disturbances in AD. The non-benzodiazepine hypnotics cause fewer side effects especially regarding morning time residual sedation and risk of falls [129]. Nevertheless, their utilization may be restricted to acute insomnia because long time use has not been evaluated. Emerging drugs like suvorexant, an orexin receptor antagonist, might be very promising in AD patients [130].

Antidepressants

Sedating antidepressants are used when depression and its accompanying sleep disturbances coexist with dementia [131]. They may decrease sleep latency, but have undesirable side effects, including somnolence, sedation, and dizziness, which may be of great concern in demented populations [132].

Antihistaminic drugs

Antihistaminic drugs are often erroneously used as first line sleep aids. Their main inconvenience is the wide range of side effects they may induce, including sedation, cognitive impairment, increased daytime somnolence, and anticholinergic responses.

Acetylcholinesterase inhibitors

The effect of acetylcholinesterase inhibitors was discussed earlier in this review.

Non-pharmacological measures

Cognitivo-behavioral or psycho-educational strategies

Cognitivo-behavioral and psycho-educational strategies consist of combined daytime physical activity, sleep hygiene and

nighttime environmental program: i) AD patients should be encouraged to regularly exercise (ideally for 30 min) during the day. ii) they should be prompted to walk outside in natural light as often as possible. iii) the time spent in bed during the day should be decreased, the daytime naps >30 min or after 1 pm avoided, regular times for going to bed and arising maintained, and bedroom should be reserved for sleep. iv) nighttime dosing of cholinesterase inhibitors and stimulating drugs should be avoided. v) sleep disruption and nighttime noise/light exposure should be reduced.

The efficacy of such measures is well established in the non-demented elderly and in patients with AD as well, both in nursing home and community-dwelling patients [133–135]. Many studies have emphasized the positive impact of sleep-education programs that teach good sleep practices, conducted at home for demented patients and their caregivers [136,137].

Bright light therapy (BLT)

Light is the main stimulus for the circadian melatoninergic system. Light perception may be altered and light exposition may be reduced in the older population and AD patients. BLT consists in exposing AD patients to bright light using a full-spectrum light box for a minimum of half an hour daily, usually in the morning. The efficiency of BLT on circadian rhythm disturbances has been tested in many studies. Overall, the results from these studies show an improvement in sleep function by significantly reducing nighttime sleep fragmentation and increasing nocturnal sleep duration. BLT slightly reduces daytime sleepiness and to a lesser extent increases alertness during the day. This intervention has no serious adverse effects and may be considered as first line treatment for sleep disturbances in patients with AD [138–142].

Combined pharmacological and non-pharmacological measures

Some studies suggest that the combination of BLT with cognitive-behavioral measures and/or melatonin may be synergistic and should be proposed in this population before starting any other pharmacological measures. Such association may ameliorate patients' quality of life by improving vigilance and diurnal activity, increasing sleep efficiency, attenuating agitated behavior, reducing depressive symptoms and even slightly reducing cognitive deficit [136,143]. Long-term efficacy of BLT + melatonin has been evaluated and seems consistent up to 3.5 y [143].

Conclusion and future directions

Sleep disturbances are frequent in AD and have significant impact on patients and caregivers. Future research is needed to clarify the contribution of the various genetic, neurodegenerative and environmental factors to sleep impairment, then testing the effectiveness on sleep of various interventions targeting these processes. Experimental and epidemiological evidence for close reciprocal interaction between cognitive decline and sleep alteration are growing but long-term longitudinal studies are necessary to draw up the relationship between chronic sleep deprivation and cognitive decline. Management of sleep disorders in AD remains pre-eminently behavioral. Association of melatonin and bright light treatment seems to be promising but standardized therapeutic protocols applicable in everyday practice are lacking. Further studies will need to establish evidence-based guidelines regarding both sleep evaluation and management in this growing population.

Research agenda

1 Gaining insight into the interaction between sleep characteristics or sleep disturbances and cognitive decline/MCI/dementia through large longitudinal epidemiologic studies
2 Clarifying the impact of sleep alterations on cognitive symptoms and on pathophysiological processes involved in AD especially through investigation of the role of arousal and hypocretin in the pathogenesis of AD.
3 Investigating the impact of sleep disorders management on cognitive function and dementia evolution in AD patients.
4 Establishing guidelines regarding both sleep evaluation and management (standardized therapeutic protocols applicable in everyday practice) in AD patients.

Practice points

1 Sleep disturbances are frequent in AD and have significant impact on patients and caregivers. They represent a major risk factor for early institutionalization.
2 Sleep disturbances encountered in patients with AD are similar but more severe than those seen in elderly (micro-architectural sleep alterations, nocturnal sleep fragmentation, decrease in nocturnal sleep duration), except for REM sleep which shows specific alterations related to abnormalities of cholinergic neurotransmission in AD.
3 AD patients experience circadian rhythm disturbances (including sleep/wake rhythm alteration) resulting from endogenous patho-neurological and exogenous environmental factors. These later factors, including environmental conditions, lifestyle habits, medical and psychiatric illness and medications, require specific attention and management.
4 The prevalence of obstructive sleep apnea increases with aging, but seems higher in patients with AD. CPAP treatment may have a positive impact on cognitive function in these patients.
5 Wrist actigraphy recording is a reliable and easy procedure to explore sleep/wake rhythm alterations in AD patients. PSG recordings are required when a specific sleep disorder (such as sleep apnea syndrome) is suspected.
6 Acetylcholinesterase inhibitors seem to have beneficial effects on both sleep pattern and memory. Time of administration of cholinergic treatment is important: morning administration should minimize side effects like nightmares and respect the physiological decrease of acetylcholine levels during SWS.
7 Management of sleep disorders in AD remains pre-eminently behavioral. Association of melatonin and bright light treatment seems to be promising but standardized therapeutic protocols applicable in everyday practice are lacking.

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