Management of Sleep Disorders in Patients with Dementia

11

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Abbreviations

AD	Alzheimer's disease
AHI	Apnoea–hypopnea index
APOE	*Apolipoprotein* E
Aß	Beta amyloid
CI	Confidence interval
CPAP	Continuous positive airway pressure
CSF	Cerebrospinal Fluid
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EOG	Electrooculography
EMG	Electromyography
FTD	Frontotemporal dementia
LBD	Lewy body disease
MCI	Mild cognitive impairment
MMSE	Mini-Mental State Examination
OR	Odds ratio
OSA	Obstructive sleep apnoea

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PET	Positron emission tomography
PSG	Polysomnography
RAVLT	Rey Auditory Verbal Learning Test
RBD	Rapid eye movement sleep behaviour disorder
RLS	Restless leg syndrome
RSBSQ	REM Sleep Behavior Disorder Screening Questionnaire
SA	Sleep apnoea
TST	Total sleep time

Introduction

Refreshing and sufficient sleep are a prerequisite for well-being, daytime functioning and cognitive performance at any age. Furthermore, disturbed sleep can lead to a reduction in quality of life, depressed mood and cognitive impairment. Sleep disturbances are common in people who are elderly, suggesting that sleep is affected by ageing itself. Additionally, neurodegeneration causes a breakdown in the neuronal networks that control sleep function. Therefore, disturbed sleep may also be a sequela of dementia. However, epidemiological evidence suggests that the relationship appears to be mutual. Sleep research has shown that sleep disorders may (1) increase the risk of dementia, (2) deteriorate the course of dementia, (3) have symptoms similar to dementia, (4) be an early marker of dementia. It is therefore essential to search for and recognise sleep disorders in patients with dementia, to establish differential diagnoses and initiate treatment for these and other comorbid conditions to positively influence the course of dementia.

These issues are of pivotal importance since sleep disorders are potentially modifiable [1].

Sleep disorders encompass a variety of disorders like insomnia, sleep disordered breathing, restless leg syndrome (RLS), hypersomnia, circadian rhythm disorders and rapid eye movement (REM) sleep behavior disorder (RBD) (Table 11.1). Since treatment differs according to the type of sleep disorder a careful evaluation of sleep is mandatory before any treatment is initiated [2].

The aim of treating sleep disorders is (1) the prevention of cognitive decline and development of dementia in older subjects without dementia and (2) to mitigate sleep-related symptoms and suffering in patients with dementia and their caregivers.

Regulation of Sleep and Wakefulness

Sleep and wakefulness result from an interaction between several nuclei and neuronal networks located in the brain stem, the basal ganglia and the forebrain. Furthermore, various neurotransmitters, molecular and genetic factors, and input from the organism and the environment have an impact on sleep regulation. This complex interaction generates circadian rhythmicity and electrical brain activity that define different stages, like wakefulness, REM sleep and three non-REM sleep

Table 11.1 Classification according to the International Classification of Sleep Disorders and core symptoms of relevant sleep disorders

Classification	Sleep disorder	Core symptoms
Insomnia	Insomnia – Acute – Chronic	Difficulties initiating or maintaining sleep more than 2–3 times per week – Acute <3 months – Chronic >3 months
Sleep-related breathing disorders	Obstructive/central sleep apnoea	Apnoeas and hypopneas caused by partial or complete collapse of the upper airways; in central apnoea there is a lack of respiratory airflow despite open upper airways
Hypersomnias of central origin	Narcolepsy	Excessive daytime sleepiness (>3 months), cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, fragmented night sleep
	Idiopathic hypersomnia	Nocturnal sleep >10 h, excessive daytime sleepiness
	Kleine–Levin syndrome	Episodes of hypersomnia with changes in personality, eating and sometimes sexual behaviour
Circadian sleep-wake rhythm disorders (all >3 months)	Sleep-phase advance syndrome	Advanced sleep times, normal sleep structure
	Sleep-phase delay syndrome	Delayed sleep time, normal sleep structure
	Non-24-h syndrome	Misalignment with the 24-h dark-light cycle
Parasomnias	Non-rapid eye movement parasomnia, sleepwalking, night terror	Emerging from slow-wave sleep, dissociated behaviour, screaming with partial or complete amnesia, inappropriate responsiveness
	Rapid eye movement parasomnias Rapid eye movement sleep behaviour disorder	Complex motor behaviours during rapid eye movement sleep, dream enactment
	Nightmare disorder	Awakening from dysphoric dreams
	Isolated sleep paralysis	Inability to move the complete body upon awakening
Sleep-related movement disorders	Restless leg syndrome	Sensory misperception of the limbs with the urge to move the limbs occurring predominantly at nighttime
Sleep disorders in neurological diseases	Fatal familial insomnia Sleep-related epilepsy Sleep-related headaches	Prion disease, insomnia and complete breakdown of sleep-wake structure Epilepsy at sleep onset, offset or during sleep Headaches at sleep onset, offset or during sleep

stages N1, N2 (light sleep) and N3 (deep slow-wave sleep). More specifically, circadian and homeostatic processes generate the sleep-wake cycle. The nucleus suprachiasmaticus is the central generator of the circadian rhythms that regulate the interactions of the "clock genes" (e.g. PER1/2/3, CRY1/2, BMAL1, CLOCK).

Altered circadian rhythmicity, which depends on behaviour, light exposure, age and genetic disposition, can induce circadian rhythm sleep disorders. The circadian rhythm is best measured by plasma melatonin, cortisol levels and core body temperature over time.

The hypothalamic sleep-wake switch is a widely accepted model that relies on the evidence that sleep-promoting neurons of the ventral lateral preoptic nucleus and wake-promoting neurons in the monoaminergic cell groups inhibit each other. The lateral hypothalamus contains the neuropeptide orexin (synonymous with hypocretin), which projects to almost the entire brain and stabilises this switch. The firing of orexin neurons stimulates awakening and the classic arousal neurons of the brain (histamine, serotonin and noradrenaline neurons).

The pathophysiology of frequently occurring RBD (e.g. in Lewy body disease (LBD)) is not yet fully understood. Intermittent release of glutamate activates non-N-methyl-D-aspartate receptors and excites motoneurons, causing muscle twitches in normal REM sleep. Glutamatergic neurons, especially in the subcoeruleus nucleus, are active during REM sleep and project to the ventromedial medulla and to the spinal cord, whereas gamma aminobutyric acid and glycine neurons inhibit motoneurons leading to REM sleep with atonia. Animal models have shown that lesions in the brainstem nuclei, specifically the subcoeruleus nucleus, cause a REM sleep behavioural phenotype with increased muscle tone and abnormal excessive motor activities, resembling the dream-like behaviours of RBD.

The sleep stages show a regular sequence that starts with light sleep (N1 and N2), followed by deep sleep (N3) and that terminates with REM sleep. This type of sequence is called a sleep cycle, which lasts 60–90 min. The number of sleep cycles is age-dependent and comprises three to five cycles. As the night proceeds, the amount of deep sleep diminishes and the amount of REM sleep increases.

Figure 11.1 contains a hypnogram showing a sequence of nocturnal electrical brain activity or macrostructure of sleep.

Deep sleep (N3) is presumed to be responsible for consolidation of declarative memory, REM sleep for procedural and emotional memory. Animal experiments indicate that information accumulated throughout the day is replayed during the night. Slow-wave oscillation generated in cortical areas coordinates the replay in the hippocampus (sharp wave/ripple activity) and plasticity-promoting spindle activity in the thalamus [3, 4]. The reduction of NREM sleep, especially reduced slow-wave

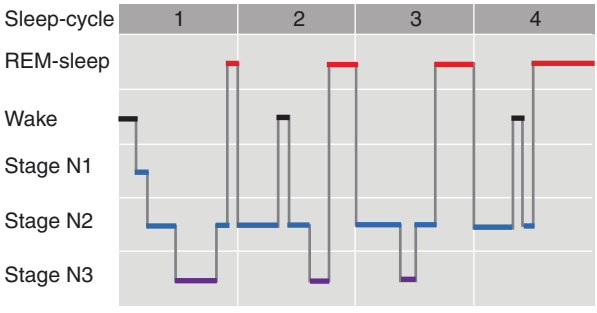

Fig. 11.1 Hypnogram of a healthy adult. (see Appendix Fig. 1). 1–4: quartiles of the time spent in sleep. REM: rapid eye movement; stage N1 and stage N2: light sleep; stage N3: deep sleep

sleep, may cause a decrease in memory consolidation and generate a feedback loop. Memory consolidation occurs normally after 3 h of sleep, but after a complete night of sleep, consolidation is much better. Daytime sleep lasting a few minutes consolidates memories, though 60–90-min naps lead to the best consolidation [4]. Sleep deprivation generally worsens encoding. The shorter the interval between learning and going to sleep, the better the recall.

Sleep Changes and Sleep Disorders in the Elderly

There are two main reasons for altered sleep in the elderly: (1) changes in sleep physiology with age and (2) comorbid conditions.

Changes in Sleep Physiology

In the elderly, the need for sleep in terms of hours needed does not change significantly, whereas the ability to get enough sleep changes. Sleep macrostructure, as presented in a hypnogram, shows a reduction in slow-wave sleep and REM sleep. Latency to slow-wave sleep (N3) and REM sleep is increased, and total sleep time (TST) is reduced. On the other hand, light sleep (N2) and wake after sleep onset are increased [5]. These changes occur mainly between the sixth and seventh decade of life in healthy humans [6]. Meta-analyses examining sleep changes in middle-aged people in their sixties found only small differences between this and younger age groups, i.e. the differences were rather small, insignificant and mainly concerned the circadian distribution [6]. Gender differences are reported, but the findings are conflicting [7].

Common Sleep Disorders in the Elderly

One of the most frequent comorbid sleep disorders is sleep apnoea (SA), mainly of the obstructive type. Obstructive SA (OSA) is characterised by apnoeas and hypopnoeas during sleep. Apnoeas and hypopnoeas lead to intermittent hypoxemia and sleep fragmentation. The apnoea–hypopnoea index (AHI), which indicates the number of apnoea–hypopnoea periods (> 10 s, desaturation >4%) per hour, is used as a measure of the severity of OSA. An AHI < 5/h is considered normal. An AHI of 5–15 events per hour is considered mild SA, an AHI of 15–0 events per hour is considered moderate SA, while severe SA shows 30 or more events per hour. The Sleep Health Heart Study reported clinically relevant AHI of >15 events per hour in 19% of people 60–69 years of age, 21% aged 70–79 and 20% aged 80–89 [8]. Various medications may further aggravated SA, e.g. sedatives and antidepressants. Immobility may destabilise the circadian rhythm and further lead to an increase in body mass index, which worsens SA. Continuous and intermittent hypoxemia and the reduction of slow-wave sleep due to apnoea-related arousals may enhance the

process of developing cognitive deficits leading to dementia. Patients with dementia have a high frequency of intermittent nocturnal hypoxemia [9] and a fivefold higher risk for OSA [10].

Patients with RLS have the urge to move their legs during periods of rest, especially in the evening and at night, to relieve uncomfortable or painful sensations in the calves, causing impaired sleep onset. Periodic leg movements during sleep in the majority of patients contribute to sleep disruption and a reduced quality of life. Secondary forms of RLS may be caused by iron deficiency, pregnancy and end-stage renal disease and associated morbidity, such as increased cardiovascular risk. RLS is the most frequent neurological sleep disorder that increases with age (up to 10% of the elderly in North America and Europe). Since patients with dementia are often not able to report symptoms, observable behaviours such as rubbing of legs or feet together, kicking, flexing against surfaces or as if pushing a gas pedal, stretching, crossing and uncrossing the legs or feet, and fidgeting may also be indicative of RLS [11].

A typical disorder of older age, RBD is most commonly seen in α-synucleinopathies like Parkinson disease, multiple system atrophy and LBD [12]. Its conversion rate into neurodegenerative diseases is 6.3% per year [13], but it has no major impact on sleep quality. RBD is characterised by the loss of physiological muscle atonia during REM sleep (REM sleep without atonia). Patients with RBD act out vivid dreams during REM sleep. RBD may be misdiagnosed on clinical interview alone in patients with LBD due to the high rate of nocturnal activity in these patients [2]. With a known prevalence of 76%, RBD should always be suspected in LBD patients. The REM Sleep Behavior Disorder Screening Questionnaire (RSBSQ) provides more evidence for the diagnosis [14], which requires video-polysomnography [15]. Since RBD is an important issue with a high potential for injury of patients and bed partners, and video-polysomnography is not broadly available, treatment for RBD should pragmatically be initiated based on RSBSQ results. RBD usually responds well to clonazepam, but clonazepam belongs to the benzodiazepines, which may worsen cognition and SA [16]. Melatonin is an alternative treatment for RBD without major adverse reactions [17].

People who are elderly frequently suffer from insomnia, which is very frequent in patients with all types of dementia [2]. Depression is a precursor for insomnia and vice versa. Insomnia with sleep maintenance problems in people >75 years without primary cognitive impairment increases the risk of cognitive decline [18].

Pathophysiology of Sleep Disturbances

It has been suggested that several mechanisms in sleep disturbances promote neurodegeneration. These mechanisms constitute increased generation and deposition of beta amyloid (Aβ) and reduced glymphatic clearance of Aβ. In addition, circadian dysfunction, sleep fragmentation, neuro-inflammation and the generation of oxidative stress via reactive oxygen species contribute to synaptic damage and neurodegeneration.

Neuronal damage may cause different sleep disorders, irrespective of the type of damage. This may explain why several types of sleep disorders may occur in the same individual and why the appearance and severity of sleep disorders change as neurodegeneration progresses.

The individual risk of developing dementia is related to several genetic factors, but emerging evidence has shown that lifestyle factors, such as sleep disturbance may also increase an individual's risk [19]. However, despite this appealing hypothesis, many unanswered questions remain. Most of the evidence about the relationship between sleep disturbances, cognitive decline, dementia and neurodegeneration derives from animal experiments, and observational, cross-sectional studies in humans. Importantly, these studies have provided insight into pathophysiological mechanisms linking sleep disorders, neuronal damage and cognitive decline with Aβ accumulation, glymphatic clearance and inflammation being the most recognised mechanisms [20–22].

Neurodegenerative dementia disorders are progressive diseases which may start with subjective cognitive impairment before developing into mild cognitive impairment (MCI) and finally dementia [23]. A study [24] examining the relationship between sleep, cerebrospinal fluid (CSF) tau and Aß, and neuropsychological results of patients with subjective cognitive impairment, MCI, mild Alzheimer's disease (AD) (Mini-Mental State Examination (MMSE) > 21) and severe AD (MMSE < 21) to those of healthy controls using polysomnography in the sleep analysis showed that TST, sleep efficiency, slow-wave sleep (N3) and REM sleep were significantly reduced in mild and severe AD. Mean TST for mild AD was 318.82 ± 44.16 min, in severe AD 252.93 ± 47.77 min and in controls 367.22 ± 60.93 min MMSE and the Rey Auditory Verbal Learning Test (RAVLT) results were significantly lower than in the other groups. A component analysis (Bartlett's test of sphericity), including sleep architecture (REM, N1, N3 and TST), CSF $A\beta_{42}$ levels, MMSE and RAVLT, was highly significant ($p < 0.001$), confirming that sleep fragmentation with reduced REM and N3 sleep is associated with Aβ pathology and with tau neurodegeneration. The changes of sleep structure in patients with subjective cognitive impairment show that these changes may be early markers of dementia [25]. However, sleep may not only be one factor in the neurodegenerative cascade culminating in cognitive decline and dementia, but neurodegeneration and the ensuing dementia itself change sleep, indicating a bidirectional relationship. Furthermore, these studies give proof to the relationship between sleep and cognitive impairment that has been described in recent years [25].

Tau protein and Aß42 in CSF show a circadian rhythm with high levels during daytime and low levels during the night [26]. Sleep fragmentation and the reduction of slow-wave sleep (N3) may cause an accumulation of these proteins via diminished glymphatic clearance during nighttime [21]. With the worsening of sleep structure and accumulation of amyloids, a vicious cycle is initiated that needs to be recognised early to interrupt its progression (Fig. 11.2).

Aggregation of Aβ begins about 20 years prior to onset of AD. Factors that promote progression of amyloid deposition are age, genetic predisposition (apolipoprotein E epsilon 4 (APOE4) and lifestyle (e.g. physical inactivity, diet and sleep).

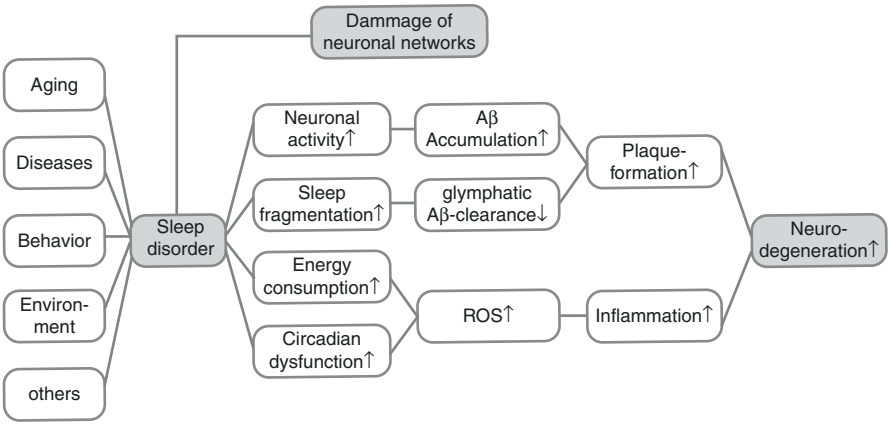

Fig. 11.2 Interaction of sleep and brain protein clearance

Deposition of Aβ starts in the entorhinal cortex and spreads to the hippocampus and the temporal lobe [3]. These structures are important for cognitive and motor functions.

Another major cause for the changes in sleep pattern in the elderly is the dampening of the circadian rhythm. This rhythm is associated with the circadian melatonin expression, which among other external factors (also called zeitgebers) is dependent on exposure to light, specifically the blue light spectrum. The low light exposure that many elderly and people with dementia live under is the result of reduced outdoor activities and low light intensity levels in homes or senior homes. This effect may be further deteriorated by the loss of melanopsin retinal ganglion cells due to amyloid deposition, also in the retina and the optic nerve in AD [27].

Comorbid diseases such as sleep-related breathing disorders and depression may contribute to the development of dementia. Patients with OSA have similar changes in sleep pattern as patients with dementia, e.g. slowing of slow-wave sleep and REM sleep, sleep fragmentation and a reduction in sleep spindles [28]. Furthermore, epidemiological studies in humans identified untreated OSA as an independent risk factor for dementia [29]. Animal studies have shown that intermittent hypoxia—which is a frequent sequela of sleep apnoea—causes an increase of Aß [30]. In a study investigating Aß1–40 and Aß1–42 in patients with severe OSA (AHI = > 30/h), moderate OSA (AHI 5–30/h) and controls (AHI < 5/h) Aß1–40 was significantly higher in the severe OSA group (age, sex, obesity, diabetes, hypertension and chronic heart failure were ruled out) and correlated with nocturnal hypoxemia [31]. No group differences were found for Aß1–42. Other studies found increases in Aß1–40 and Aß1–42 [32]. A longitudinal study of 2.52 ± 0.51 years using amyloid positron emission tomography (PET) imaging compared elderly patients with normal cognition, patients with MCI and AD with OSA and without OSA. In

cognitively normal people and MCI groups, patients with OSA experienced a faster annual increase in florbetapir (a PET tracer with affinity to amyloid plaques) uptake and decrease in CSF Aβ-42 levels, as well as increases in CSF T-tau and P-tau compared with participants without OSA, indicating faster accumulation of AD pathology. In the AD group no significant changes in biomarkers were observed [33]. OSA-induced pressure changes in the upper airway and the brain may cause a reduced glymphatic clearance [34] of these proteins.

Insomnia and sleep fragmentation are also considered to be associated with an increased risk for AD. This association is bidirectional as AD leads to sleep fragmentation and insomnia. To explore this relationship in detail 615 (36.5%) middle-aged, cognitively unimpaired individuals from the Alzheimer Family Study with insomnia were compared to those with no insomnia [35]. Patients underwent neuropsychological testing, MRI, diffusion weighted imaging, voxel-based morphometry, APOE genotype and the World Health Organisation's World Mental Health Survey Initiative version of the Composite International Diagnostic Interview for the assessment of insomnia. APOE-e4 carriers with insomnia displayed lower grey matter volumes in regions that also affect patients with AD. This finding underpins the importance of insomnia in the development of AD. Diffusion tensor imaging revealed that some white matter tracts were affected.

Furthermore, patients with long-standing insomnia aged 50–65 years had a higher risk of dementia (OR, 5.22; 95% confidence interval (CI), 2.62–10.41) than over 65-year-old patients without insomnia (HR, 2.33; 95% CI, 1.90–2.88). In addition, the use of high dose hypnotics with a long half-life increases risk of dementia [36].

In a population-based Italian study, 86 out of 750 people over 65 years of age were classified as having dementia according to Diagnostic and Statistical Manual IV. Of them, 84.7% reported insomnia, 26.2% snoring and apnoeas, 25.7% nocturnal leg movements and 30.6% excessive daytime sleepiness (EDS). EDS was the only predictive factor for cognitive deterioration [37].

Another sleep questionnaire study with almost 500 patients with early stages of LBD, AD and Parkinson's dementia found insomnias in 29.9%, nocturnal cramps in 24.1%, EDS in 22.6%, RLS in 20.7% and RBD in 18.5% of all patients. Patients with Alzheimer's dementia had less sleep problems than the other forms [38].

In patients >55 years of age with MCI of a mean duration of 5.4 years, 29% developed AD dementia. In people with comorbid affective disorders the risk of developing AD dementia was reduced significantly (odds ratio (OR) 0.35, $p < 0.001$). Symptoms of depression and anxiety showed the same tendency [39].

The cited studies show the relevance of various sleep disorders as comorbid disorders as well as possible predictors for neurodegenerative diseases and dementias in particular.

Figure 11.3 presents putative mechanisms involved in the complex interplay of sleep disorders and neurodegeneration.

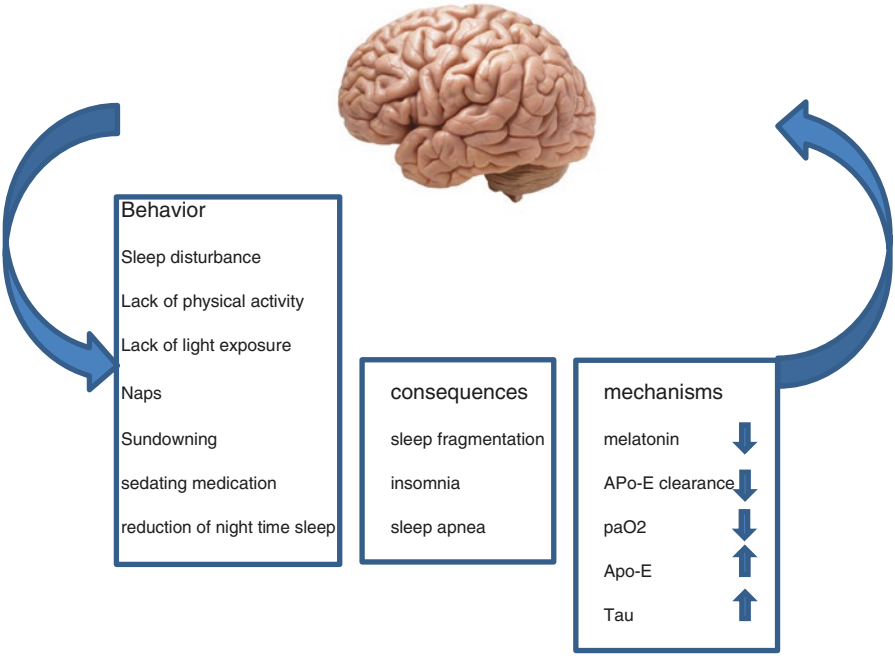

Fig. 11.3 Simplified presentation of putative mechanisms linking sleep disorders and neurodegeneration. *ROS* reactive oxygen species; *Aβ* beta amyloid; ↑: increase; ↓: decrease

Sleep in Patients with Dementia

Sleep and the circadian rhythm are disturbed in most patients with dementia regardless of the subtype of dementia [2]. Furthermore, these disturbances worsen as the disease progresses. Rest activity rhythms may be stable in the early stages of dementia but deteriorate when the disease progresses. Patients with dementia often display fragmentation in their sleep-wake patterns, such that they frequently wake up during the night and frequently fall asleep during the day. In end-stage dementia there is a complete breakdown of sleep wakefulness regulation in which sleep occurs only sporadically across the 24-h day. The cause of this breakdown is a progressive neuropathological change in brain centres involved in sleep regulation [40]. In advanced dementia patients often show little evidence of any rhythmicity.

However, in the early stages of dementia, the prevalence and type of sleep disturbances differ somewhat between subtypes of dementia. Importantly, most patients with dementia usually suffer from a mixture of sleep disorders at the same time.

Sleep Disturbance and Comorbidities in Different Types of Dementia

Alzheimer's Disease (AD)

Sleep disturbances in patients with AD are qualitatively similar to those seen in older persons. However, the severity of the changes is usually greater, and REM sleep has specific alterations. The prevalence of any sleep disorder is estimated to range from 30 to 60% [2]. Sleep is usually more disrupted, with an increasing amount of wakefulness during the night, resulting in shorter TST, reduced sleep efficacy and a lower percentage of slow-wave sleep. Furthermore, characteristics of sleep stage N2, such as k-complexes and spindles become poorly formed with lower amplitude and lower frequencies. These alterations in sleep quality deteriorate as the dementia progresses.

The main change in sleep in AD is the intrusion of wakefulness into sleep time. Furthermore, REM sleep diminishes very early in patients with amyloid deposition and might be a very early biomarker for impending dementia [25]. Other sleep disorders in mild AD patients are sleep disordered breathing (54%), EDS (45%), insomnia (48%), REM sleep behaviour disorder (21%) and RLS (6%) [2]. Since Aβ plaques are also present in the retina and the optic nerve, circadian rhythm may be affected additionally in these patients.

A further important issue in sleep disturbance in patients with AD and other types of dementia is sundowning, which occurs in 2.4–66% of patients with AD [41]. Not all patients with dementia sundown, but nearly all patients with sundowning have dementia [42]. Sundowning is diagnosed clinically. Signs and symptoms of sundowning cover a wide variety of cognitive, affective and behavioural patterns. Furthermore, the abnormalities are usually temporal, with worsening of symptoms in the late evening or in the night. The time course of sundowning allows differentiation from delirium. Although the exact cause of sundowning is unknown so far, both delirium and sundowning seem to share some common risk factors [43]. Unfortunately, there is very little research on sundowning in terms of genesis, prognosis and treatment [44, 45]. Therefore, treatments focused on prevalent clinical signs and symptoms are discussed in more detail elsewhere.

Sleep in Patients with Vascular Dementia

About 80% of patients with mild vascular dementia show any sleep disorder [2]. The most frequent disorder is OSA, with a frequency of more than 70%. OSA causes daytime sleepiness, insomnia, agitation and cognitive and functional impairment. The comorbidities of patients with vascular dementia are insomnia disorder (67%), EDS (58%), REM sleep behaviour disorders (25%) and RLS (5%) [2].

Sleep in Patients with Frontotemporal Dementia

Sleep disorders are present in about 70% of patients with early frontotemporal dementia (FTD). These patients more often show an advancement of the circadian rhythm. Furthermore, sleep disordered breathing (68%), EDS (64%), insomnia (48%) and RLS (8%) are frequent findings [2]. A study with 14 FTD patients confirmed significantly increased sleep duration measured by actigraphy at night and more EDS than the caregivers who served as controls [46]. In addition, a small study compared sleep patterns of patients with FTD, AD and healthy controls with polysomnography [47]. In this study cognitive impairment of patients with AD and FTD was comparable. Also, sleep complaints did not differ between patient groups, but sleep parameters and sleep macrostructure were better preserved in patients with AD.

Sleep in Patients with Lewy Body Dementia

The prevalence of any sleep disorder reaches nearly 90% in patients with LBD. Patients show sleep disordered breathing (76%), EDS (71%), insomnia (67%), REM sleep behaviour disorder (48%) and RLS (0%). According to the revised criteria for the clinical diagnosis of probable and possible LBD [48] sleep disturbance is a core clinical feature in REM sleep behaviour disorder and a supportive feature with hypersomnia.

Assessment of Sleep Disorders in Patients with Dementia

Subjective Measures of Sleep and Wakefulness

Based on current guidelines the management of sleep disorders in patients with and without dementia does not differ in principle [49]. However, cognitive and behavioural symptoms in patients with advanced dementia often require individualised diagnostic and treatment procedures.

The basic diagnostic measure in any patient with presumed sleep disorders is to take a complete history on sleep habits and daytime functioning. Table 11.2 provides a list of relevant questions to ask [49]. Contributing factors should also be assessed, including depression and anxiety, pain, comorbidities that cause awakenings, prescribed medication with an impact on sleep, living and sleep arrangements, degree and frequency of physical activity, including outdoor activity, daytime structure and exposure to light during the day and the night. Of note, in patients with moderate to advanced dementia, a proxy should also always be inquired too, because some patients with dementia may lack insight or may not be able to remember details about their sleeping patterns.

Table 11.3 shows results from pharmacological treatment trials of sleep disorders in patients with dementia.

Table 11.2 Relevant questions when taking a complete history on sleep habits and daytime functioning

Question	Presumed sleep disorder
What time do you normally go to bed at night?	Poor sleep hygiene, circadian rhythm disturbance REM sleep behaviour disorder
What time do you normally wake up in the morning?	Circadian rhythm disturbance, depression
Do you often have trouble falling asleep at night?	Insomnia with difficulties in terms of sleep initiation, depression
About how many times do you wake up in the night?	Insomnia with difficulties in terms of sleep maintenance, nocturia, somatic disorder
If you do wake up during the night, do you usually have trouble falling back asleep?	Insomnia with difficulties in terms of sleep maintenance, depression
Does your bed partner say that you frequently snore, gasp for air or stop breathing?	Sleep disordered breathing, sleep apnoea
Does your bed partner say that you kick or thrash about while asleep?	Parasomnia, restless leg syndrome, REM sleep behaviour disorder
Are you sleepy or tired during much of the day?	Clinical sequelae of a relevant sleep disorder, excessive daytime sleepiness
Do usually take one or more naps during the day?	Clinical sequelae of a relevant sleep disorder, excessive daytime sleepiness
Do you usually doze off without planning to during the day?	Clinical sequelae of a relevant sleep disorder, excessive daytime sleepiness
How much sleep do you need to feel alert and function well?	Subjective sleep need
Are you currently taking any medication or other preparations to help you sleep?	Insomnia, use of hypnotics

Table 11.3 Results from pharmacological treatment trials of sleep disorders in patients with dementia

Drug name	Doses applied in trials	Trial results for disturbed sleep in dementia and comorbid disorders	References
Melatonin	10 mg 2.5 mg slow release	Efficacy for disturbed night sleep and comorbid RBD	[50, 51]
Trazodone	50 mg	Efficacy for disturbed night sleep	[52]
Mirtazapine	15 mg	Not indicated due to lack of effect	[53]
Modafinil	200 mg	Not indicated due to lack of effect and side effects (EDS, apathy, severe side effects)	[54]
Benzodiazepines	Multiple doses	Not indicated due to lack of effect	[55]
Suvorexant	Multiple doses	Not indicated due to lack of effect	[56]

The next step is to document the above-mentioned sleep habits in a sleep diary for about 2 weeks by a proxy. This type of a diary provides pivotal basic information, and it is needed to evaluate changes over time due to therapeutic interventions.

Furthermore, there are many validated retrospective questionnaires available to assess subjective sleep. However, despite the current lack of questionnaire validated

in patients with dementia, it appears possible to apply retrospective questionnaires in patients with MCI or with mild dementia. In moderate and severe dementia, the application of observational tools is meaningful.

Scales and questionnaires typically applied to evaluate sleep are the Pittsburgh Sleep Quality Index [57] for the measurement of sleep quality and the Epworth Sleepiness Scale [58] to assess daytime sleepiness. However, despite a lack of validation of these scales in patients with dementia, using them if the dementia is mild appears reasonable [59].

In patients with more advanced dementia, behavioural symptoms often preclude the application of a questionnaire. Of note, a validated and meaningful observational tool to assess daytime sleepiness in older subjects with dementia of any stage is the Epworth Sleepiness Scale [60].

Proxies may report additional sleep disturbances with an obvious impact on daytime function and wakefulness in the night, reflecting also caregiver burden. However, there is no consensus on the best way to measure sleep disturbances in people with dementia.

Objective Measures of Sleep and Wakefulness as Assessed by Polysomnography

Sleep and wake states are usually measured by electroencephalography (EEG), electrooculography and electromyography. The last two measurements allow detection of rapid eye movements and muscle atonia that represent REM sleep. Electrical brain activity is the gold standard of the objective measurement of sleep [61].

Polysomnography (PSG) measures EEG, eye movements, muscle activity, breathing, blood oxygenation, snoring, body position and leg movement. PSG performed in a sleep laboratory is used to confirm the diagnosis of sleep disorders, e.g. sleep-related breathing disorders, parasomnias, sleep-related epileptic seizures and periodic limb movement disorders. In subjects with insomnia and RLS, PSG is not the first-line diagnostic procedure and used only in unclear and complex clinical situations in need of further clarification.

PSG provides a great amount of useful information about sleep, but it is expensive and difficult to obtain. Importantly, it is uncomfortable for the patient and therefore only useful in mildly demented patients [62]. PSG requires analysis and interpretation based on special expertise in sleep medicine.

Actigraphy, a method designed to profile sleep-wake behaviour over days and weeks, is cost effective and much more convenient than full PSG. Actigraphy results correlate highly with PSG data. Actigraphy records movement using a watch-like device worn on the non-dominant hand over a given threshold [62]. An event marker is used to score bedtime, awakenings during the night, getting up time in the morning, daytime sleep and also napping. These data can be used to estimate sleep-wake patterns in all subjects with dementia irrespective of disease severity.

The steering committee of the American Academy of Sleep Medicine recommends the routine use of actigraphy and sleep diaries to assess irregular sleep-wake rhythms in dementia and RLS [63].

Treatment

Non-pharmacological Treatment (Table 11.4)

The treatment of sleep disorders in people with dementia is similar to that in individuals without dementia. However, primary and secondary sleep disorders must be identified before any treatment is initiated.

Non-pharmacological interventions are the first choice of treatment for sleep disorders, also in patients with dementia. However, evidence for this approach is scare since there is a lack of large studies of good quality [64]. But the advantage of a non-pharmacological approach to sleep disorders is that interventions are free of any adverse reactions, which is why they should be applied despite the lack of evidence.

The first step is to search for and to remove personal or environmental factors with a negative impact on sleep. Optimal sleep hygiene (going to bed at regular sleep times, avoiding heavy meals and strong physical activity prior to bedtime, using the bedroom exclusively for sleep) constitutes the basic procedure before any other treatment is initiated. Additionally, regular daily routines, physical activity, bright light exposure and social interactions improve daytime alertness and nighttime sleep [65]. For example, a combination of walking and light exposition >4 days/week over 6 months in AD dementia patients improved sleep time measured by actigraphy [66]. A recent meta-analysis considering non-pharmacological interventions in patients with dementia and sleep disorders concluded that multifactorial approaches are most likely to be successful. However, high quality intervention trials and strong evidence for any non-pharmacological intervention are not available. Further studies are warranted. An on-going study called the DISCO trial aims to show if remote online cognitive behavioural therapy for insomnia intervention can improve cognition [67].

Light exposure interventions, which have a definite biological action, are looked upon as a non-invasive, low-cost therapy [50]. However, study results are inconsistent due to the high heterogeneity of the studies [64]. Furthermore, light exposure is applied over a prolonged period of time (typically 30 min or more daily), causing a considerable treatment burden of time, effort and organisation to control adherence. Adherence (to any therapy) has a major impact on health, well-being and quality of life and should not be ignored [68].

Behavioural treatments like cognitive behavioural therapy for insomnia or sleep restriction require sufficient compliance by the patient and therefore may only be applied successfully in people with mild dementia.

Table 11.4 Non-pharmacological treatment for sleep disorders

Sleep hygiene
Daytime activity
Social interaction
Bright light exposure
Cognitive behavioural therapy
Complementary alternative procedures

Treatment of patients with various types of dementia with OSA with continuous positive airway pressure (CPAP) breathing is feasible if dementia is mild, and if patients can tolerate and adhere to the therapy. Effective PAP treatment with different modifications (CPAP, bi-level PAP, automatic PAP) may remove daytime sleepiness and improve physical and cognitive function [59].

Alternative medicine procedures like acupuncture and acupressure, a child-like robot for older women or taking a bath before bedtime were investigated in small studies with small to moderate effectiveness [69]. Double-blind, randomised trials are difficult to perform in patients with dementia and are therefore not available. Nevertheless, non-pharmacological interventions should always be used irrespective of evidence, since individual effectiveness is possible and adverse reactions are nearly absent [70].

Pharmacological Treatment

Pharmacological treatment for sleep disorders must be applied with caution in patients with dementia, who frequently have many co-medications and can tolerate only lower doses due to their age and a general tendency to be more sensitive in terms of drugs affecting the brain. Hypnotics such as benzodiazepines and benzodiazepine receptor inhibitors are contraindicated because they can cause nocturnal falls and delirium. Many antidepressants with sleep-inducing properties have anticholinergic properties and can cause delirium. Only very few evidence-based studies targeting sleep have been performed. Given the importance of sleep in people with dementia the need for such studies is high.

Treatment with melatonin, up to 10 and 2.5 mg slow release has no effect on sleep disorders in AD dementia [52]. In an additional study, melatonin [50] improved sleep onset latency and TST, cognitive and emotional performance and daily sleep-wake cycles. Side effects can be a depressed mood and withdrawal behaviour. In combination with bright light, 2500 Lux reduced the side effects of melatonin.

A meta-analysis on the efficacy of melatonin showed a significant prolongation of TST but sleep efficiency did not improve (McCleery). Of note, the cut-off value to constitute normal sleep efficiency was 85% and may be inappropriate for patients with dementia.

Trazodone 50 mg improves TST and sleep efficiency but does not have an effect on sleep fragmentation and wake after sleep onset [52]. Patients who did not use trazodone had a 2.6-fold faster decline on the MMSE in this 4-year retrospective study. Long-term use of trazodone therefore seems to be promising [71].

A placebo-controlled study using 15 mg mirtazapine at 9 pm for 2 weeks in patients with AD with sleep disturbance as assessed by actigraphy showed no beneficial effects on sleep. Instead patients on mirtazapine were sleepier during daytime than those on placebo. Due to the very low number of patients (mirtazapine (n = 8), placebo (n = 16)) the study's findings should be interpreted with caution [53].

Unfortunately, there is no literature on the impact of cholinesterase inhibitors, which are frequently used for treatment of cognitive decline, on sleep in patients with dementia, but they may cause lucid, disturbing dreams [72]. Dosing in the morning may improve such side effects.

Medications for EDS in patients with dementia have not explicitly been studied. In two studies reporting on apathy in patients with AD, one study had 23 patients with mild to moderate dementia who received 200 mg of modafinil in addition to cholinesterase inhibitors. Modafinil did not improve the activities of daily life or apathy compared to the patients on placebo [54]. In the other study, a 6-week double-blind, placebo-controlled multi-centre randomised trial with 60 patients, 29 received 20 mg methylphenidate and 31 placebo. Apathy scores improved in two out of three efficacy outcomes and showed significant improvement [73].

Modafinil may cause agitation and hallucinations in patients with DLB [74]. In a meta-analysis on the use of benzodiazepines in patients with dementia (i.e. meeting the authors criteria for dementia) 18 out of 657 articles were included. Benzodiazepines were used in 8.5–20% of all patients. Lorazepam was the most frequently used medication (35%). Benzodiazepines were found to cause deterioration in cognition. There was no effect at all on sleep problems [55]. Another issue regarding benzodiazepines is risk of daytime sleepiness, increased risk of falls and a paradoxical reaction in some elderly, leading to agitation, depression and anxiety.

A review by Schroeck et al. [56] on safety and the efficacy of sleep medicines in older adults highlighted suvorexant as a possible therapy with few adverse events and only mild sedation during daytime. However, the results have not been confirmed in patients with dementia.

There are no studies investigating the effect of drugs for the treatment of RBD in patients with dementia. Since melatonin is among the first-line medications for RBD and has little or no side effects, it may be tried [51].

Conclusion

Growing evidence derived from large epidemiological studies suggests that any sleep disturbance in humans is associated with an increased risk for the development of cognitive decline or dementia. The ORs range from 1.3 to 2.5 and vary between the distinct types of sleep disorders.

Further, animal studies yield compelling evidence that deposition of βA, neuroinflammation and reactive oxygen species cause synaptic dysfunction and neurodegeneration. It is tempting to hypothesise that the treatment for sleep disorders in middle-aged people without cognitive impairment may prevent the development of cognitive decline or dementia. However, to prove this hypothesis large prospective randomised controlled trials are needed. However, this type of trial would involve leaving the sleep disorders of many patients untreated. Since effective treatments for sleep disorders are available, such a trial appears to be unethical. Nevertheless, the available evidence warrants vigilance on the part of the clinician to be attentive

to possible symptoms and signs of sleep disorders and to treat them with the intention to prevent cognitive decline.

Only few studies have rigorously investigated the occurrence of specific sleep disorders in patients with dementia. However, these studies have shown that sleep disorders are very common in people with dementia and that one or more comorbid sleep disorders in the same patient is more the rule than the exception. Sleep disorders can have detrimental effects on patients with dementia and should be treated.

A careful evaluation should be performed before treatment of sleep disorders is started. Several validated questionnaires for the assessment of sleep disorders are available and should be applied in patients with MCI or mild dementia. In patients with advanced dementia an interview of proxies is required. The use of diagnostic tools like polysomnography, polygraphy and actigraphy should be used in patients with dementia who can cooperate. In most cases, this means that the investigations are limited to patients in the early stages of dementia and in MCI.

The multifactorial aetiology and co-existence of various sleep disorders in people with dementia imply that the use of complex multimodal treatment strategies is required. Non-pharmacological treatments for sleep disorders show no adverse effects in patients with dementia and are first-line treatments (modification of the environment, sleep hygiene, bright light therapy, reduction of time in bed, activation during daytime and education of the caregiver) despite the lack of convincing evidence available. Furthermore, the evidence for pharmacological treatment of sleep disorders in patients with dementia is also very poor since large randomised controlled trials with sufficient duration are scarce. Furthermore, the side effects of this type of pharmacological treatment are common and may be serious, warranting caution.

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