Dementia and Sleep

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KEYWORDS

• Dementia • Sleep • REM sleep behavior disorder (RBD)
• Irregular sleep-wake rhythm (ISWR) • Sundowning • Insomnia • Hypersomnia
• Sleep-disordered breathing

KEY POINTS

- Sleep disorders are common in patients with dementia and are a primary trigger for institutionalization.
- Treatment of sleep disorders in patients with dementia can produce improved cognitive function and reduce caregiver distress.
- Treatment of sleep disorders in patients with dementia should include consideration of a broad spectrum of factors that can affect sleep and wake cycles, including caffeine consumption, the effect of medications, and mood.
- Agitation and delirium can be a sign of obstructive sleep apnea (OSA) and treatment of OSA can produce complete resolution of symptoms in some cases.
- Dementia associated with synuclein disorders (including Lewy body dementia, Parkinson's disease with dementia, and multisystem atrophy) is associated with rapid eye movement sleep behavior disorder (RBD). RBD-like symptoms can also be seen in sleep-disordered breathing, and a polysomnogram study is necessary to exclude OSA as a cause or contributor to symptoms.
- Irregular sleep-wake rhythm is common in Alzheimer's dementia and treatment should focus on behavioral interventions rather than pharmacologic management.
- Sundowning is a nonspecific descriptor. The possibility that pacing and wandering may represent forms of restless leg syndrome should be considered.
- Whether sleep-disordered breathing and/or sleep deprivation is a risk for dementia is controversial and is an active area of investigation.

INTRODUCTION

Sleep disturbances are common in patients with dementia, affecting from 25% to 80% of patients depending on the dementia subtype.[1] Although sleep disturbances are also common in the elderly in general, the impact of sleep disorders in dementia can be greater. Sleep disturbances can magnify the cognitive impairments and mood

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dysregulation that patients with dementia already face, and can be a major reason for loss of function.[2,3] Sleep disturbances also create psychological, physical, and financial burdens for caregivers.[4–7] In addition, sleep disturbances a primary reason for the institutionalization of patients with dementia, and can be a more common trigger for institutionalization than even the cognitive problems.[3,8–11]

Degenerative dementias affect brain systems that are critical for regulation of the sleep-wake cycle. Depending on the areas of the brain affected in a specific dementia, different patterns of sleep disorder can result. Recognizing which specific sleep disorder might be occurring in a patient, based on a recognition of how particular dementias affect sleep systems, can lead to better targeting and treatment of sleep disorders. This article reviews specific sleep disorders that are seen more commonly in specific types of dementia, and the treatment of these disorders. It also offers a practical approach to addressing other external factors that may be affecting patients with sleep-wake problems and dementia, and how these factors should be addressed with the vulnerabilities of the patient with dementia in mind. When evaluating a new patient with apparent cognitive problems, the impact of a sleep disturbance on the presentation needs to be inquired about carefully. In rare, but important, cases, a sleep disturbance such as obstructive sleep apnea (OSA) can lead to agitation, cognitive impairment, and delirium that is completely reversible with treatment. Evaluation and treatment of sleep and wake disturbances in patients with all forms of cognitive impairment and dementia can improve patient function and, in many cases, address a major cause of distress for caregivers and families.

DEMENTIA, DEMENTIA SUBTYPES, AND ASSOCIATION WITH SLEEP DISORDERS

Dementia is common and increasing in prevalence. The prevalence and incidence of dementia is age related and doubles with approximately every 5 years after the age of 65 years. Estimates based on a number of studies generally suggest that approximately 2% of the population has dementia between the ages of 65 and 75 years, 10% between 75 and 85 years, and 35% of people older than 85 years. The prevalence of dementia is increasing as the general population ages and lives longer. In the World Health Organization 2012 report,[12] it was estimated that the number of people with dementia in America, Europe, Asia, and worldwide would nearly double by 2030 and triple by 2050. Approximately 4 million people have dementia in North America and this is expected to nearly triple to 12 million by 2050. An increasing number of dementia subtypes have been recognized in recent years. Alzheimer's disease (AD) is the most common dementia, especially in old age. However, in patients younger than 60 years, frontal temporal lobe dementia (FTLD) is the most common, and, in patients from the ages of 60 to 70 years, it can be as common as AD. Dementia with Lewy Bodies (DLB) is thought to account for about 20% of all dementia. Approximately 40% of patients with Parkinson disease (PD) have dementia, and 80% of patients with PD develop dementia before death. Vascular cognitive impairment is sometimes cited as the second most common cause for dementia overall. It comprises a significant proportion of dementia, given that the lifetime risk for stroke is equal to that of AD, and about one-third of elderly individuals have silent cerebrovascular disease.[13]

As the underlying genetics and neuropathology of dementia-related diseases have become better known, there has been a move toward classification based on the underlying disorder (**Table 1**). The underlying neuropathologic process can be relevant to understanding some of the sleep problems associated with dementia, and knowledge of these associations can help to raise awareness of specific sleep-related issues

Table 1
Basic dementia subtypes: overview

Dementias associated with parkinsonism

- **DLB**
  - Synuclein neural inclusions (more cortical vs PDD)
- **PDD**
  - Synuclein neural inclusions (less cortical vs DLB)
- **Multisystem atrophy**
  - Synuclein glial inclusions
- **PSP**
  - Tau neural inclusions in 4-repeat form, especially affecting brainstem
- **CBD/CBS**
  - Tau inclusions in 4-repeat form, with astrocytic plaques, oligodendroglial coiled bodies, threadlike lesions, achromatic neurons
  - Syndrome is also seen with PSP and C17-TDP43 progranulin deficiency
- **FTD-parkinsonism**
  - PD with FTD most commonly seen in familial genetic forms of FTD: FTD17-Tau, C17-TDP43 progranulin deficiency, C9orf72
- **Vascular dementia with parkinsonism**
  - Typically crural parkinsonism, gait apraxia, no tremor

FTLD

- **Behavioral variant FTLD**
  - 48% Tau inclusions (sometimes Pick bodies, occasional CBD)
  - 48% TDP43 (Tar DNA binding protein), ubiquitin positive inclusions. Hippocampal sclerosis common
  - 5% fused in sarcoma protein RNA binding protein, ubiquitin positive inclusions, onset usually early before age 50 y (30s–40s)
  - 10%–20% of FTLD is autosomal dominantly inherited. Each of the following account for 5%–10% of familial cases:
    - FTLD17-Tau; 100% penetrance; early onset (30–60 y)
    - C17-TDP43 with progranulin deficiency; lens-shaped neural inclusions, variable penetrance, mean onset age 62 y
    - C9orf72-TDP43; hexanucleotide repeat with RNA, can have ALS or family history of ALS
- **Language variant: progressive nonfluent aphasia**
  - Tau in most, TDP43 in 20%. Can be seen with PSP, CBD, FTLD-TDP 43 progranulin, and ALS
- **Language variant: semantic dementia**
  - TDP43

Vascular dementia

- **Multi-infarct dementia**
  - Large complete infarcts in cortex, subcortical areas
- **Strategic infarct dementia**
  - Infarct of angular gyrus, thalamus, hippocampal branch PCA artery, anterior choroidal artery
- **Subcortical ischemic vascular dementia**
  - Leukoencephalopathy, should also have at least 1 lacune

Dementia with Alzheimer's features

- **Alzheimer's dementia**
  - Tau in 3-repeat form causing inclusions (neurofibrillary tangles) and amyloid accumulation causing β-amyloid plaques
- **Language variant: logopenic progressive aphasia**
  - Alzheimer's features most common, occasionally TDP-43
- **Posterior cortical atrophy**
  - Alzheimer's features most common, occasionally CBD
- **Mixed dementia**
  - Alzheimer's features and vascular disease

ALS-associated dementia

- **15% patients with FTD develop ALS; many with ALS develop FTD**
  - Familial ALS-FTD most commonly caused by C9orf72-TDP43
  - 50% of ALS have dysexecutive syndrome, may not have FTD

Abbreviations: ALS, amyotrophic lateral sclerosis; CBD, corticobasal degeneration; CBS, corticobasal syndrome; FTLD, frontal temporal lobe dementia; FTD, frontotemporal dementia; PSP, progressive supranuclear palsy.

that may be more common in particular dementia syndromes. In later sections each sleep disorder type will be considered individually in more depth. But here a few of the most prominent sleep problems and the associations of these sleep problems with particular types of dementia are noted. Dementias that have synuclein inclusions, sometimes also referred to as synucleinoptahies, are associated with rapid eye movement (REM) behavior disorder. Synucleinopathies include, DLB, Parkinson's disease with dementia (PDD), and multisystem atrophy. The synucleinopathies are also more often associated with disorders of arousal, and can more commonly have reduced responsiveness periods, and hypersomnia. Parkinson-related dementias have an increased prevalence of restless leg syndrome (RLS) and periodic limb movements. Progressive supranuclear palsy is associated with particularly prominent insomnia, likely caused by several factors including difficulties with swallowing, rigidity, and nocturia, as well as underlying changes in brain-related sleep mechanisms that are more affected in that disease process. Alzheimer's dementia is the prototype dementia affected by an irregular sleep-wake rhythm, and this is thought to be caused by dysfunction and lack of coordination of the circadian rhythm mechanisms of the brain. Vascular dementia is associated with obstructive sleep-disordered breathing (SDB). Although SDB may be more common in vascular dementia, SDB is generally common in elderly patients, and can be seen across all patients with dementia. Patients with dementia of the moderate to severe stage may be more susceptible to the phenomenon commonly described as sundowning, characterized by increased agitation and sometimes even hallucinations that occur in the late afternoon or evening periods. A variety of factors can contribute to this phenomenon in the specific dementias. Dementia subtypes such as AD, vascular dementia, and DLB/PDD are associated with more significant deficiency in cholinergic systems that can contribute to anxiety and agitation, and cholinesterase inhibitor agents can be helpful for neuropsychiatric symptoms in those patients. FTLD is often associated with a more marked deficiency of the presynaptic serotonergic systems, and medications that increase serotonin may be especially effective in improving neuropsychiatric symptoms in these patients, but sometimes cholinergic medications make them worse. Changes in electroencephalography (EEG) and sleep architecture have been studied in relation to specific dementias. For example, progressive supranuclear palsy (PSP) is associated with the most marked loss of REM sleep compared with other dementias. In AD, sleep spindles and K complexes deteriorate more than in other dementias.

Table 2 summarizes the specific sleep-related symptoms that may be most prevalent with particular dementia types and the major changes in sleep architecture that have been observed. In the sections that follow the individual sleep disorders including RBD, Irregular sleep wake rhythm (ISWR), Sundowning, SDB, hypersomnia, restless leg syndrome (RLS)/periodic Limb movements of Sleep (PLMS), and issues of sleep encountered in nursing homes are discussed.

SPECIFIC SLEEP DISORDERS AND DEMENTIA

REM Sleep Behavior Disorder

In REM sleep behavior disorder (RBD), patients briefly act out their dreams because of the loss of normal musculoskeletal inhibition during REM sleep. Dream content is often altered and patients report dreams in which they are being chased by people they do not know or attacked by animals. The patients may act out dreams with fighting or running away, and injuries to self or bedpartners frequently occur. To diagnose RBD definitively, an overnight polysomnogram with video recording is necessary. This can be important to rule out other underlying disorders that can mimic RBD, such

as parasomnias or vivid dreams caused by OSA that would require different treatment. During the polysomnogram, patients with RBD may have episodes of complex motor activities in phasic REM or loss of REM atonia.

The full pathophysiology underlying RBD is not completely understood,[14] but it is likely caused by loss of the normal inhibitory mechanisms in REM sleep and excessive motor drive during REM. In animal models, lesions to the perilocus coeruleus region of the cat, and the sublateral dorsal nucleus in the rat, can result in complex behaviors in REM, and it is thought that in humans most RBD is likely to be related to disease affecting the analogous pericoeruleus region located in the human pontine tegmentum. RBD has been found to occur commonly in association with degenerative diseases that have synuclein disorders, in particular when that disorder affects the pontine region. The pericoeruleus region sends glutaminergic projections to the medullary magnocellular reticular nucleus, and this in turn activates glycinergic neuron projections that inhibit anterior horn cell spinal neurons. When pericoeruleus regions are affected by synuclein disease, it is thought that the spinal neurons could become less inhibited, and allow patients to act out their dreams.

In a series of patients with RBD who had dementia and/or parkinsonism, 97% (35/36) had an underlying synucleinopathy. In contrast, in 300 cases of autopsy confirmed non–synuclein-based neurodegenerative disorders, performed by the same group, none had a history of dream reenactment.[14] RBD can therefore sometimes be helpful in the differential diagnosis of dementia disorders. If patients with dementia have RBD, they are more likely to have a synucleinopathy, such as DLB, compared with another dementia such as AD, or those in the FTLD category. The frequency of RBD in the various types of synucleinopathies has been estimated to range from 50% to 80% for DLB,[15] 30% to 60% for PD,[16,17] and 80% to 95% for multisystem atrophy.[18,19] It has been suggested that DLB affects the lower brainstem structures earlier in the disease compared with PD, and this may account for RBD being more prevalent in DLB compared with PD. However, when PD is associated with dementia, there is higher likelihood of RBD than when it is not. Approximately 25% of patients with PD had RBD in 1 series of 65 patients, but, if they had PD and dementia, 77% had RBD.[20] With respect to onset of dementia, those with RBD had earlier onset of dementia compared with patients with PD without dementia. RBD can also be the first manifestation of a synucleinopathy-based degenerative disease and precede the onset of dementia or other manifestations of the disease. Thus, its presence may provide an early indication of a future neurodegenerative disease, and, if early treatments become available for these diseases, the presence of RBD may allow identification of patients at risk when early interventions could be initiated. In the earliest report of RBD as a predictor of neurodegenerative disease, 38% of male patients developed a degenerative disorder associated with parkinsonism 5 years after diagnosis of idiopathic RBD, which was typically 13 years after onset of symptoms.[21] In another longitudinal series of 93 patients older than 50 years diagnosed with RBD without a neurodegenerative disease, the estimated 5-year risk of development of a degenerative disease was about 20%, 10-year risk was 40%, and 12-year risk was 52%.[22] RBD is also more often diagnosed in male patients, although there has been some suggestion that women may have as much REM sleep without atonia (RWSA) in sleep in association with synucleinopathies, but be less likely to manifest it with more active behaviors. In some cases of RBD associated with degenerative disease symptoms can subside as the disease becomes more advanced.[23]

Certain medications can worsen RBD when patients have underlying susceptibility to it, or even trigger RBD. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), venlafaxine, mirtazapine, excessive caffeine or chocolate intake,

Table 2
Sleep-related symptoms and major changes in sleep architecture associated with dementia types

Dementia Type	Prominent Signs	Associated Sleep Disorders	Highlights Wake/Sleep EEG Changes
Alzheimer's dementia 25%–50% have sleep problems	Early memory loss, early difficulty with naming and word finding, early preservation of social comportment	**ISWR:** chronobiological changes, among others caused by SCN degeneration and pineal/melatonin dysregulation **Sundowning** **Possible more OSA** (OSA associated with APOE4)	Increased stage I sleep NREM dedifferentiation in later stages → poorly formed K complexes/spindles, poorly formed true δ waves, indeterminate NREM sleep Late stages → reduced REM quantity
DLB Up to 85% have sleep problems	Executive/attentional dysfunction occurring before or at the same time as parkinsonism. Visual hallucinations, sensitivity to neuroleptics, fluctuations in arousal	**RBD** (50%–80% of patients with DLB) **Hypersomnia** (changes in lateral hypothalamus) **PLMS** (high index in up to 74% of DLB) **ISWR** (phenotypically like ISWR in AD, unlikely to be caused by same changes as in AD)	REM without atonia
PDD 60%–90% have sleep problems	Parkinson's (asymmetric resting tremor, bradykinesia, akinesia, rigidity) responsive to Sinemet. PD at least 1 y before any cognitive symptoms. Cognitive symptoms primarily dysexecutive	**RBD** (30%–60% of patients with PD) **Sleep maintenance insomnia** **Hypersomnia** **RLS/PLMS**	Rapid blinking at sleep onset REM intrusion in NREM sleep EEG dedifferentiation in later stages in some cases → indeterminate REM and NREM with wake interspersed. Rapid and slow eye movements throughout sleep

Multisystem atrophy Includes former entities: Shy-Drager, olivopontocerebellar atrophy, and striatonigral degeneration	Axial parkinsonism, less common tremor, variable cerebellar (OPCA), variable autonomic symptoms (Shy-Drager). Dysexecutive cognitive syndromes	**RBD** (70% dream reenactment, 90% REM without atonia) **Nocturnal stridor** (vocal cord abductor paralysis can lead to sudden death at night. Treatment: tracheostomy) **Autonomic dysregulation** (may contribute to sudden risk sudden cardiac death at night)	REM without atonia
Progressive supranuclear palsy	Early falls, vertical eye movement paresis. Pseudobulbar affect. Can have aphasia and frontal cognitive syndromes	**Insomnia** **Hypersomnia** (patients can have low hypocretin) **RBD is uncommon** (except in the Guadalupean form)	Complete absence or large reduction of REM sleep No vertical eye movements in REM
Vascular dementia	History of vascular disease, stroke	**OSA** (possibly more frequent than in AD)	
FTLD	Early social comportment problems in behavioral variant	No characteristic disorders, can be phase advanced	
ALS dementia	Behavioral change in social comportment, dysexecutive syndrome with fasciculations and motor signs of ALS	**OSA in bulbar ALS**	

Abbreviations: ISWR, irregular sleep-wake rhythm; NREM, non-REM; OPCA, olivopontocerebellar atrophy; PLMS, periodic limb movements with sleep.

and alcohol withdrawal can produce an acute RBD syndrome. It is likely that patients with underlying synucleinopathies or mild RBD would be susceptible to aggravation of their symptoms with these medications and substances. Thus it might be prudent to ensure that none of the medications or substances are exacerbating symptoms in patients with dementia and RBD.

The main treatments that have been shown to be effective for RBD are clonazepam and melatonin. Clonazepam does not reduce the loss of motor atonia in REM, but seems to reduce the impulse to have complex motor activity during phasic REM. Clonazepam at a dose of 0.5 to 2.0 mg at bedtime is approximately 90% effective. Melatonin can also be effective[24,25] and in one series 87% of patients responded.[25] Melatonin can be used alone or in combination with clonazepam. In the setting of dementia, it might be best to start with melatonin because it is likely to have fewer effects on cognition. Starting doses are 1 to 3 mg, which can be increased to 6 and 9 mg if necessary. High doses of melatonin may be associated with headache or gastrointestinal (GI) symptoms. Other treatments that have been tried have variable efficacy. Quetiapine can be helpful in some patients. Pramipexole and carbamazepine can improve RBD, possibly by reducing the amount of REM sleep. Cholinesterase inhibitor agents have variable effects on RBD, and can sometimes exacerbate symptoms. For a summary of a practical approach to evaluation and treatment of RBD in dementia, see the box which summarizes the practical assessment and treatment of sleep disorder in patients with dementia at the end of the article.

Irregular Sleep-Wake Rhythm

Irregular sleep-wake rhythm (ISWR) is a circadian rhythm disorder and is the most common sleep disturbance in AD. Patients with ISWR lack a well-defined sleep period. They may only sleep for 2 to 3 hours at a time, and then be awake for 2 to 3 hours, and continue this pattern throughout the 24-hour light and dark cycle, irrespective of day and night. At night, therefore, when more sleep is expected, they are noted to have lengthy wake periods, and in the day, when more wake is expected, they are noted to have repeated long naps. Typical complaints of the patient or the caregiver relate to issues of insomnia at night, and hypersomnia or sleepiness during the day.

The changes in the circadian rhythm seen in AD are more profound and different than those seen in normal aging, and may underlie in part the symptoms of ISWR. In normal aging there is a reduction of the amplitude of the core body temperature rhythm as well as changes in other circadian rhythm markers that indicate that the rhythm is not as robust. Elderly people also tend to wake about 1 hour before what would be expected based on their circadian period, a possible sign that the circadian rhythm has become less synchronized with wake-sleep cycles. In AD, the suprachiasmatic nucleus (SCN), which is the master biologic clock in the hypothalamus that regulates and coordinates all circadian rhythms, is affected by the disease process. The SCN of patients with AD has been shown to have tangles,[26] and has neuronal cell loss with reactive gliosis.[26,27] Vasopressin, one of the main peptides produced by SCN cells, has been found to be produced at one-third the normal rate, and its production no longer has a normal rhythmicity.[28] The pineal gland and melatonin systems are also affected in AD.[29] Melatonin is usually secreted from the pineal gland at the transition from daylight to evening. It acts on the SCN, and may play a role in resetting the phase of the circadian clock. Patients with AD have melatonin levels lower than age–matched controls, with some studies finding levels one-fifth that of age-matched normals. There is also a reversal of the relationship between night and day, such that nighttime levels are lower than normals, and daytime levels are higher. The pineal gland has several changes in AD that may alter

its function. The adrenergic axons that synapse on the pineal gland are abnormal and swollen, the clock-related genes, per 1 and cry 2 genes, no longer oscillate normally, and monoamine oxidase (MAO) levels are increased. Increased MAO levels could deplete serotonin, which is a precursor to melatonin. Patients with AD with E4/E4 alleles, which predisposes to early-onset AD, have been shown to have greater reductions in melatonin levels compared with those with E3/E4 alleles. Some of the dysfunction in the pineal gland may be related to a functional disconnection between the SCN and pineal gland.[29]

Melatonin levels, and the loss of rhythmicity in the per1 and cry2 genes can be apparent early in AD, even before there are clinical symptoms in patients (in pathologic Braak stages I and II).[29] Even when asymptomatic, and when patients have no cognitive decline, cerebrospinal fluid levels of melatonin in these patients are also lower than in aged-matched controls.

The early loss in melatonin seen in patients with AD has stimulated consideration with regard to how this might play a role in the pathophysiology of the underlying degenerative disease. Melatonin has been shown to have neuroprotective and antioxidant properties, as well as reducing hyperphosphorylation of tau and neurofilaments, one of the abnormal processes that occurs in AD. Thus, it has been suggested that the low melatonin levels found in early AD might facilitate the disease process, which has led some to suggest that supplementation with melatonin might warrant study with respect to whether it might alter the course and progression of the disease in the earliest stages.[30]

Besides the SCN and the pineal gland/melatonin systems, patients with AD have changes in the zeitgebers that are critical for reinforcing and entraining regular circadian rhythm patterns. Zeitgebers are environmental cues that include social and physical activities, eating patterns, and light/dark environment cycles. The strongest zeitgeber for circadian rhythmicity is light, and patients with dementia often have disturbed patterns of light exposure, which can be a consequence of the nursing home environment, or caused by inactivity during the day, including sleeping during the day. Even patients with AD living at home may be exposed to only half the bright light stimulation ($\geq$2000 lux) of young adults and normal healthy elderly.[31,32] Light exposure may also not reach brain centers in AD as effectively because of disruption of the visual system. Cataracts and macular degeneration are common in elderly people and can interfere with the light signal reaching the brain, as well as retinal and optic nerve degeneration.

The circadian rhythm disturbances in AD have been found to worsen cognition and strongly affect function in patients with AD in several studies.[2,3] The sleep-related issues associated with it can also be a major cause for caregiver stress.[4,5]

ISWR treatment

The recommended approach to treatment of ISWR currently involves nonpharmacologic measures designed to strengthen zeitgebers and reduce factors that cause disruption of sleep at night. These approaches typically involve efforts to promote stimulation, activity, and light during the day, while reducing stimulation at night and trying to produce a more consolidated quiet period. Various specific types of interventions have been evaluated, including social activity programs, daytime exercise, daytime bright light therapy, and sleep hygiene recommendations (such as setting more regular bedtimes and reducing arousal factors at night). Approaches that implement multiple interventions simultaneously have been called mixed modality treatments and may be the most effective, although more evidence is still needed.[31]

Bright light therapy is one of the most studied therapies for treatment of ISWR. It makes sense that increasing light exposure could be helpful, because in healthy people it is one of the strongest zeitgebers, and light exposure is known to be suboptimal in many patients with dementia. In general, daytime bright light therapy seems to offer some benefit for patients with dementia and for patients in nursing homes, although there are mixed results. In one study, when high-intensity light wall fixtures were installed in a nursing home, sleep time improved by 15 minutes.[33] In another study, when morning outdoor light exposure was combined with physical exercise, reduction of daytime in bed, and reduction of noise and light at night, daytime sleep time was reduced, but there were minimal changes in nighttime sleep continuity and duration measured by actigraphy.[34]

A social intervention study also found promising effects on ISWR.[35] The social intervention program was provided for 1 hour daily for 3 weeks to 137 institutionalized patients with dementia. Sleep-wake rhythms were improved in those patients who had been poor sleepers at the beginning of the study. In poor sleepers with a baseline sleep efficiency of less than 50%, the intervention increased sleep time at night by about 40 minutes, reduced nighttime sleep latency by 40 minutes, and reduced daytime napping by about 40 minutes.

A mixed modality approach to treatment was tried in a randomized controlled study of community-dwelling patients with AD who had mean mini mental state evaluation scores of 12.[36] The treatment included a systematic sleep hygiene program including setting individualized rise times and wake times and reducing nighttime arousal factors in the first week, the addition of daily exercise of 30 minutes in the second week, and the addition of 1 hour of daily light therapy in the third week. Sleep parameters were measured by actigraphy at 6 weeks and 6 months later. Benefits were seen at 6 weeks with a 32% reduction in nighttime wakenings, as well as reduction in daytime sleepiness and depression. The benefits also persisted for 6 months. A larger mixed modality treatment study of 132 community-dwelling patient with AD examined the effects of light therapy, walking therapy, and individualized education regarding nighttime bedtime/rise time and arousal reduction.[37] Light therapy and walking therapy were tested alone and in combination with individualized education. All groups had improvements with therapy compared with a control group provided with only sleep hygiene information that was not individualized. Those who adhered more to therapy had greater gains. At 6 months, the gains did not persist, but there was variability in adherence.

Given that changes in melatonin are postulated to underlie some of the circadian rhythm disturbance in AD, melatonin might be expected to benefit treatment of ISWR in dementia. However, several carefully designed randomized trials with melatonin have been generally disappointing. These trials have included both large-scale multisite studies and smaller randomized studies.[38,39] An exception was the study by Dowling and colleagues[40] (2008) who found that melatonin and light therapy together seemed to produce benefit in reduction in daytime sleep and rest-activity rhythm, even when light therapy alone did not. Thus it might be that melatonin is only effective when used in combination with light therapy in patients with dementia. Differences with respect to the benefits of melatonin may also reflect heterogeneity in patient populations. It is known that later in the course of AD there is loss of melatonin receptors on the SCN (MT1 receptors), and it is possible that this might reduce benefits in that population.[41] Melatonin has occasionally been reported to cause some negative mood-related side effects, but that was not seen in one of the best controlled studies.[38] In one large study of dementia that examined the effects of light therapy and melatonin, benefits were seen for therapy with melatonin and for light, but some patients with melatonin had a deterioration in mood.[42]

Use of medications for treatment of ISWR: potential for harm

Another approach taken to treat the disrupted sleep at night in patients with ISWR is to use standard hypnotic medications. This approach might seem easier to implement from the perspective of caregivers or institutions, relative to the multimodal behavioral strategies described earlier. In general, there is no evidence that pharmacotherapy can help ISWR, and because hypnotics can have adverse effects, especially in dementia, the recent American Academy of Sleep Medicine guideline for treatment of ISWR does not recommend their use.[43]

Several studies have indicated that the use of sedative hypnotics in elderly patients may not alleviate sleep complaints in the chronic state.[44–46] Side effects such as increased sleepiness, sedation, forgetfulness, confusion, or rebound insomnia can occur and worsen overall status and satisfaction about sleep. In a meta-analysis of 24 studies of hypnotic use for treating insomnia in the elderly,[47] hypnotics had a 4.78 odds ratio (OR) for altered cognition and a 3.82 OR for daytime fatigue and sleepiness. The benefit for sleep was only small in this general elderly population, such that the overall risk/benefit ratio was considered unfavorable. The meta-analysis, did not target patients with dementia, only elderly patients, but it might be expected that the risk/benefit ratio for patients with dementia would be even poorer, because of being more vulnerable to the negative cognitive and sedating side effects.

The Beers list was recently updated and identifies medications that are associated with higher risks of side effects in elderly patients.[48] This list contains several medications that have been used for treatment of sleep, and these should be used cautiously in patients with dementia, who are even more likely than the general elderly to have adverse side effects. Included on this list is diphenhydramine (contained in Benadryl, Tylenol PM, and Advil PM), which has a strong anticholinergic profile and potential to cause delirium, as well as other anticholinergic medications including hydroxyzine (Visteril), promethazine (Phenergan), chlorpheniramine (Trimetron), and tricyclic antidepressants like amitriptyline (Elavil). Other medications to be avoided include the long-acting benzodiazepines (eg, flurazepam [Dalmane], diazepam [Valium], clorazepate [Tanxene], chlordiazepoxide [Librium], clidinium-chlordiazepoxide [Librax]), and the muscle relaxants and antispasmodics. It is recommended that the shorter acting benzodiazepines be only used at the smallest doses. Some argue that it is even reasonable to avoid these (eg, temazepam (Restoril), and oxazepam (Serax)) in patients with dementia.

There have been no placebo-controlled trials of newer hypnotics such as zolpidem (Ambien), zaleplon (Sonata), and eszopiclone (Lunesta) in patients with dementia. One study implicated zolpidem as causing a fall risk in an elderly group of patients hospitalized for hip fractures. One of the problems with the studies of fracture risk is that patients who have greater degrees of insomnia might be those who are more likely to get up during the night and are at higher risk of falls independent of taking the medication. One retrospective study showed that fall risk seemed to be higher in patients with insomnia who were not taking sedatives, compared with those on sedatives who did not have any complaints of insomnia.[49] One open-label study reported that trazodone was effective in treating sleep disturbance in two-thirds of patients with dementia with minimal adverse side effects.[50] With respect to other medications, there have been few systematic studies in dementia. Sedating antidepressants, including mirtazapine (Remeron), are sometimes used, but mirtazapine can exacerbate RLS/periodic leg movements syndrome (PLMS) and RBD, and therefore has the potential to worsen nighttime sleep, and can also be associated with morning sedation in some patients. Sedating antipsychotic medications are sometimes used for treatment of nighttime sleep in dementia, but a new black box warning has been added to these

medications indicating that they are associated with an increased risk for sudden death in dementia. In general, for agitation, other measures to reduce agitation and hallucinations should be tried first. These alternatives can also include pharmacologic therapy with cholinesterase inhibitor agents, or with antidepressants such as SSRIs for treatment of anxiety (discussed later).

Although ISWR has been examined most extensively in AD and is the prototypical dementia associated with ISWR, other dementia subtypes may exhibit similar dissolution of the circadian rhythm. Although the underlying pathophysiology may be different from that of AD, DLB and PDD can have marked disruption of sleep at night with greater amounts of sleepiness during the day leading to the picture of ISWR. Patients with vascular dementia can also develop highly fragmented sleep at night, and sleepiness in the day. All institutionalized patients with dementia are likely to have reduced strength of zeitgebers that are likely to lead to deterioration of the regular circadian rhythm, independent of dementia subtype.

Sundowning

Sundowning is a term used broadly to refer to agitated neuropsychiatric behaviors in patients with dementia that first appear, or become evident, in the late afternoon or evening. Typical sundowning symptoms include delirium, physical combativeness, loud vocalizations, and wandering. In individual patients, symptoms can occur regularly beginning at a certain time, often between 4 and 11 PM. The prevalence of sundowning in institutionalized patients with AD ranges from 10% to 25%,[51,52] but, in community-dwelling patients, it may be as high as 66%.[6] It is hypothesized that sundowning may in part be related to the alterations in underlying chronobiological rhythms in patients with dementia, although there is little direct evidence for this. Changes in melatonin secretion, delay in the body temperature rhythm, alterations in the cholinergic projections from the nucleus basalis of Meynert, and the dysfunction of the SCN could all contribute to altered brain processing capacities or mood changes in the evening hours. Klaffke and Staedt[53] (2006) proposed that sundowning could be caused by a mismatch in the arousal signals that have to be processed around the evening hours, and the capacity of the neocortex to process these signals when the cortex is becoming deactivated and preparing to sleep. Factors that can worsen sundowning include exhaustion, reduced lighting, increased shadows, new environments, changes in caregivers, or changes of shifts in nursing homes.

Some investigators have questioned the legitimacy of the concept of sundowning, partly because the term is so nonspecific and includes so many different behaviors.[54] A few studies have also found that agitation is sometimes worse in the daytime than in the evening.[52] Investigators have suggested that sundowning might partly be caused by the perception of caregivers and staff who are more fatigued or understaffed in the evening and thus are less able to redirect or offer support to the patient with dementia, which results in increased agitation.[55] In contrast, one study of institutionalized patients found that there were individualized patterns of peak agitation, even when all residents were exposed to the same environment, which argues for a biologic basis for the agitation.[56]

It might be best to understand sundowning as an underlying vulnerability to having increased symptoms around a certain time of day, usually in the evening hours, which can be triggered by environmental circumstances or other individual intrinsic biologic conditions around that time. Thus, factors in the environment such as poor lighting, unfamiliar circumstances, and changes in staff might trigger increased agitation especially around the vulnerable time, and factors related to the patient's underlying biologic state, including a patient's underlying anxiety, sleepiness from sleep disorders,

or the side effects of medications, could become more apparent and trigger agitation during the vulnerable period.

Treatment of sundowning

Interventions in the environment to reduce sundowning can include ensuring that lights are bright in the evenings to reduce the likelihood of misperceiving stimuli because of poor visual processing; arranging schedules so that patients are not exposed to unfamiliar environments in the evening; and, in institutions, being careful to minimize disruption and noise associated with staffing changes while offering greater reassurances to the patient around the time that sundowning occurs. Addressing the underlying biologic predispositions of patients to agitation and confusion includes treatment of any underlying anxiety (first-line pharmacologic treatment in patients with dementia might be a morning dose of an acetylcholinesterase inhibitor agent and/or an SSRI) and reduction of medications that could increase the likelihood of development of confusion. Medications that might be used to calm the patient down might be counterproductive if they cause more prolonged changes in arousal that could contribute to confusion (eg, muscle relaxants or diphenhydramine [Benadryl]). Medications that could directly induce a higher likelihood of having hallucinations need to be carefully reviewed and preferably eliminated or used at the lowest necessary doses (eg, amantadine, MAO inhibitors, selegiline). Caffeine can promote a mismatch between processing of information and fatigue as well as contributing to disrupted sleep at night, and therefore might be best carefully controlled or eliminated. If the patient is not getting enough sleep at night, this could lead to increased sleepiness and fatigue at the end of the day, making the patient more vulnerable to confusion. Thus, further factors that cause sleep disruption at night might be carefully reviewed and treated accordingly, see the box "Hallucinations-agitation in evening or night: treatment algorithm" at the end of the article. Several case reports describe resolution of delirium and agitated states after treatment of OSA, showing that disrupted sleep patterns at night can contribute to agitation.

In some cases, especially in patients with more severe dementia, patients may have difficulty communicating their physical needs, and agitation might be related to underlying physical needs that have not been met, such as hunger, pain, or needing to use the bathroom. In individual cases, especially when communication is poor, it might be important to determine whether these issues could be contributing to the agitation. To reduce the likelihood that these factors are playing a role in such patients, such patients could be tried on a scheduled snack before the time that they typically develop agitation, or be scheduled for regular bathroom breaks. If the problem is worse acutely, or the sundowning is of recent onset, the possibility that there might be an acute delirium also needs to be considered. Acute delirium could be caused by underlying infection or drug toxicity and, if the agitation is of recent onset, these possibilities need to be evaluated. Also, symptoms of wandering and pacing, which is often included as one of the symptoms seen with sundowning, may be a presentation of RLS. The symptoms of RLS, like sundowning, occur according to a circadian schedule, and are worse in the evenings (further discussion in section on RLS later).

Various interventions to treat sundowning have been evaluated and investigated in the literature, but there have been no studies of mixed modality approaches, which target a combined group of possible contributors in a specific case, like any combination of those discussed earlier. When isolated interventions for sundowning have been evaluated alone, there have been mixed results. One study evaluated the effect of increasing lighting in the 19:00 to 21:00 period. In this small study, 8 of 10 patients had improved sundowning symptoms, and those who benefitted most had the worst

symptoms.[57] However, a review of 8 trials did not find evidence of overall benefit for lighting.[58] As discussed in the context of ISWR, melatonin has been tried for treatment of sleep disturbances, but most trials have not specified the impact on sundowning in particular. Small case reports and open-label studies have found some benefit in afternoon agitation.[59–61] Neuroleptic agents are perhaps the most prescribed medications for agitation and delirium or disruptive behaviors, but the evidence that they help with sundowning is limited.[62] In addition, these agents can worsen confusion, cause sedation, and impair cognition of patients with dementia[63,64] and may contribute to the problems of patients with dementia or even perpetuate agitation.[65] A meta-analysis found that patients with dementia have a higher risk of sudden death with the use of antipsychotics[66] and, as previously mentioned, a black box warning has been added specifically for the use of these agents in patients with dementia because of this risk. Cholinesterase inhibitor agents have consistently been shown to reduce neuropsychiatric symptoms, including hallucinations in patients with dementia,[67] and the evidence suggests that they therefore might be useful in sundowning. One case report found sundowning symptoms to be decreased in a patient with DLB after starting donepezil.[68] Because donepezil can cause increased vivid dreaming, this might not be the first choice of medication to try, and galantamine and rivastigmine might be better. All cholinesterase inhibitor agents should be dosed in the morning, despite package insert instructions, because they can cause insomnia.

Since sundowning includes so many varied behaviors, and treatment often depends on the symptoms in the individual case, including the factors that could be promoting the syndrome in a particular case, and the patient's underlying biologic issues (pain, anxiety, and so forth); some investigators have suggested that it is better to speak to caregivers in terms of the individual symptoms rather than refer to the problem as sundowning. The use of the term sundowning might imply a more unitary concept that would be expected to be treated with a unitary solution. Emphasizing the particular symptoms of the patient may help the caregiver to recognize that there can be varied approaches to treatment depending on the person's symptoms. This approach might also help to facilitate acceptance of a multifactorial approach to treatment that targets environmental as well as intrinsic biologic factors.

Sleep Disordered Breathing (SDB)

Prevalence and association of cognitive impairment and dementia with SDB

Dementia is common in elderly people, with estimates of a prevalence of up to 60%.[69,70] Because dementia is a disease affecting mostly elderly people, SDB would be expected to be common in patients with dementia on that basis. However, dementia may also confer a further risk for having sleep apnea. In institutionalized patients with dementia, one study found that 70% to 80% had an apnea hypopnea index (AHI) of greater than 5 events per hour.[71] SDB has also been reported to be particulary common in patients with vascular dementia. New studies have been indicating that SDB may be an independent risk factor for stroke and cerebrovascular disease, thus it might be expected that patients with vascular disease should have an increased risk for SDB.[72] There have also been studies suggesting that SDB may be more common in AD than in the general population.[73,74] The APO E4, lipoprotein allele, which is linked with a higher risk for AD, has been associated with an increased risk for OSA in some studies,[75,76] although other studies did not find this association.[77,78] Why AD should be associated with an increased risk for SDB is unknown, but some have speculated that it might be because of degeneration of respiratory nuclei in the brainstem. Another possibility is that the hypoxia of apnea in some manner increases the risk for dementia or accelerates manifestation of AD in those who are vulnerable to it.

Signs that a patient might have SDB include snoring, witnessed apneas, and restless behaviors at night that do not respond to usual therapy. If apnea is suspected, then a sleep study can be obtained. A particularly high suspicion for apnea may need to be maintained for patients with vascular dementia, because they may not have the same symptoms as the general population with apnea. Patients with cerebrovascular disease and SDB are less obese and are less likely to be sleepy than other SDB populations.[79,80]

Relationship of SDB to cognition and delirium

The relationship between cognitive impairments and SDB is complex, and variable from individual to individual. At the extreme, there are cases in which SDB can be responsible for severe cognitive impairment and even delirium, which can be completely reversed by continuous positive airway pressure (CPAP) therapy.[81–84] Such cases serve as a reminder that it is important to consider SDB in all patients presenting with cognitive dysfunction and concern for dementia, because, if found, treatment might completely restore normal function.

In most cases of SDB, the impact of OSA on cognition may be less severe. Meta-analyses that have examined nondemented patients indicate that SDB most often affects measures of vigilance, attention, and possibly psychomotor function, whereas its impact on language and memory performance is less consistent.[85,86] Studies that include elderly populations and might be expected to show a stronger relationship between cognitive impairment and apnea have not always found consistent associations between apnea and cognition.[70,87,88] One large study of community-dwelling healthy elderly patients, including 827 subjects with an average age of 68 years, found no relationships between apnea and cognitive measures, despite the use of a sophisticated neuropsychological battery.[70]

However, other studies show associations between SDB or symptoms of SDB and dementia or cognitive impairment.[71,89–91] One recent study followed an elderly group of women with an average of age 82 years and found that those who had an AHI greater than 15 had an increased risk of dementia compared with those of the same age without apnea, when adjusted for a variety of other comorbidities.[91] The adjusted OR was 1.85 for being diagnosed with mild cognitive impairment or dementia when tested 5 years after the initial sleep study.

Discrepancies in the results of studies examining the relationship between cognitive impairment and apnea in the elderly could be caused by differences in the age of patients included, and whether the study was more or less likely to include patients with dementia. Studies including higher age groups, and those with known cognitive problems, might be expected to increase the ability to examine the relationship between cognition and apnea. There may also be a subpopulation of people who are more vulnerable to the cognitive impact of sleep apnea in the elderly, which could vary from study to study. Two recent studies examining cognition in elderly patients found that only those who were APO E4 positive, and not those who were APO E4 negative, had impairment on memory tests that correlated with apnea.[92,93] Thus, the carrier status of the APO E allele might be a marker for patients more vulnerable to the effects of apnea.

The mechanisms by which apnea might impair cognitive function or directly affect dementia include the potentially negative effects of intermittent hypoxia on neuron health, or the effects of chronic sleep deprivation or sleep fragmentation. Sleep may protect against the development of degenerative processes and poor sleep may make the brain more vulnerable. Animal models have suggested that cell death and even amyloid deposition may both be furthered by sleep deprivation.[94,95] However,

it should be noted that insomnia in humans has not been shown to be associated with increased risk for dementia.

Treatment of SDB in the setting of cognitive impairment and dementia

With regard to whether apnea treatment improves symptoms of patients with dementia, there are reports of those who do extremely well and can have remarkable improvements (discussed earlier). Other studies have shown generally positive effects, although these are not usually as marked as in the case reports with instances of great improvements. In one small sham-CPAP controlled randomized 6-week cross-over study of 52 patients with mild Alzheimer's dementia, PAP therapy resulted in improvements in sleepiness and mood and had a small positive impact on neuropsychological test performance.[96] A further small continuation study compared the profile of patients with AD who were able to sustain CPAP use over 1 year versus patients with AD who discontinued use.[97] Although not randomized, the 5 patients who remained compliant on CPAP showed less cognitive decline, had stabilization of depressive symptoms and sleepiness, and had subjectively improved sleep quality compared with those who discontinued use.

In patients with vascular dementia, CPAP therapy may have a particular role in reducing progression of disease, because apnea treatment may reduce the risk for vascular events.[98,99] In this population of patients with stroke or vascular disease, the symptoms and signs that increase suspicion for apnea may not be present, because patients with apnea and stroke are less often obese, and less often sleepy.[79,80] Thus, a high index of suspicion for apnea should be maintained in these patients.

Patients with dementia are generally able to tolerate PAP therapy at about the same rate as healthy individuals.[96,100] Therefore, it should not be assumed that the presence of dementia will present an insurmountable barrier to CPAP adherence. The caregiver may have to be more involved in ensuring that the patient uses PAP therapy and provide reminders to continue to use it. CPAP therapy has been reported to help with the sleep of caregivers because it can reduce nighttime awakenings.[96,97] This benefit to caregivers should also be taken into account when considering recommending PAP treatment, because patients with dementia are reliant on caregivers and caregiver distress is one of the main reasons for institutionalization of patients with dementia.

When CPAP is not tolerated, alternative therapies can be considered. In elderly patients apnea is sometimes highly positional, and positional therapy with a strict lateral sleep positioner may treat apnea. Other alternatives to PAP therapy include dental appliances. In cases of complex apnea that are more difficulty to treat with PAP therapy, positional therapy might be an alternative option. ASV PAP devices can also be tried and can be well accepted in patients with dementia.

Hypersomnia

Hypersomnia can be the consequence of poor sleep at night, ISWR, as well as other factors. Refer Box "Excessive daytime sleepiness and napping: treatment algorithm", addresses factors that should considered in the assessment of hypersomnia in the patient with dementia.

However, hypersomnia can also be the result of an intrinsic disorder affecting the sleep-wake cycle that is specific to certain types of dementia. For example, in DLB, reduction of arousal during the day is a prominent symptom. In one small study of 31 patients with DLB who were not selected for sleepiness, the average latency to fall asleep on the Multiple Sleep Latency Test was markedly abnormal at 5 minutes, compared with more than 10 minutes in patients with AD.[101] The fluctuations in

arousal in DLB can cause large fluctuations in attention and cognitive capacity. These fluctuations are different from the cognitive impairments seen with sundowning, because they are not associated with agitation or active behaviors. Instead they are associated with a tendency to be sleepy and a failure to communicate or engage in activities. In the case of DLB, the arousal dysfunction can be variable from day to day and from hour to hour, and does not occur with a circadian pattern. This distinctive arousal fluctuation has been recognized as prominent and specific to DLB, such that it is currently included as one of the 3 core features in the diagnostic criteria used to make the diagnosis (along with visual hallucinations and extrapyramidal/parkinsonism symptoms). Patients with Parkinson-related dementia, like DLB, can similarly descend into somnolent states from which they can be difficult to arouse. Dopaminergic agents such as pramipexole (Mirapex), ropinarole (Requip), or bromocriptine, which are often used in these patients, can induce sleep attacks and sleepiness, but the arousal dysfunction seen in the cases of DLB and PDD is not completely attributable to medications and can occur independently of them.

The pathophysiology underlying the loss of alertness and arousal in PDD and DLB is not fully understood but may have something to do with dysfunction of the lateral hypothalamus, which contains histamine and orexin/hypocretin cells that are important for maintaining alertness during the day. Initial studies failed to show changes in hypocretin/orexin levels in patients with DLB, but recent studies have shown that some DLB and patients with PD have neuropathologic evidence of loss of hypocretin/orexin cells.[102,103] DLB shares some features of narcolepsy, which is also characterized by sleepiness in the day. Patients with DLB can have hallucinations that can occur when they are awakened out of sleep like in narcolepsy.[104] Narcoleptic patients have an increased risk of RBD, which is also seen in patients with DLB. The sleepiness of PD-related diseases is less dependent on nighttime sleep quality.[105,106] Patients who sleep longer at night can still have increased daytime sleepiness, which suggests that the sleepiness is caused by a central mechanism rather than sleep deprivation. Although nighttime sleep in patients with PD can be disrupted for a variety of reasons, the presence of PLMS, sleep apnea, and sleep fragmentation does not necessarily correlate with the degree of daytime symptoms in PD and DLB.

Stimulants like those used in narcolepsy, such as modafanil (Provigil) and armodafanil (Nuvigil), might be helpful for treatment of symptoms in DLB and PDD. One open-label pilot drug sponsored trial showed that armodafanil (Nuvigil), which started with a dose of 150 mg and was titrated to 250 mg after 30 days, caused marked improvement in alertness in patients with DLB, and also improved quality of life for both patient and caregivers.[107]

RLS and Periodic Limb Movements of Sleep

RLS

RLS is an important diagnosis to consider in dementia because it can manifest as increased agitation or wandering and pacing in the evenings, as well as insomnia. RLS may be the underlying disorder responsible for symptoms in some cases described as sundowning if wandering and pacing are prominent symptoms. More than 80% of patients with RLS have problems either falling asleep or getting back to sleep during the night because of their symptoms, and, if RLS is present, this could also be a major cause for sleep disturbance during the night. If the patient has RLS, targeted treatment of RLS may resolve these symptoms. RLS is more common in patients with renal disease, iron deficiency anemia, neuropathy, rheumatoid arthritis, and Crohn's disease, among other conditions, and, if a patient with dementia has any of

these conditions, the possibility of this condition should be considered with even more care.

To make the diagnosis of RLS, the patient must endorse 4 essential clinical features of the syndrome: (1) the presence of an urge to move the legs that may or may not be accompanied by uncomfortable sensations; (2) the urge to move or sensations is partially or totally relieved by movement such as walking or stretching as long as the activity continues; (3) the urge to move or sensation has a circadian pattern and occurs more in the evening or at night; and (4) the urge to move or sensation is worsened with rest, inactivity, lying down, or immobility (eg, in a car, airplane, train). Because the diagnosis is based on subjective features, it can be challenging to know whether someone has this syndrome when they are not able to answer questions for themselves reliably, as occurs in some patients with dementia. Supportive information that might help to make the diagnosis in patients with dementia can include a positive family history and a high Periodic Limb Movement Index (PLMI) on a polysomnogram. The caregiver input can also be useful for making the diagnosis. RLS is typically more common in women, and can peak in elderly people. One study showed that 16% of women aged 60 to 69 years met criteria for the syndrome, and up to 10% of people between 65 and 85 years have been reported to have RLS.[108,109] The percentages of patients with RLS in dementia is not known, but RLS may be more common in Parkinson dementia compared with other dementia subtypes. If it seems possible that the patient has the condition, it can be worthwhile trying interventions that might help the condition and evaluate for any benefits.

A few common look-alike conditions in the elderly should be distinguished from RLS. Akathisia may be mistaken for RLS, but akathisia has some different characteristics. It does not vary according to a circadian pattern and gets better when lying down. Pain syndromes caused by arthritis or joint symptoms should be distinguished from RLS as well. In the case of joint pain syndromes, pain relief may be achieved by repositioning, but continued movement is not required for resolution of symptoms once a better position is found. Leg cramps should also not be mistaken for RLS. Leg cramps affect a single muscle suddenly, and are not associated with a general feeling of discomfort or need for continuous movement other than the movement to relieve the cramp.

RLS treatment

RLS can be worsened by a variety of medications, and the first consideration with regard to intervention should be to review whether any medication might be worsening symptoms. Diphenhydramine (in Benadryl, Tylenol PM, and Advil PM) or other centrally acting antihistamines like hydroxyzine (Visteril) can strongly aggravate symptoms and cause markedly increased agitation, which is the opposite to the response that is typically desired when these medications are being used. Other medications and substances that worsen RLS include tricyclic antidepressants, lithium, dopamine blocking agents (including all the antipsychotic medications), and alcohol. Antipsychotic agents are often tried in an attempt to treat agitation or sundowning in patients with dementia, but, if there is a component of RLS, these may provoke greater agitation. SSRI and SNRI medications should preferably be dosed only in the morning because these can also aggravate symptoms. If the patient is not already on an antidepressant, and one is being considered, bupropion might be a best choice, because it can be associated with less of an impact on RLS. Substances such as caffeine and chocolate can aggravate RLS symptoms and should be eliminated. Structured daytime exercise can be helpful, as can massage of the legs, both of which have been shown to lessen RLS symptoms. RLS has been associated with low iron stores,

and iron supplementation is another therapeutic approach to treatment. Patients should always have iron stores checked, and iron should be supplemented if it is in the lower end of normal range. Iron supplementation can be helpful for any patients with ferritin less than 45 to 50 ng/ml). Supplementation is typically started orally, although iron infusions can also be considered. Oral iron should be dosed with vitamin C to improve absorption. If iron deficiency is present, the patient should also be evaluated for any causes of iron loss that might need further evaluation.

Pharmacologic management of RLS symptoms has typically included dopaminergic agonists as first-line agents (eg, pramipexole, ropinirole); in patients with dementia, gabapentin and gabapentoid agents are better first-line agents because of their better side effect profile and lower risk of hallucinations. Doses of 100 to 600 mg of gabapentin may be helpful, and can be dosed 1 hour before symptoms and again before sleep at night to help with sleep onset.

Periodic limb movements of sleep

Periodic limb movements of sleep are common in the elderly and may affect up to 50% of people older than 65 years.[110,111] These movements typically consist in dorsiflexion of the foot, but may involve upper limbs as well; and they occur in repeated sequences at regular intervals while a person is sleep and unconscious (typically at intervals of 20–60 seconds). The vigor of the movements and whether they cause arousals from sleep varies from individual to individual. Although the RLS syndrome is more common in women, PLMS are typically present equally commonly in men and women. In the case of dementia, and dementia subtypes, the prevalence PLMS is not known, but PLMS may be especially common in dementia associated with parkinsonism, including PDD, and DLB. Depending on the vigor of the movements and the depth of the patient's sleep, as well as the patient's underlying arousal threshold, the movements may or may not induce arousals from sleep. Patients with RLS typically have periodic limb movements (>80% of patients with RLS have PLMS), but it is only a minority of patients with PLMS who have RLS (<20%).

Periodic limb movements in adults are usually considered clinically significant when they occur at a rate of at least 15 movements per hour (PLMI >15) and result in a daytime symptom. Patients who are elderly, especially in the setting of Parkinson-related disorders, commonly have PLM indices ranging from 50 to 150 per hour. But even in the setting of these high indices, patients may be unaware of the movements. It is sometimes difficult to know how clinically significant the PLMS symptoms might be in a particular patient. When there are symptoms such as disrupted sleep or unrefreshing sleep that are associated with PLMS, the condition is sometimes referred to as PLM disorder (PLMD). In the setting of a patient with dementia, if the PLMI is greater than 20 per hour, and if they are also often associated with arousals, it might be prudent to consider the possibility that these movements could be contributing to sleep disruption.

PLMS treatment

There has been considerable controversy and debate with regard to whether PLMS needs to be treated. If a patient is not symptomatic and does not have a sleep disturbance, then there is little need for treatment or interventions. In contrast, in patients with dementia, who often have problems with sleep-related symptoms, it may be worth targeting treatment to the possibility that the limb movement disturbance is clinically significant. Treatment approaches for high PLM indices typically parallel those of RLS. Most medications that aggravate RLS can aggravate PLMS. Caffeine, chocolate, and alcohol should also be avoided, and daily exercise can be helpful. Oral iron

supplementation with vitamin C should be tried if ferritin is less than 45 ng/ml. If pharmacotherapy is desired, gabapentin might be tried as a first-line option, due to the undesirable side effects of dopamine agonists in dementia. However, if gabapentin, or gabapentoid agents, are not effective, then agents such as ropinirole or pramipexole could be tried.

The Nursing Home and Institutional Environment: Specific Considerations

Certain circumstances in nursing homes and institutions can specifically disrupt sleep-wake rhythms in patients with dementia. When reviewing the environment in a nursing home or hospital, the clinician should consider how often residents might be awakened at night by nurses entering their rooms, whether they have a well-matched roommate who is quiet at night, and whether the nighttime bedroom environment is quiet and dark from the perspective of nursing stations and light that might be present in the room. In the daytime, it is preferable that the institution be brightly lit and that there are opportunities to go outside in the natural sunlight. Daytime activities are important to enhance wakefulness during the day. Ample opportunity for walking and aerobic exercise as part of structured physical activity programs is especially important for patients with RLS, but can also be helpful for mood and the circadian rhythm in all patients with dementia. In patients with nighttime sleep disruption, caffeine (including so-called decaffeinated drinks) should be eliminated, including in the morning (see the case example in this article). In patients with insomnia and sleep disruption at night, it is important to review whether patients are being provided too many napping opportunities during the day. Some nursing homes implement structured bedroom rest schedules during the day. If this is the case, consider having these shortened for patients with nighttime sleep difficulties.

PRACTICAL ASSESSMENT AND TREATMENT OF SLEEP DISORDER IN PATIENTS WITH DEMENTIA

A practical approach to treatment of patients with dementia includes identification of general factors in addition to those that might be recognized as reflecting primary sleep disorders. Patients with dementia are more vulnerable to the effects of any external factors on their physiology and sleep, and thus the factors that are known to affect sleep at all ages and under all circumstances need to be scrutinized carefully. A sample initial interview inventory is provided in **Box 1**, which covers some of the most important information needed to identify general factors that might need to addressed to best treat sleep problems. Although OSA, or periodic limb movements of sleep, or REM behavior disorder may be causing sleep disruption in a specific patient, the patients with these specific primary sleep disorders will not have their sleep problems fully addressed even if these specific issues are treated unless other general factors that can have magnified effects in patients with dementia are also considered.

Boxes 2.1, 2.2 and **2.3** provide guidelines for how to use the information gathered in the general inventory when addressing the main complaint of the patient with dementia. These tables are divided into 3 main categories of sleep complaint: (1) insomnia, cannot sleep at night; (2) hallucinations and agitation, in the evening or night; and (3) hypersomnia, including excessive daytime sleepiness and napping. As can be seen in these tables, each of these complaints can be caused by multiple factors, and all these factors need to be considered to best address the underlying sleep problem. For example, if someone is not sleeping well at night and a complete caffeine inventory is not taken and considered, it is unlikely that many other interventions will be fully effective unless caffeine is also eliminated. It is common to see

Box 1
Practical guide to evaluating sleep in dementia: individualized assessment sleep inventory

Initial interview questions

1. Main complaint (identify what concerns or bothers the patient most without the help of the caregiver first; then from the caregiver perspective). Identify targets/main goals for treatment.
2. After listening to the patients/caregiver, review 3 major categories of sleep related symptoms, and identify which are affected. (1) Insomnia – cannot sleep at night, (2) Hallucinations/anxiety at night, (3) Excessive daytime sleepiness.
3. Perform an inventory of symptoms associated with primary sleep disorders: (1) OSA (loud snoring, witnessed apneas), (2) RLS (discomfort in limbs, worse in evening, relieved by movement, worsened when confined or still), (3) RBD (acting out dreams). Any history of premorbid sleep disorders (prior history of insomnia, hypersomnia; prior concern for OSA).

Amount, timing, and quantity of sleep inventory (gives more objective overview of sleep time and pattern, and can also request sleep log or obtain actigraphy for additional information)

1. Bedtime, wake time.
2. Time to fall asleep: if not falling asleep, any activities (TV, getting up to eat, and so forth)?
3. Waking up at night: number of times, how long each time, any activities associated with wake episodes (eg, bathroom, TV, eating).
4. Daytime naps and dozing: what times, how long.

General intake information related to individual habits, history (these can be major targets for intervention)

1. Caffeine: specifically ask about tea, sweet tea, iced tea, soda, diet soda, coffee, decaffeinated coffee, and chocolate.
2. Alcohol.
3. Detailed and accurate review of all medications.
4. Detailed review of all over-the-counter medication including Tylenol PM, Advil PM, diphenhydramine.
5. Reflux, nasal congestion, coughing at night, pain at night?
6. Temperature at night?
7. Dark at night, light in day? Quiet environment at night, active environment in day?
8. Mood: depression, anxiety?
9. Nocturia?
10. Habits before bedtime? Dinner time, eating after dinner, dozing before bedtime, TV in BR, TV/computer before bedtime.

Epworth Sleepiness Scale (ESS; a useful inventory for comparing treatment efficacy for future; may need caregiver responses if patient is not reliable). How likely are you to doze off or fall asleep in these conditions? 0, never; 1, slight chance; 2, moderate chance; 3, high chance. Reading, watching TV, talking to someone, lying down in the afternoon if circumstances permit, sitting in public place, sitting after lunch, passenger in a car for an hour, driver in traffic a few minutes. Total possible = 24; ESS $\geq$10 is sleepy. (Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–5.)

a patient in clinic with dementia on a sleep aid at the same time that the patient is drinking excessive amounts of caffeine. It would be preferable to eliminate all caffeine, and be able to avoid using the sleep aid, which has the potential for negatively affecting the patient's cognition. In part because of their age, patients with

Box 2.1
Insomnia - cannot sleep: treatment algorithm

1. Eliminate all forms of caffeine, including hidden forms, based on careful interview. Inform that caffeine can have effects for more than 24 hours and affect sleep at night even if taken in the morning.
2. Attempt to eliminate alcohol. In patients with dementia, this may require removal from premises or limiting amount provided to patient.
3. If suspicion of reflux (major cause for arousals at night; can be silent or with cough): avoid food and fluids 3 hours before bedtime, consider raising head of bed, consider trial of PPI or other antacid).
4. If any suspicion of allergic rhinitis (a cause for worsening of snoring/apnea, increased arousals at night, postnasal drip, and coughing): trial of nasal steroid spray at bedtime, if more persistent, consider adding daytime antihistamine such as fexofenadine or loratadine.
5. If any suspicion of chronic pain at night, consider scheduled acetaminophen dosing; if not effective, consider gabapentin at night (starting dose 100–300 mg, may increase to 600–900 mg). Avoid opiates. May need mattress foam topper if there are joint difficulties. Ensure firm bed (with or without mattress topper) if there is back pain.
6. Address circadian rhythm factors/ISWR: avoid or time daytime naps, eliminate opportunities for daytime dozing (hard-back chair for TV in living room, no recliners during the day, and so forth), attempt to offer stimulating activities in the day especially at times when the patient might take naps or doze, ensure bright light in day, lower lights in evening and night, consider nighttime melatonin in combination with morning light and strict wake time. Avoid overstimulating activities at night, and eating at night.
7. Try to dose medication with sleep-disrupting effects earlier in the day (β-blockers, cholinesterase inhibitor agents, SSRIs, venlafaxine, bupropion). Consider alternatives to activating antidepressants if insomnia seems related. Donepezil (Aricept) is associated with more sleep disruption than other cholinesterase agents in some studies. Consider trial of switching to alternative galantamine or rivastigmine. Try always dosing cholinesterase inhibitor agents in the morning.
8. Remove TV from the bedroom.
9. Ensure that hands and feet are not cold before bed; if so, suggest feet soaks, warm socks, bath before bedtime. Then ensure that bedroom is not overly hot during the night.
10. If patient is worried about sleep and worries in bed when not able to sleep, review sleep time versus time in bed and consider setting later bedtime, and strict wake time for mild sleep restriction. Make clock not visible in bedroom.
11. Ensure that environment is free of noise and is dark at night (this can be of particular concern for patients in nursing homes).
12. Ensure that patient does not have other primary sleep conditions that affect sleep, like RLS (can cause sleep onset insomnia and arousals and awakenings) and OSA (can cause nighttime sleep disruption and maintenance insomnia). See text for discussion.
13. Nocturia: eliminate all access to fluids in 3 hours before bedtime. Consider taking twice daily medications at dinner rather than immediately before bed to reduce fluid load. Have routine in place to void immediately before bed. Dose diuretics earlier in the day if possible. Recognize that nocturia can be a symptom of OSA, and consider obtaining PSG.
14. Appropriate treatment of anxiety and depression: the cholinesterase inhibitor agents can help neuropsychiatric symptoms in dementia and may be particularly effective in AD and DLB. SSRI agents are first-line mood medication treatment. Both should be dosed in the morning.
15. Avoid use of sleep aids unless all other possible factors that might eliminate the problem without requiring medication have been addressed. Patients with dementia medications have more potential for side effects that can worsen cognition. If a sleep aid is used, target temporary use.

Box 2.2
Hallucinations-agitation in evening or night: treatment algorithm

1. Are the hallucinations benign? As long as they do not worry the patient, do not have paranoid or scary content, or interfere too much with activities, these are not necessary to treat; just educate the caregivers. Benign visual hallucinations/illusions are common with DLB.
2. Ensure that the patient is not taking medications that increase vivid dreams that might be interpreted as hallucinations or cause confusion in patients with dementia. If on donepezil, try alternative such as galantamine or rivastigmine. β-Blockers might be dosed in the morning. Tricyclics might be used at the lowest doses and, if possible, completely avoided because they also typically are anticholinergic. Zolpidem can cause vivid dreams and confusional arousals. If on this medication, then consider alternatives including reevaluation of factors causing sleep disruption that might be addressed without use of medications.
3. Can be secondary in part to sensory deprivation, especially in elderly patients with additional confusion from dementia. Ensure that hearing is good (ears cleaned), cataracts removed, using glasses if needed, good lighting before bedtime and in evening, bathroom lighting.
4. If it is possible that anxiety/depression is fueling hallucinations, consider cholinesterase inhibitor agents in AD, DLB (less so in FTLD) because these can sometimes reduce hallucinations. Rivastigmine or galantamine might be preferred for nighttime hallucinations because donepezil can cause vivid dreams. Could also consider SSRIs. Typical SSRIs: sertraline (Zoloft), escitalopram (Lexapro), citalopram (Celexa). Paroxetine (Paxil) has a more anticholinergic profile and is generally not as good a choice in patients with dementia. Fluoxetine (Prozac) is typically more activating and is not optimal for use in patients with dementia with nighttime sleep disruption. Other agents for mood regulation in dementia include venlafaxine and buproprion. Both these are activating and should be dosed in the morning. bupropion has less effect on PLMS/RLS than SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs).
5. Reduce use of medications that can increase confusion or cause sedation. These medications can lead to greater misinterpretation of sensory stimuli at night. If the patient is on a chronic benzodiazepine, consider tapering (should taper slowly to avoid withdrawal symptoms and increased anxiety). Should also avoid medications such as opiates, muscle relaxants, and all medicines with anticholinergic side effects (especially in AD and DLB) that might worsen confusion. Amantadine, which is anticholinergic, can cause hallucinations. Any medication being used as a sleep aid might exacerbate the confusion and it can be worth a trial of tapering off that medication while considering alternative behavioral interventions.
6. Reduce factors that cause arousals at night (see **Box 2.1**; eg, any caffeine, reflux, nasal, medications). Arousals in patients with dementia may be associated with more confusion than simply arousals, as might be seen in patients without dementia.
7. Consider basic needs as a cause for arousals and agitation in patients who cannot communicate well. Patients may be trying to communicate needs such as hunger, thirst, urination, pain.
8. If agitation occurs at a regular time every day, this could be sundowning. Consider possible environmental triggers (see text).
9. Is it RBD? Could the agitation or hallucinatory activity be related to brief acting out of dream content? Ensure safety in the environment. Start with trial of melatonin and use PSG to ensure that there is no other cause like OSA for acting out confused.
10. Agitation, delirium, and excessive dreaming can be caused by OSA. Consider evaluation for OSA.
11. Periodic limb movements of sleep and RLS can cause wandering and pacing.

Box 2.3
Excessive daytime sleepiness and napping: treatment algorithm

1. Ensure adequate nighttime sleep. Patients with dementia may not be reliable reporters of nighttime sleep quality or duration. Maintain high suspicion for (1) inadequate or disrupted sleep at night as a cause for daytime sleepiness, and attempt to address factors that might be causing arousals at night (See **Box 2.1**). (2) OSA or PLMS/RLS in selected cases. (3) insufficient sleep time (going to bed late, waking up too early). Inadequate nighttime sleep may be the most common cause of sleepiness during the day, and all the factors noted in **Box 2.1** should be reviewed.
2. Reduce or remove medications causing sedation. Rule out the possibility that hypersomnia might be induced by the use of sedating medications and remove any possible offending agents. Such agents might include muscle relaxants, benzodiazepines, and opiate medications. In the case of opiate medications, these can be slowly tapered, and, if patient had both day and nighttime pain, dose gabapentin generously throughout the day (eg, 300–600 mg 4 times a day and 600–900 mg at bedtime). Other medications that can cause sedation include tricyclic antidepressants; sedating neuroleptic medications, including olanzapine (Zyprexa), quetiapine (Seroquel), and clozapine (Clozaril); hydroxyzine (Atarax); clonidine; cetirizine (Zyrtec); diphenhydramine (Benadryl); and lyrica (Pregabalin). Medications previously well tolerated in middle age, or before dementia, may have more sedating side effects when taken with dementia. Dopamine agonist agents can cause sleepiness and sleep attacks (eg, carbidopa/levodopa (Sinemet), ropinarole (Requip), pramipexole (Mirapex). All nighttime sleep aids can cause residual daytime sleepiness. Need to be suspicious and aware of side effects of sleepiness with all psychoactive medications. Patients with dementia are more likely to be living with the side effects of medications, because they are less likely to report them.
3. Daytime increased sleepiness caused DLB and PD. In a patient with DLB or PDD, hypersomnia may be caused by the underlying physiologic disorder as well as use of dopamine agonist medications. Even in DLB and PDD, consider other possible contributors to hypersomnia that may respond to other interventions. These patients may be especially vulnerable to the effects of other sleep disrupters or factors that produce sleepiness that can be addressed.
4. Daytime sleepiness caused by circadian rhythm disruption (see discussion on ISWR in text earlier, and in **Box 3.1**) is especially common in AD. Treatment is directed at consolidating nighttime sleep and reinforcing activity and stimulation in the day. Treatment suggestions include increased bright lighting in the daytime, increased daytime stimulation and exercise, ensuring quiet nighttime environment, avoiding situations in the daytime that are conducive to dozing (eg, sitting in recliner in front of TV after lunch or in evenings), trial of melatonin at night given at same time every night (0.5–3 mg), and setting a regular sleep-wake cycle with the same bedtime and same wake time. Eliminate caffeine, which can cause nighttime sleep disruption resulting in increased daytime sequelae of sleepiness.
5. Consider the possibility of depression. Depression can be associated with lowered activity levels and increased sleepiness. Such patients may benefit from a trial with an activating antidepressant, such as bupropion or venlafaxine.
6. Consider thyroid screening because it is readily treatable and levothyroxine may have a role in treatment of hypersomnia.

dementia may also be on multiple medications. It would similarly be desirable to eliminate certain medications or change to alternatives that might have less impact on sleep if these could be affecting the main sleep complaint, rather than simply adding medications that would be more likely to have a negative impact on cognition. Patients with dementia also often have anxiety or mild mood-related issues. These issues should be addressed with appropriate medications that can result in a positive benefit for both daytime alertness and nighttime sleep. Typical first-line choices are

Box 3.1
Treatment algorithm: SDB, ISWR in dementia

SDB

1. Obtain polysomnogram (PSG) to diagnose and characterize disorder. PSG determines presence and severity of SDB, Cheyne-Stokes breathing, and whether positional therapy is an option for patient.
2. Always maximally treat nasal congestion/allergic rhinitis in the setting of SDB, usually with nightly steroid spray with or without daytime antihistamine such as loratadine because this can worsen obstructive breathing and interfere with treatment, and is treatable.
3. If a patient is taking opiate medications, attempt to taper and substitute with high-dose gabapentin and/or scheduled Tylenol, because opiate medications worsen SDB. For example, if patient has pain in the day, add gabapentin and work up to 300 to 600 mg 4 times a day with 600 mg at bedtime, and taper off opiate medications.
4. If patients have Cheyne-Stokes breathing, ensure that heart failure is not present and, if it is, ensure that it is maximally medically treated.
5. After initiating treatment of rhinitis, and tapering off opiates if present and possible, obtain trial for positive airway pressure (PAP) therapy. In patients with dementia who are elderly with more comorbidities, this is usually best done in an attended PSG study setting. Patients with Cheyne-Stokes breathing or central components to apnea may be more comfortably and effectively treated with adaptive servoventilation (ASV) PAP therapy.
6. Elderly patients may be more likely to have mouth breathing and jaw laxity and may be more comfortably treated with masks that cover both mouth and nose.
7. If starting PAP therapy, it is essential to have good follow-up to work on mask fit issues, and to motivate for treatment adherence. This work can be provided by sleep specialists, or by informed primary physicians, or allied personnel. In follow-up, remind patients that adherence can help sleep continuity, reduce nocturia, reduce arousals with agitation at night, improve daytime alertness, and emphasize any gains to help motivate adherence. PAP may also reduce stroke risk.
8. If a strong positional component is present and REM sleep was evaluated in the lateral position in the diagnostic study, clinicians can consider strict lateral positional therapy as an alternative to PAP. Strict lateral sleep positioners need to be used (eg, commercial vendors are sometimes easier for patients to use and adhere to and include Rematee [www.rematee.com] and zzomaosa [www.zzomaosa.com]). Homemade lateral positional devices (eg, tennis balls in a sock attached to the back of a t-shirt with safety pins) can be used, but elderly patients are sometimes more compliant with commercial options.
9. Patients who are intolerant of PAP therapy, or not candidates for lateral positional therapy alone, can be treated with dental appliances. These can also be used adjunctively with lateral positional therapy if apnea is still present in a lateral position. Sleep studies should ideally be obtained after adjustment of dental appliances to ensure adequate treatment.

Irregular sleep-wake rhythm

1. Review all the factors in **Boxes 2.1** and **2.3** that can be affecting sleep at night or arousal level during the day.
2. Increase bright light exposure throughout the day, reduce ambient light and noise at night.
3. Increase stimulation and activity during the day if possible (scheduled walks, social activities), reduce exposure to environments conducive to sleep during the day (recliners, quiet TV watching).
4. Consider removal of cataracts that reduce light exposure to brain during the day, ensure glasses are provided if necessary, ensure ears are clean and hearing aids provided if necessary.
5. Trial of melatonin at night (0.5–3 mg) before bedtime (in conjunction with bright lights during the day).
6. Eliminate all caffeine except in early morning.

Box 3.2
Treatment algorithm: RBD, RLS/PLMS in dementia

RBD

1. Obtain PSG to ensure diagnosis is accurate and reported activity is not caused by underlying OSA causing arousals and confusion. If OSA present, treatment of OSA, as described later.
2. Immediately on considering diagnosis, advise measures to help ensure safety of patient and bed partner. RBD can be associated with sudden violent activity and lead to serious harm of patient or bed partner. Advise bed partner to sleep in another room until condition is treated. Remove all sharp objects, night stands, and lamps from immediate bedside environment. Consider advising use of light sleeping bag to restrict movements if acting out during sleep.
3. Remove or change dosing of medications/substances that may precipitate activity: MAO inhibitors, tricyclic antidepressants, SSRI, SNRI, alcohol, caffeine, chocolate. In the case of caffeine and chocolate, eliminate all consumption, including in the morning.
4. See **Box 2.2** regarding other causes of hallucinations and agitation at night to ensure that these factors have also been addressed.
5. Consider initiating pharmacologic treatment of RBD. If RBD is not confirmed on PSG, but OSA is found, consider treatment of OSA first.
6. If advice has been given on behavioral therapies, pharmacologic therapy can simultaneously be started. First-line pharmacologic treatment is not necessarily clonazepam in patients with dementia because of cognitive side effects. Instead, recommend first-line trial of melatonin (1 mg and increase to 3 mg, may increase to 6 mg, can increase to 9 mg, but high doses produce more headache and GI side effects). If melatonin not fully effective alone, may add adjunctive clonazepam, starting at lowest necessary adjunctive doses (0.5 mg). Temazepam may also be effective, but has more potential side effects than melatonin.

RLS/PLMS

1. Remove all medications and substances that could be worsening RLS/PLMS. These substances include all caffeine, chocolate, alcohol, tricyclic antidepressants (including amitriptyline), dopamine blocking medications (including antipsychotics, promethazine (Phenergan), metoclopramide (Reglan), prochlorperazine (Compazine), and diphenhydramine (Benadryl, Advil PM, Tylenol PM). SSRI and SNRIs can worsen RLS/PLMS and should be dosed away from bedtime, and, if necessary, an alternative medication for depression such as buproprion (Wellbutrin) might be used that has less effect on RLS/PLMS.
2. Behavioral measures can be helpful including daily aerobic activity, stretching exercises (especially of the legs), and massage of legs.
3. Obtain iron levels and supplement accordingly (for ferritin less than 45 ng/ml, advise supplemental iron every day dosed with tablet of vitamin C to help with absorption). Consider obtaining vitamin B_{12} level, treat if less than 350 pg/ml.
4. Consider initiate pharmacologic treatment of RLS/PLMS. See table.
5. First-line pharmacologic treatment with fewest side effects on cognition is supplemental iron in patients with low iron status (ferritin <45 ng/ml). In elderly patients with systemic disease, ferritin may be falsely increased and may need full iron panel. Iron treatment may be helpful in these cases if there is percent iron saturation <16%, total iron binding capacity >400 Mcg/dl, or total iron <60 Mcg/dl. Advise taking iron with vitamin C to increase absorption. If iron is in clinically deficient range, may also need work-up for sources of iron loss. If additional therapy is needed, try gabapentin at night 1 to 2 hours before bedtime or symptom onset (100–600 mg). Third-line therapy: dopamine agonists (ropinarole, pramixole) but these may cause more confusion. Fourth-line therapy: opiate analgesics (eg, tramadol, but ideally should avoid in patients with dementia).

Box 4
Medication strategies for non-specific sleep problems in dementia (see also discussion in text for specific cautionary information about use of medications (in "Use of medications for treatment of ISWR"))

Rules to remember prior to considering use of medications

1. Always remove medications that cause problems first.
2. Always implement behavioral measures first.
3. Always attempt to identify underlying problems and target specific issues before treating general symptoms.

Insomnia – cannot sleep: pharmacological approaches

Target temporary use, only if removal of agents, changing habits, and addressing other issues has failed (See **Box 2.1**).

First line: gabapentin at low dose can improve sleep symptoms and continuity (100–600 mg at bedtime). Melatonin is helpful in some patients.

Second line: trazadone and mirtazapine (Remeron) can worsen autonomic issues, and are typically associated with more daytime effects than gabapentin or melatonin. Zolpidem (Ambien) and eszopiclone (Lunesta) are also associated with more side effects than gabapentin and melatonin, and should be used at the lowest possible doses (Ambien, half a 5-mg tablet, or one 5-mg tablet; Lunesta, 1 mg). Sedating antipsychotic medications such as quetiapine (Seroquel) can worsen PLMS/RLS (but may help RBD) and are best used in patients with paranoia that is not responsive to cholinesterase inhibitor agents and used at lowest necessary doses (start with half of a 25-mg tablet). Use of benzodiazepines (e.g., lorazepam, diazepam) are not routinely recommended for sleep disruption in dementia, and, if being used chronically, should be tapered off slowly. Temazepam (Restoril) is the benzodiazepine with shortest half-life. Clonazepam is likely to be more effective for sleep than other benzodiazepines and helps RBD (but use at lowest possible doses). Zaleplon (Sonata) has the shortest half-life of newest generation sleep aids and may be useful for sleep-onset insomnia or waking in the middle of the night, but can have more side effects than gabapentin or melatonin. Diphenhydramine (Benadryl), Tylenol PM, and Advil PM have anticholinergic side effects that can worsen confusion/memory and PLMS/RLS.

Escessive daytime sleepiness and napping: pharmacological approaches

If other measures fail (See **Box 2.3**), pharmacologic therapy can be considered. First line, modafanil (Provigil), armodafanil (Nuvigil). Second line, methylphenidate (Ritalin) or other amphetamines can be used but have more side effects. Could also consider low-dose Synthroid (25 μg each morning) to boost wakefulness, especially if the patient has subclinical hypothyroidism (one study showed benefit with use of Synthroid in idiopathic hypersomnia, but this has not been studied in dementia). Consider use of activating antidepressants if there is comorbid mood difficulty: venlafaxine, bupropion.

Agitation in evening or night: pharmacological approaches

If other measures fail (See **Box 2.2**), pharmacologic approaches to treatment can be considered. Cholinesterase inhibitors in DLB, PDD, and AD can improve neuropsychiatric symptoms and should be tried, but dosed in the morning. Donepezil can be associated with causing vivid dreams, and thus galantamine or rivastigmine might be preferable in the setting of hallucinations. Should also address anxiety and depression, which can worsen at night. Use of SSRIs dosed in the morning may help with anxiety. Generally, avoid paroxetine (Paxil) because of anticholinergic side effects and fluoxetine (Prozac) because of activating profile, but can consider sertraline (Zoloft), citalopram (Celexa), escitalopram (Lexapro). Gabapentin (Neurontin) can be helpful at night to reduce arousal tendencies that can be associated with confusion, and typically is not associated with as much sedation as other sleep aids (doses might range from 100–600 mg). Melatonin can be tried. If paranoid content, can consider trials of low-dose antipsychotics (except in the setting of patients with DLB, in whom these should be carefully avoided because they can precipitate more rigidity that may not be reversible). Can consider Seroquel 25 mg tablets, starting with half a tablet at night. If agitation is also present in the day, can add half a tablet in morning. May titrate up to

1 tablet twice a day or higher doses if necessary. Need to be aware that antipsychotics increase risk of death in patients with dementia. Other sleep aids are also often used at night to reduce agitation episodes, including trazodone, but this can cause residual daytime effects and negatively impact cognition. Mirtazapine (Remeron) is sometimes used to help with sleep at night, as noted earlier, and may be helpful in depression or in the setting of weight loss, but can worsen PLMS/RLS, and may be associated with more confusion than gabapentin or melatonin. Typical mirtazapine doses start with 7.5 mg, and may be increased to 15 mg; higher doses are less sedating. See section on Insomnia, above, for other pharmacological approaches to improving sleep continuity which may also reduce agitation at night.

sertraline (Zoloft), escitalopram (Lexapro), or citalopram (Celexa) dosed in the morning.

Primary underlying sleep disorders including sleep apnea, RLS/PLMS, REM behavioral disorder, and ISWR should also be addressed in patients with dementia. Details of the treatment approach to these issues in the setting of dementia are provided in **Boxes 3.1** and **3.2**. It is also important to note that OSA can present as simply sleep maintenance insomnia in some patients, or restless movements at night.

Box 4 addresses the use of medications for the treatment of symptoms in patients with dementia having sleep-related problems. As emphasized, medications

General rules for treatment of sleep in patients with dementia

1. When using medications, only start one medication at a time.
2. Always write down the list of recommended interventions at each visit, so the caregiver/patient has a copy for their reference. This list is especially important because of the complex nature of patient care with dementia, in which the patient is not always able to be fully responsible, and the caregiver may be overburdened. In addition, comprehensive behavioral recommendations for sleep health can include many components, which are best written down for reference and can be reviewed specifically at follow-up (eg, recommendations of new set wake-up times, lighting, and reduction of medications).
3. Encourage the caregiver/patient to keep a binder with an accurate list of all medications, and lists from prior visits regarding recommendations.
4. Ensure that medications are being taken reliably. Patients with dementia might be taking repeated doses mistakenly, forgetting doses, or taking them at the wrong times. Pill boxes with structured checking to ensure accurate dosing is important for all medications (even if not prescribing sleep-specific medications, mistakes with regard to other medications can affect arousal, sleep, confusion, and agitation).
5. At clinic visits, first ask patients to provide their perspective on issues while caregivers are quiet for at least 5 minutes to allow patients the opportunity to show knowledge of their condition and their perspective. This opportunity helps clinicians to be able to later explain treatment goals to patients from the perspective of the patient's concerns. Having caregiver input throughout the interview can increase efficiency, but listening to the patient without caregiver input initially, even if information is not always accurate, shows respect for the patient and can help to build a stronger clinical relationship and rapport with the patient.
6. Although a comprehensive review of symptoms and treatment is essential, always target primary underlying sleep disorders such as OSA, RLS/PLMS, or RBD. These primary sleep issues can have as much, if not more, impact on patients with dementia than on patients without dementia. In the absence of targeted treatment of specific underlying sleep disorders, patients may not improve.

When to get a PSG in a patient with dementia and sleep problems

1. In the setting of sleep difficulties, first advise removal of all potentially offending agents and habits as per **Boxes 2.1, 2.2** and **2.3**.
2. Obtain PSG if:
   a. Has symptoms of OSA
   b. Has symptoms of acting out dreams at night (to evaluate for RBD and OSA, which can mimic RBD)
   c. Has nighttime sleep disruption that has not been responsive to other interventions (eg, treatment-resistant sleep maintenance insomnia, agitation, or hypersomnia that may be related to OSA in the absence of snoring)

for improving nighttime sleep are typically used as a last resort because they are more likely to be associated with side effects in the patient with dementia, and the effects of performing the general overall sleep assessment and addressing the underlying factors can be effective, and sometimes obviate the use of additional medications. An exception is the case of RBD when medications, starting with the type that is least likely to have side effects in dementia (melatonin), are likely to be needed. Activating medications such as armodafinil and modafinil can also be well tolerated in dementia, but other causes for hypersomnia should be addressed first. Studies examining the effects of newer sleep aid medications in patients with dementia are few, or are not designed to compare treatment with best alternative practice assessments for addressing sleep problems. Because of the lack of high-level evidence that compares the use of different types of sleep aids, the discussion in the table with respect to sleep aids to some degree reflects institutional practice habits.

SUMMARY

Dementia is common and increasing in prevalence worldwide. Sleep-related problems are a major source of caregiver distress and cause for nursing home placement. A practical knowledge of how to assess the patient with regard to whether they have (1) problems with sleep at night, (2) sleepiness during the day, or (3) agitation episodes is provided in this article. Although there are specific types of sleep problems that occur more commonly in patients with dementia and in patients with particular types of dementia, it is still essential at the initial evaluation to address first the common basic factors that might also be affecting sleep disruption, sleepiness, or agitation, because patients with dementia are often vulnerable to these factors. New knowledge has allowed clinicians to understand more directly the reasons why certain types of dementia are more often associated with certain types of symptoms, and it is expected that as knowledge of the underlying pathophysiology of dementias increase these will be refined further and may help in the selection of appropriate treatments. Whether sleep-related disorders including OSA, or limited sleep time, predisposes to the development of dementia is another area that is being explored. Comprehensive sleep evaluation is essential in the treatment of dementia, given that sleep-related issues are common, often treatable, affect patient function, and are a major cause of caregiver distress.

Case example

A 72-year-old woman presented to a sleep clinic with a complaint of sleep onset and maintenance insomnia. She had recently been diagnosed with probable mild dementia of the mixed type (AD and vascular dementia), and had been moved to a nursing facility. She reported having had problems with insomnia throughout her life, but that these had become worse recently. Bedtime was 10 PM and it would take hours to fall asleep. She also had difficulty staying asleep, awakening multiple times, and it was hard for her to get back to sleep. She estimated she would get only about 3 hours of sleep and would leave the bed for the day about 5:30 AM to get ready for breakfast. She also reported a history of snoring at night, chronic nasal congestion, leg jerks at night, leg discomfort at night possibly related to diabetic neuropathy, and nocturia (3–4 times per night). In the facility, she had been paired with a roommate with AD who would yell loudly for about an hour after she was awakened by staff at 2 AM most nights. Caffeine included 1 to 3 cups of half decaffeinated and half caffeinated coffee in the morning, and occasional additional coffee in the afternoon. Donepezil (Aricept) had been started around the time that the sleep problems worsened and she had been taking it at night before bedtime.

Initial recommendations to improve sleep were the following: she was advised to switch donepezil (Aricept) 10 mg to an alternative acetylcholinesterase inhibitor agent, galantamine ER (Razadyne) 16 mg, and to take this in the morning instead of at night. She was advised to discontinue caffeine, she was advised to limit all fluids 3 hours before bedtime, and she was referred for a sleep study.

At a return clinic visit, sleep had improved. She thought that the change was primarily caused by changing the donepezil medication. She now thought she was sleeping about 5 to 6 hours per night. She was still waking up during the night, but could fall sleep a little more easily. She expressed concerns about the facility environment. She continued to have difficulty with her roommate's agitation and she was worried people were stealing her possessions. The sleep study showed mild OSA with an AHI of 9, periodic limb movements of sleep (PLMS) associated with arousals (PLM Index of 15 per hour), increased electromyogram (EMG) in REM with arousals and disruption, and nasal stuffiness with mouth breathing.

During the course of subsequent follow-up visits, a variety of additional sleep-related interventions were implemented. She was treated for nasal stuffiness, underwent a PAP trial, and was started on PAP therapy. She was started on a low dose of gabapentin (200–300 mg at night) for limb movements and nighttime pain, and started on melatonin to help improve REM sleep continuity. Gabapentin and melatonin were started in a staggered fashion so that side effects and benefits could be monitored.

After all interventions had been implemented, sleep was improved. She was falling asleep immediately, and waking up only to go to the bathroom, after which she was readily able to fall back to sleep. She also reported less fatigue in the day when using CPAP therapy. Even though she still had a roommate with agitation, it did not bother her as much. She was generally sleeping well from 11 PM to 7 AM.

Three years later, the patient returned to clinic with new problems with sleep. She again was not able to fall asleep or stay asleep. She had moved to a new facility, where her environment was better, even though sleep onset and maintenance insomnia were worse. All environmental factors and medications were reviewed. The patient reported drinking only decaffeinated beverages, but the facility was contacted and it was determined that they were providing her with regular caffeinated beverages, which she had not realized. She was advised to discontinue drinking all tea and coffee. Sleep once again improved.

Case example comment

This case of insomnia in a patient with mild dementia highlights how many factors can simultaneously affect sleep in patients with dementia. It also highlights some of the special challenges faced when treating patients in the nursing home setting. Although this patient had OSA, it was also critical to consider how to adjust medications that could contribute to insomnia (in this case donepezil) and later to carefully inquire about a caffeine history. Additional interventions included limiting fluids 3 hours before bedtime and treating nasal stuffiness. The choice of sleep aids (gabapentin and melatonin) were made based on a consideration of the presence of periodic limb movements and comorbid pain problems, as well as the finding of increased EMG activity in REM with REM sleep disruption. Patients with vascular dementia are reported to have a higher risk for apnea. In addition to the benefits that apnea treatment may offer for sleep continuity and function, treatment might reduce risk of future strokes.

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