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Update on the Diagnosis and Management of Sleep Disturbances in Dementia

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Overview

Sleep disturbances in patients with dementia are common, and are a major cause of reduced patient and particularly caregiver quality of life, often leading to patient institutionalization. While there are several excellent reviews on sleep disturbances in dementia, the principal goals of this chapter are to 1) review the most common and pertinent sleep disturbances in the home/ambulatory setting, 2) provide a relatively simple diagnostic scheme for clinicians (and caregivers) to determine the likely cause(s) of the sleep disturbances, and 3) provide a summary of nonpharmacologic and pharmacologic strategies for managing the disturbances. The ultimate purposes of such a review is to maximize quality of life for patients and their bedpartners, and enable patients with challenging sleep disturbances to remain in the home environment as long as possible.

There are several dozen causes of cognitive impairment and dementia. The principal causes of irreversible dementia are shown in Table 1; the reader is directed to other sources for a more complete discussion of irreversible dementing illnesses.^{1–3}

Alzheimer's disease (AD) is the most common such cause, with the dysfunctional proteins in this disorder being amyloid (the major constituent of neuritic plaques) and tau (the major constituent of neurofibrillary tangles). Thus AD is considered an "amyloidopathy," and also a "tauopathy." Dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) are the primary dementia syndromes associated with underlying Lewy body disease (LBD). The choice of the DLB versus PDD label relates to the timing of the onset of dementia and parkinsonism – DLB is applied to those who develop dementia prior to the onset of parkinsonism or within one year from the onset of parkinsonism, whereas PDD is applied to those who develop dementia anytime after one year from the onset of parkinsonism. Alpha-synuclein is the primary dysfunctional protein in the Lewy bodies and Lewy neurites of LBD, and LBD (along with multiple system atrophy (MSA) and primary autonomic failure (PAF) are collectively considered "synucleinopathies." LBD is now considered the second most common irreversible cause of degenerative dementia, accounting for approximately 15–25% of cases. Frontotemporal lobar degeneration (FTLD) is a spectrum of disorders which principally affect the frontal and temporal lobes. It typically manifest clinically as a behavioral/dysexecutive syndrome (known as frontotemporal dementia or FTD) or an aphasic syndrome (known as primary progressive aphasia or PPA).

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FTLD likely accounts for 5–15% of dementia cases. Among those with dementia whose onset of cognitive decline begins before age 65, the FTLD disorders are particularly common (in the 20–50% range). Pick's disease, corticobasal degeneration, progressive supranuclear palsy, argyrophilic grain disease, and the rare genetically-mediated disorder of frontotemporal dementia with parkinsonism linked to chromosome 17 associated with mutations in the gene encoding microtubule associated protein tau (FTDP-17*MAPT*) are collectively considered “tauopathies.” FTLD with ubiquitin- and TAR-DNA binding protein-43-positive inclusions (FTLD-U/TDP-43), FTLD with motor neuron disease, and frontotemporal dementia with parkinsonism linked to chromosome 17 associated with mutations in the gene encoding progranulin (FTDP-17*PGRN*) are considered “tardopathies.” Approximately 40% of patients presenting with an FTD or PPA syndrome have an underlying tauopathy, 40% have a tardopathy, and the other 20% have either atypical AD or a more obscure disorder. Huntington's disease (HD) is a relatively uncommon genetically-mediated disorder associated with the dysfunctional gene product from *huntingtin*. Therefore, among the neurodegenerative disorders which present in an insidious fashion and have a slowly progressive course, a spectrum of disorders and their associated proteinopathies can underlie their symptoms. The primary symptoms *and inherent sleep disturbances* are likely linked to the dysfunctional proteins and associated topography of neurodegeneration and neurochemical alterations.

Multi-infarct dementia is now considered within the spectrum of vascular dementia (VaD). While the prevalence of VaD continues to be debated, and cerebrovascular disease is quite common in both cognitively impaired and cognitively normal elderly individuals,^{4, 5} pure VaD as the sole cause of dementia appears to be relatively uncommon. There are several sets of criteria for the diagnosis of VaD, with the main concept being the onset of dementia occurring within 3 months following a cerebral infarct, particularly when the infarct involves the neocortex or thalamus..

Sleep disturbances are also common in the prion disorders (eg, Creutzfeldt-Jacob disease (CJD), fatal familial insomnia (FFI), and Gerstmann-Straussler-Scheinker disease (GSS), and marked insomnia is a defining feature of FFI.

It is worth emphasizing that most of the literature on sleep disturbances in dementia involve patients clinically diagnosed with AD. However, as noted above, a significant minority of patients with typical AD clinical features do not have AD when examined postmortem, and instead have the non-AD disorders listed in Table 1. Therefore, readers of this literature must keep in mind that these studies have very likely included cases with non-AD disorders and thus the findings may not be specific for AD. Despite these inconsistencies, there is ample data and clinical experience from which to develop strategies for managing common and often challenging clinical problems in the demented population.

Diagnostic Approach

This paper will provide data and strategies which are updated from an earlier review⁶ using a diagnostic approach as follows (Table 2). Essentially all sleep disturbances in dementia relate to one of four primary symptom complexes: insomnia, hypersomnia, excessive motor activity at night, and nocturnal hallucinations/behavioral problems. Within each symptom we will review how the symptom relates to the dementing illnesses themselves, which primary sleep disorders may be at play, which medications employed for dementia may impact on the symptom, the role of depression in that symptom, and finally how circadian dysrhythmias can underlie that symptom. The management strategies—pharmacologic and nonpharmacologic—will be then be reviewed. Details regarding specific medications are presented in Table 3.

Symptom Complex - Insomnia

Dementing illness

The incidence and prevalence of insomnia per se in patients with dementing illnesses are not known, although sleep disturbances in general are known to exist in patients with Alzheimer's disease.⁷⁻⁹ Such disturbances, which include insomnia, circadian dysrhythmia, nocturnal awakenings and agitation, and nocturnal wandering can cause considerable caregiver burden and lead families to decide on nursing home placement.^{7, 10, 11} The medications used to treat these disturbances can worsen obstructive sleep apnea and daytime symptoms.¹² Thus, the management of sleep disturbances in patients with dementia is a complicated and important clinical and societal problem. Issues relating to specific sleep disturbances are described in the following sections. Insomnia as an isolated disturbance may improve with one or more of the agents presented in Table 3. Studies using sodium oxybate (Xyrem®) and ramelteon (Rozerem®) in patients with dementia plus insomnia are underway.

Sleep disorders

Restless legs syndrome—The incidence and prevalence of restless legs syndrome (RLS) in patients with AD and other dementing conditions are not known, nor are there any studies that address the safety and efficacy of various agents in this population. Insomnia and/or hypersomnia can result from untreated RLS. RLS is a clinical diagnosis and purely based on a patient's symptoms. If a patient with dementia does not already carry an RLS diagnosis, one must rely on the patient's response which by virtue of their illness may or may not accurately reflect whether any symptom is present or not. One must therefore rely on the bedpartner's determination of the degree of restlessness at night rather than solely basing one's impression on the patient's recall of typical RLS symptoms. Our clinical experience suggests that RLS occurs with relative frequency in patients with AD, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia. Several agents (e.g., carbidopa/levodopa, pergolide, pramipexole, and gabapentin – see Table 3) appear to be generally well-tolerated and efficacious. However, the dopaminergic agents should be used with caution in patients with psychotic features as these agents can escalate hallucinations and delusions.

Clinicians should keep in mind the association of iron deficiency and RLS; when these coexist, it is often challenging if not impossible to effectively treat RLS. One should not rely on routine results obtained from a standard complete blood count – it is the ferritin level that is most important. Those with RLS and ferritin levels below 50 ng/mL typically have limited responses to therapy. In such patients, daily use of iron supplementation (Vitron C® – ferrous fumarate plus vitamin C is particularly well-tolerated) for at least two months, and perhaps longer, to achieve and maintain ferritin levels well above 50 ng/mL. It is reasonable to also administer a dopaminergic agent or gabapentin over this same time period, and some patients no longer require continued use of dopaminergic therapy or gabapentin once ferritin levels exceed 50 ng/mL.

This same logic for assessing iron deficiency and treating with iron replacement therapy applies for periodic limb movement disorder (see section on excessive motor activity at night).

Central sleep apnea—Central sleep apnea (CSA) can cause profound hypersomnia and/or insomnia; this topic is discussed in the section on hypersomnia.

Medication effects

The only agents approved by the United States Food and Drug Administration for the management of dementia are the acetylcholinesterase inhibitors (ie, tacrine, donepezil, rivastigmine, and galantamine) and the NMDA antagonist memantine. The acetylcholinesterase inhibitors (AChEI) act by blocking acetylcholinesterase activity, thereby leaving more acetylcholine in the synaptic cleft to continue activating the post-synaptic neuron. Memantine blocks NMDA receptors, and is believed to provide benefits by decreasing glutamatergic excitotoxicity. The usual starting doses and titration schedules are shown in Table 3. The AChEI agents and memantine can improve cognitive and neuropsychiatric symptoms and improve functional abilities; there is no convincing evidence that any of the agents slow the course of any of the dementing conditions.

It is common practice for patients to be commenced on either an AChEI or memantine first, and once the maintenance dose is achieved, to then add the other class or agent such that a combination of memantine plus one of the AChEI is being administered. While the clinical benefit from these agents is typically modest at best, rare patients do experience rather dramatic improvement in symptoms and functional abilities, particularly with the AChEI. Based on head-to-head studies and clinical experience, none of the AChEI appear to be superior to the others. However, there is variability in the clinical benefits and side-effects for each individual, so changing from one AChEI to one of the others is reasonable depending on the response to therapy. Despite the often disappointing efficacy of these agents, and potential side-effects which can impact sleep and alertness, the progressive nature and universally fatal result of the irreversible dementing disorders certainly justifies using the AChEI and/or memantine at least for trial periods to determine if efficacy warrants continued use.

Tacrine—Tacrine (Cognex®) was the first AChEI marketed for management of cognitive impairment in Alzheimer's disease, but is rarely used anymore due to liver toxicity and need for frequent dosing during the day. Insomnia can occur with this agent.

Donepezil—Donepezil (Aricept®) was the second AChEI to become available on the market, and is widely used in the United States and abroad. Donepezil effects acetylcholinesterase activity. The manufacturer recommended that it be dosed at night to minimize the development of nausea, although many clinicians now dose this agent with breakfast as nausea tends to be mild and infrequent and insomnia, nightmares, and nocturnal hallucinations can be problematic for some patients.

Rivastigmine—Rivastigmine (Exelon®) effects both acetylcholinesterase and butylcholinesterase activity, and this agent also is widely used in patients with dementia. Oral and transdermal formulations are available. The manufacturer recommends that the oral form be administered twice daily, and most patients take the pill with breakfast and with supper. If insomnia is problematic with this agent, the latter dose can be taken earlier in the day such as with lunch. The transdermal formulation should be applied each morning, with the previous day's patch removed and the current day's patch placed on a different location of the skin (this is often changed after a patient takes a shower in the morning).

Galantamine—Galantamine (formerly Reminyl, now Razadyne®) effects acetylcholinesterase and nicotinic receptor activity. This agent comes in liquid, capsule (given twice daily), and extended-release capsule (given once daily) formulations. The extended-release pill should be given in the morning. If insomnia is problematic with the liquid or standard capsule formulations, the latter dose can be taken earlier in the day such as with lunch.

Memantine—Memantine (Namenda®) is an NMDA receptor antagonist, and it is often used in combination with one of the acetylcholinesterase inhibitors as noted above. The medication is typically titrated upward over 3–4 weeks to a maintenance dose of 10 mg twice daily. While efficacy has been demonstrated in placebo-controlled trials, clinical experience has shown that improvement in cognition and neuropsychiatric issues is typically subtle rather than dramatic. Side-effects are relatively uncommon and minor. Insomnia due to memantine is rare; when it does occur, taking the latter dose earlier in the day such as with lunch often alleviates insomnia.

Depression

Depression is common in patients with dementia, and can cause insomnia in demented individuals similarly to those without any cognitive impairment. Antidepressant medications can also lead to insomnia, particularly those with “activating” properties such as fluoxetine (Prozac®), venlafaxine (Effexor®), and bupropion (Wellbutrin®). The choice of when to treat depression and with which agent is up to the clinician, but since tricyclic antidepressants have mild to severe anticholinergic side-effects, these agents should generally be avoided in patients with dementia. Sertraline (Paxil®) also has some anticholinergic activity and is not ideal for patients with dementia.

Circadian dysrhythmia

Although precise data on the incidence and prevalence of circadian dysrhythmia in the demented population do not exist, several groups have observed a high frequency of sleep fragmentation and circadian dysrhythmia in the institutionalized elderly.^{8, 9, 13, 14} The symptoms of insomnia and hypersomnia can reflect a primary circadian dysrhythmia. Degenerative changes in the suprachiasmatic nucleus (SCN) of the hypothalamus and decreased melatonin production are thought to be contributing factors in the circadian dysrhythmic abnormalities in patients with AD and other dementing conditions.^{15, 16}

Two primary management strategies center around this knowledge—exogenous melatonin and phototherapy. Data from relatively small numbers of patients with dementia suggest that melatonin can improve sleep continuity and lengthen total sleep time.^{17, 18} A multicenter placebo-controlled trial using 2.5 mg slow-release and 10 mg formulations of melatonin failed to demonstrate efficacy over placebo, although there were individual patients who clearly appeared to benefit from melatonin.¹⁹ Studies with ramelteon (Rozerem®) for management of circadian dysrhythmia in patients with dementia are in progress, and clinical experience thus far has yielded variable efficacy but good tolerability. Phototherapy has shown some promise in the management of circadian dysrhythmia in demented individuals, although the optimal timing and duration of phototherapy and illumination intensity have not yet been determined.^{20–23}

Symptom Complex - Hypersomnia

Dementing illness

The incidence and prevalence of hypersomnia in the various dementing conditions are not known, and there are no published reports of hypersomnia directly related to an underlying degenerative dementing disorder. Experience at our center indicates some individuals with dementia with Lewy bodies or frontotemporal dementia have objective evidence of hypersomnolence as measured by the multiple sleep latency test, which is not associated with another primary sleep disorder, and such hypersomnolence can improve with psychostimulant therapy. More recent evidence in DLB patients from our center has revealed marked hypersomnolence (mean initial sleep latencies less than five minutes), sometime associated with two or more sleep onset REM periods, on the MSLT - suggesting

a “narcoleptic” profile [Ferman et al, unpublished data]. Low dose methylphenidate (5 mg or less) has been shown to improve alertness in very old patients residing in nursing homes,²⁴ and there is very recent evidence suggesting methylphenidate in older individuals might reduce fall risk.²⁵ In our experience, modafinil, methylphenidate, dextroamphetamine, and dextroamphetamine/metamphetamine have been moderately helpful in managing hypersomnolence in patients with dementia without inducing untoward neurobehavioral or cardiovascular side-effects (Table 3). The anatomicophysiology underpinnings of hypersomnia in dementing conditions are unclear, although alterations in hypocretin production or physiology may be at play.²⁶

Sleep disorders

Obstructive sleep apnea—The relationships between obstructive sleep apnea (OSA), cognitive status, and dementia are complex and not fully understood. Although there appears to be an association between OSA and dementia, there is conflicting data on whether OSA is causally related to dementia.^{27–32} Since there is a marked increase in intracranial pressure and change in cerebral perfusion during apneic events,^{33, 34} one would expect that if OSA is causally related to any etiologic mechanism for dementia at all, that vascular dementia would be most likely related. Evidence accumulated over the past 20 years indicates that untreated OSA in the non-demented population causes cognitive impairment, excessive daytime somnolence (EDS), and diminished mood and quality of life, and that treatment of OSA [particularly with nasal continuous positive airway pressure (CPAP)] improves cognitive performance, EDS, mood and quality of life.^{35–50} Neuropsychological analyses have revealed that in patients with OSA, cognitive flexibility, attention, processing speed, and memory all improve with CPAP therapy.^{39, 46, 51} The challenge is that many patients with OSA do not experience an obvious clinical benefit from CPAP therapy, or cannot tolerate nightly CPAP use, so compliance of CPAP therapy even in non-demented individuals is far from ideal.

There are instances in which patients have been diagnosed with delirium,^{52, 53} dementia (not otherwise specified),⁵⁴ and a degenerative dementing illness⁵⁵ who are found to have untreated OSA, and delirium or dementia disappears with CPAP therapy. *Hence, OSA can be considered one of the reversible causes of delirium and dementia.* The frequency of such cases is not known, but the fact that some individuals have dramatic functional and neuropsychometric improvement with CPAP therapy, and the high prevalence of OSA in the elderly,²⁸ underscore the need to consider OSA in any patient with cognitive impairment. Furthermore, as CPAP therapy has now been shown to improve the sleep quality in bedpartners of patients with OSA,⁵⁶ caregivers of patients with dementia and OSA could enjoy improved quality of sleep/quality of life with their bedpartners’ use of CPAP therapy.

There are recent data showing that cognition and alertness improve with CPAP therapy in patients with OSA and a coexisting dementing illness, and that CPAP therapy is tolerated in demented individuals.^{57, 58} No published data exists on the effects of CPAP therapy on the bedpartners/caregivers of patients with OSA and dementia. Experience at our center has also revealed the following regarding patients with dementia and OSA: 1) a minority of patients *do* experience significant functional and mild neuropsychometric improvement with CPAP therapy, 2) a significant proportion of patients *do* tolerate CPAP therapy and use it nightly, 3) some patients with positional OSA *do* tolerate positional therapy and experience mild clinical improvement, and 4) some caregivers of patients enjoy less fragmented sleep and less EDS while their bedpartners with dementia use CPAP therapy. Therefore, importantly, it should not be assumed that patients with dementia and OSA cannot tolerate nor benefit from CPAP therapy – most deserve a PSG and CPAP trial similar to any individual without dementia.

Central sleep apnea—Central sleep apnea (CSA) is known to occur in patients with primary cardiac and primary central nervous system dysfunction. The dysregulation of the brainstem respiratory neuronal networks is presumed to be responsible for CSA in degenerative dementing illnesses, and likely contributes similarly in vascular dementia. The frequency of CSA in the degenerative and vascular dementing conditions is not known, but in our experience this is far less common than OSA in those with mild to moderate dementia. As in CSA related to cardiac dysfunction, management can be quite challenging. Nasal CPAP therapy, bilevel PAP therapy, adaptive servoventilation devices, supplemental oxygen, benzodiazepines, or a combination of two or three of these can provide symptomatic improvement in some cases. Therapeutic trials typically require one or two nights of polysomnography to determine which single or combination of therapies provide the maximal benefit.

Complex sleep apnea syndrome—Some patients with OSA develop a high frequency of central apneas and/or a disruptive Cheyne-Stokes respiratory pattern after application of CPAP, which has been termed ‘complex sleep apnea syndrome’ (CompSAS).^{59, 60} Adaptive servoventilation (ASV) has been shown to be effective in treating CompSAS.⁶¹ The incidence and prevalence of CompSAS in patients with dementia have not been well-studied, but in our experience, this disorder does occur with some frequency in the dementia population, and ASV can be tolerated and effective.

Periodic limb movement disorder—See section on excessive motor activity at night.

Medication effects

The AChEI rarely cause hypersomnia, but in those who do experience this side-effect, it may be worthwhile to change to another agent in this class as it is very rare to experience hypersomnia as a side-effect across all of the acetylcholinesterase inhibitors. Hypersomnia due to memantine is also rare.

Depression

Hypersomnia related to underlying depression can certainly occur, and if suspected, an antidepressant with few or no sedating properties could be employed.

Circadian dysrhythmia

See section on insomnia. Also, as noted above, wake-promoting agents can be used effectively and without side-effects in patients with hypersomnia whether related to a circadian dysrhythmia or not. Sometimes strategies directed at minimizing insomnia (eg, a sedative/hypnotic and/or phototherapy) plus a wake-promoting agent during the day can provide the best response.

Symptom Complex - Excessive Motor Activity at Night

Dementing illness

See section on nocturnal hallucinations/agitation for more details..

Sleep disorders

REM sleep behavior disorder—REM sleep behavior disorder (RBD) is characterized by simple or complex limb movements and/or vocalizations during rapid eye movement (REM) sleep, and such behaviors typically mirror the content of the dream when a patient is awakened and questioned.⁶² Behaviors can be violent, and patient and bedpartner injuries can occur. The frequency and severity of RBD is variable between patients, and during the

course of symptoms in individual patients, but when RBD is associated with a neurodegenerative disorder, the symptoms tend to wane as the degenerative illness progresses. Differentiating RBD from nocturnal wandering, somnambulism, and sleep terrors can usually be done by taking a careful history.⁶³ RBD is more short-lived, involves more vigorous limb movement, is often associated with vocalizations, dream content mirrors behaviors, dream often involves chasing or attacking theme, and behaviors tend to occur more in second half of the night when more REM sleep typically occurs. Nocturnal wandering is typically more prolonged, less violent, not associated with any apparent dream, and with a pacing or rummaging quality. Somnambulism is less violent, more prolonged, tends to occur in first half of the sleep period when more non-REM sleep occurs, and is not associated with any dream recall. Sleep terrors are typically not associated with any dream, involve more vocalization than limb activity, occurs in first half of sleep period. Some patients have elements of more than one of these distinct non-REM sleep parasomnias. When the diagnosis is in question, particularly when the potential for injury is present, polysomnography is warranted and preferably performed with additional EMG leads on the arms and with synchronous video/PSG monitoring.

The association of RBD with neurodegenerative disease is now well-established, and occurs particularly frequently in dementia with Lewy bodies (DLB), Parkinson's disease with (PDD) or without dementia, multiple system atrophy, and pure autonomic failure (known collectively as the "synucleinopathies."^{63–68}) The sensitivity and specificity of RBD for DLB and PDD in the setting of dementia has not yet been determined, but detailed antemortem analyses and the lack of any pathologically-confirmed cases of RBD in pure AD, Pick's disease, frontotemporal dementia, corticobasal degeneration, or vascular dementia suggests that RBD may be predictive of underlying Lewy body disease in most patients with dementia.⁶⁸ Recent analyses have also shown that in those patients with dementia and RBD, the pattern of impairment on neuropsychological testing (e.g., impaired visuospatial functioning, verbal fluency, and attention/concentration, with relative preservation of memory and confrontational naming) is quite consistent, and parallel to what has been described in autopsy-proven Lewy body disease.^{69, 70} Therefore, a careful sleep history and neuropsychological testing may provide diagnostically-relevant information in the evaluation of patients with dementia.

Ensuring safety in the sleep environment is the simplest recommendation for managing RBD (i.e., remove all potentially injurious objects away from the bed, place mattress on floor next to bed, etc.). Clonazepam has been the drug of choice and is usually effective in the 0.25 to 1.0 mg/night dose range (Table 3).^{71, 72} As benzodiazepines can precipitate or aggravate OSA, it is important to ensure that no OSA exists before using this agent, or ensure nasal CPAP therapy is successfully treating OSA if this is present. There is often concern expressed by clinicians about using this long-acting benzodiazepine in patients with dementia, but in our experience it has been tolerated quite well with few or no cognitive side-effects in the vast majority of cases. Melatonin has also been shown to be effective at minimizing RBD, either by itself or in combination with clonazepam.^{73, 74} We typically commence 3 mg nightly, and depending on clinical response and side-effects (which are typically rare), titrate upward in 3 mg those rare individuals who have pervasive RBD which is not adequately responding to clonazepam plus melatonin, adding quetiapine can be effective. Some patients derive benefit from controlled-release carbidopa/levodopa for RBD, so in those with RBD plus RLS and/or PLMs, this agent may be a good first option.

Periodic limb movement disorder—As in the other primary sleep disorders, the incidence and prevalence of periodic limb movement disorder (PLMD) in patients with dementia are not known. In our experience, PLMD does occur with some frequency in this population, and PSG is sometimes very helpful diagnostically in hypersomnolent demented

patients when they and their bedpartners are entirely unaware of the existence of PLMs. Some unresolved issues are what frequency of PLMs, and what frequency of arousals due to PLMs are clinically significant. It should be remembered that the snapshot that one night's PSG provides is an approximation of the nightly presence and frequency of key sleep indices, so it is probably not necessary to rely on hard cut-offs for PLM frequency and PLM arousal frequency to make treatment decisions.

If the sleep issue is patient hypersomnolence, then a PLM arousal frequency of at least 5 or 10 per hour (similar to the suggested arousal frequency for treating sleep-disordered breathing) would be reasonable to treat. If the sleep issue is bedpartner sleep disruption due to the patient's excessive motor activity at night, then the mere presence of PLMs may be sufficient to warrant treatment.

Like in RLS, treatment with carbidopa/levodopa, pramipexole, ropinirole, or gabapentin is generally efficacious and well-tolerated. Again, the dopaminergic agents should be used with caution in patients with psychotic features as these agents can aggravate psychosis. Measuring ferritin may also be worthwhile to ensure relative iron deficiency is not contributing to PLMs; for values below 50 ng/mL, iron replacement therapy is reasonable.

Medication effects

The cholinesterase inhibitors and memantine rarely induce or aggravate RBD or PLMs. If any appear to do so by the temporal association of worsening RBD or PLMs with adding one of these drugs, then the timing when the medication is administered could be altered. There is one report which suggested donepezil can alleviate RBD.⁷⁵

There are reports of some of the antidepressants inducing or aggravating RBD, particularly venlafaxine and mirtazapine,^{76, 77} but theoretically any agent designed to affect mood could alter RBD frequency and severity. It would be prudent to shy away from these two agents if RBD is bothersome and depression is sufficiently problematic to warrant treatment. Due to its dopaminergic effects, bupropion may be preferable to several other agents in managing depression in patients with significant RBD, but no clinical studies have been carried out to prove its efficacy in this clinical setting. While the SSRIs can also theoretically worsen PLMs, this is rarely clinically significant.

Circadian dysrhythmia

In the setting of day-night reversal and other circadian dysrhythmic disorders, demented patients will tend to sleep more during the day and be active more during the night. This increased motor activity at night can result in significant caregiver distress. Melatonin and/or phototherapy could be considered—see discussion in section on insomnia.

Symptom Complex – Nocturnal Hallucinations/Behavioral Problems

Dementing illness

Nocturnal Hallucinations—As patients develop more cognitive impairment with progression of the dementing illness, the differentiation between dream mentation, visuoperceptual dysfunction, and reality can become blurred. This appears to be particularly evident in end-stage dementia with Lewy bodies and Parkinson's disease with dementia (arguably the same underlying substrate for dementia), although visual hallucinations, illusions, and misidentification can occur in AD and FTD as well. Whether the visual hallucinations that occur with DLB and Parkinson's disease with dementia represent fragments of REM sleep invading into wakefulness versus some other process is a matter of debate, but there is evidence in patients with PD to suggest dream imagery of REM sleep

may be contributing to daytime visual hallucinations.⁷⁸ Patients may converse or yell at, swing limbs toward, or kick toward apparent objects, animals, or people. When hallucinations are mild and not frightening to patients, reassurance often suffices; pharmacologic intervention should be reserved for those who are frightened or bothered by them.

One should ensure that no medical illness has arisen (e.g., urinary tract infection, pneumonia), and all medications with potential hallucinatory side-effects should be decreased or eliminated (e.g., levodopa, amantadine, selegiline). While the acetylcholinesterase inhibitors can aggravate hallucinations, there are reports (confirmed by our experience) that they can significantly ameliorate hallucinations and delusions (Table 3).^{79–81} Risperidone and olanzapine are purported to be effective in managing these symptoms without causing extrapyramidal side-effects, but this is not always the case. Clozapine can be quite effective in this setting, but the need for frequent laboratory monitoring due to rare agranulocytosis can pose inconveniences for patients, families, and clinicians. Quetiapine appears similar in efficacy to clozapine, and since agranulocytosis is not an issue, no laboratory monitoring is necessary. This agent is rather costly, but quetiapine is now widely used as it can provide adequate management of hallucinations, delusions, and problem behaviors with tolerable side-effects.

Conventional neuroleptics such as haloperidol should generally be avoided in patients with dementia, and they are absolutely contraindicated in patients with DLB, PDD, and PD.^{79–81}

Nocturnal agitation/behavioral dyscontrol

One must consider medical issues such as pain, infection, etc. when agitation during day or night evolves, especially when it does so abruptly. One should also employ behavioral techniques before proceeding to pharmacologic intervention. Techniques such as acknowledging the source of agitation if it can be identified, then using gentle redirection, can be quite effective, but the caregiver or nursing home staff need to be trained how to use behavioral techniques which some master but many do not. A variety of medications can be effective for managing nocturnal agitation (Table 3). The acetylcholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine), memantine, atypical neuroleptics (e.g., olanzapine, quetiapine), antiepileptics (e.g., carbamazepine, valproic acid), benzodiazepines (e.g., clonazepam), as well as trazodone and chloral hydrate, can be considered if drug therapy is needed.¹ If agitated depression is suspected, psychiatric consultation for consideration of electroconvulsive therapy can be helpful.

Sleep disorders

REM sleep behavior disorder—Discussed in the section on excessive motor activity at night.

Medication effects

There is ample data that the acetylcholinesterase inhibitors and memantine can improve hallucinations and agitation, as well as cognition (Table 3).^{82–86} Yet there are some patients who appear to have hallucinations or agitation precipitated or aggravated by one or more of these drugs; nocturnal hallucinations appear to be more commonly associated with cholinesterase inhibitor therapy, especially when administered before bedtime. Decreasing the dose, moving the timing of the dose to earlier in the day, or discontinuing the drug altogether may be necessary in such instances.

Circadian dysrhythmia

Sundowning—Sundowning is a nebulous term. Delirium, confusion, disorganized thinking, impaired attention, restlessness, hyperactivity, wandering, agitation, insomnia, hypersomnia, hallucinations, illusions, delusions, anxiety, and anger have all been considered features of the “sundowning syndrome.”^{13, 87} The term implies that problem symptoms or behaviors develop during the evening or night. Although many clinicians have heard caregivers or nursing home staff describe the escalation of symptoms toward the late afternoon or evening, there is actually little data to support that this indeed occurs.¹³ Bliwise and colleagues have suggested that “some components of sundowning may reflect disruptive behaviors occurring with identical frequency throughout the day but with differential impact upon nursing staff” (p. 277).¹³ The same phenomenon could be occurring with caregivers of patients residing at home.

There are likely several different physiologic substrates for the various problem symptoms and behaviors, and the optimal strategies for management may reflect the physiologic underpinnings which have yet to be fully characterized. Therefore, in communicating between health care professionals, patients, caregivers, and researchers, it may be more appropriate to use descriptive terms or phrases such as “agitation and physically aggressive behavior” or “wandering and pacing” rather than “sundowning.” Furthermore, administering medications to patients is only one facet of management, as caregiver education, psychological support, time away from patients via respite care, etc. are also critical.

Several modalities have been suggested to ameliorate various features of the “sundowning” syndrome (see excellent review by McGaffigan and Bliwise.⁸⁸) Table 3 presents several agents which are variably effective for problem symptoms and behaviors. The dictums of therapy are a) use a trial and error approach, and b) “start low and go slow”. Combination therapy is sometimes necessary.

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Table 1**Principal causes of irreversible dementia**

<u>Degenerative</u>
Alzheimer's disease (AD)
Dementia with Lewy bodies (DLB)
Parkinson's disease with dementia (PDD)
Pick's disease (Pick)
Corticobasal degeneration (CBD)
Progressive supranuclear palsy (PSP)
Argyrophilic grain dementia (AGD)
Frontotemporal dementia with parkinsonism linked to chromosome 17 associated with mutations in the gene encoding microtubule associated protein tau (FTDP-17 <i>MAPT</i>)
Frontotemporal lobar degeneration with ubiquitin- and TAR-DNA binding protein-43- positive inclusions (FTLD-U/TDP-43)
Frontotemporal lobar degeneration with motor neuron disease (FTLD-MND)
Frontotemporal dementia with parkinsonism linked to chromosome 17 associated with mutations in the gene encoding progranulin (FTDP-17 <i>PGRN</i>)
Huntington's disease (HD)
<u>Vascular</u>
Vascular dementia (VaD)
<u>Prion</u>
Creutzfeldt-Jacob disease (CJD)
Fatal familial insomnia (FFI)
Gerstmann-Straussler-Scheinker disease (GSS)

Table 2**Diagnostic approach for assessing sleep disturbances in patients with dementia**

Essentially all sleep disturbances in patients with dementia fall into one of four major symptom complexes. Within each symptom complex, one can then consider five potential underlying causes for that symptom, which can then be pursued further and managed.

Symptom Complex

- Insomnia
- Hypersomnia
- Excessive motor activity at night
- Nocturnal hallucinations/behavioral problems

Underlying Causes

- Dementing illness and its associated neuronal degeneration/ischemia/death and alterations in neurochemical systems
 - Primary sleep disorder
 - Medication effect
 - Depression
 - Circadian dysrhythmia
-

Table 3

Management of sleep disorders, hallucinations, and nocturnal agitation in patients with dementia: Selected medications with suggested dosing schedules*

Symptom/Behavior/Disorder	Medication	Starting Dose	Suggested Titrating Schedule	Typical Therapeutic Range
Insomnia	trazodone	25 mg qhs	Increase in 25 mg increments every 3–7 days as necessary and tolerated, up to 300 mg/night	50–200 mg/night
	chloral hydrate	500 mg qhs	Increase in 500 mg increments every 3–7 days as necessary and tolerated, up to 1500 mg/night	500–1000 mg/night
	melatonin	3 mg	Increase in 3 mg increments every 3–7 days as necessary and tolerated, up to 12 mg/night	3–12 mg/night
	ramelteon Rozerem®	8 mg	8 mg 30–60 minutes before bedtime; may require 3–4 weeks of nightly use to determine efficacy	8 mg/night
	zolpidem Ambien®	2.5 mg qhs	Increase in 2.5 mg increments every 3–7 days as necessary and tolerated, up to 10 mg qhs	2.5–10 mg/night
	zolpidem CR Ambien CR®	6.25	If standard zolpidem is effective at inducing sleep, but effect lasts < 4 hours, can change to controlled-release zolpidem 6.25 mg/night (approx. = 5 mg standard zolpidem) or 12.5 mg/night (approx. = 10 mg standard zolpidem)	6.25–12.5 mg/night
	zaleplon Sonata®	5 mg qhs	Increase in 5 mg increments every 3–7 days as necessary and tolerated, up to 20 mg qhs	5–20 mg/night
	eszopiclone Lunesta®	1 mg qhs	Increase in 1 mg increments every 3–7 days as necessary and tolerated, up to 3 mg qhs	1–3 mg/night
	clonazepam Klonopin®	0.25 mg qhs	Increase in 0.25 mg increments every 3–7 days as necessary and tolerated, up to 2 mg qhs	0.25–1 mg/night
	quetiapine Seroquel®	25 mg qhs	Increase in 25 mg increments every 3–7 days as necessary and tolerated, up to 300 mg qhs	25–100 mg/night
Restless legs syndrome/Periodic limb movement disorder	carbidopa/levodopa Sinemet®	25/100	1 tab qhs, increase to 2 tabs 1 week later if necessary	1–2 tabs mg/night
	carbidopa/levodopa controlled-release Sinemet CR®	25/100 CR	1 tab qhs, increase to 2 tabs 1 week later if necessary	1–2 tabs mg/night
	pramipexole Mirapex®	0.125 mg qhs	Increase in 0.125 mg increments every 2–3 days as necessary and tolerated, up to 2 mg qhs	0.25–1 mg/night
	ropinirole Requip®	0.25 mg qhs	Increase in 0.25 mg increments every 2–3 days as necessary and tolerated, up to 4 mg qhs	0.5–2 mg/night
	gabapentin Neurontin®	100 mg qhs	Increase in 100 mg increments every 2–3 days as necessary and tolerated, up to 2700 mg qhs	300–1200 mg/night
Hypersomnia	modafinil Provigil®	100 mg qam	Increase in 100 mg increments every 5–7 days in the morning, up to 400 mg po qam. Alternatively can dose 200 mg in am and 200 mg at noon	100–400 mg qam or 100–200 mg bid (am and noon)

Symptom/Behavior/Disorder	Medication	Starting Dose	Suggested Titrating Schedule	Typical Therapeutic Range
	methylphenidate Ritalin®	2.5 mg qam	Increase in 2.5–5 mg increments every 3–5 days as necessary and tolerated in bid dosing (am and noon), up to 40 mg bid	5 mg qam – 30 mg bid (am and noon)
	dextroamphetamine Dexedrine®	5 mg qam	Increase in 5 mg increments every 3–5 days as necessary and tolerated in bid dosing (am and noon), up to 40 mg bid	5 mg qam – 20 mg bid (am and noon)
	dextroamphetamine Spansules®	5 mg qam	Increase in 5 mg increments every 3–5 days as necessary and tolerated, up to 40 mg bid	5–20 mg qam
	amphetamine/dextroamphetamine Adderall®	5 mg qam	Increase in 5 mg increments every 3–5 days as necessary and tolerated in bid dosing (am and noon) dosing, up to 40 mg bid	5 mg qam – 20 mg bid (am and noon)
REM sleep behavior disorder	clonazepam Klonopin®	0.25 mg qhs	Increase in 0.25 mg increments every 3–7 days as necessary and tolerated, up to 2 mg qhs	0.25–1 mg/night
	melatonin	3 mg	Increase in 3 mg increments every 3–7 days as necessary and tolerated, up to 12 mg/night	3–12 mg/night
Nocturnal hallucinations or delusions or behavioral dyscontrol or agitation/aggression or nocturnal wandering or disinhibition	carbidopa/levodopa controlled-release Sinemet CR®	25/100 CR	1 tab qhs, increase to 2 tabs 1 week later if necessary	1–2 tabs mg/night
	quetiapine Seroquel®	25 mg qhs	Increase in 25 mg increments every 3–7 days as necessary and tolerated, up to 300 mg qhs	25–100 mg/night
	donepezil Aricept®	5 mg qam	Increase to 10 mg qam 2–4 weeks later	5–10 mg qam
	rivastigmine Exelon®	1.5 mg bid	Increase in 1.5 mg increments for both doses every 2–4 weeks, maximum 6 mg bid	1.5 mg bid – 6.0 mg bid
	rivastigmine transdermal Exelon® Patch	4.6 mg/24 hr patch daily	Increase to the 9.5 mg/24 hr patch 2–4 weeks later	4.6 mg/24 hr – 9.5 mg/24 hr patch qam
	galantamine Razadyne®	4 mg bid	Increase in 4 mg increments for both doses every 2–4 weeks, maximum 12 mg bid	4 mg bid – 12 mg bid
	galantamine extended release Razadyne® ER	8 mg qam	Increase in 8 mg increments every 2–4 weeks, maximum 24 mg qam	8–24 mg qam
	memantine Namenda®	5 mg qd	Increase gradually over 3–4 weeks up to 10 mg bid	5 mg qd – 10 mg bid
	melatonin	3 mg	Increase in 3 mg increments every 3–7 days as necessary and tolerated, up to 12 mg/night	3–12 mg/night
	quetiapine Seroquel®	25 mg qhs	Increase in 25 mg increments every 3–7 days as necessary and tolerated, up to 300 mg qhs	25–100 mg/night
	olanzapine Zyprexa®	5 mg qhs	Increase in 5 mg increments q7 days in bid dosing (am and hs)	5 mg qhs – 10 mg bid

* Disclaimer and important points:

The choice of which agents to use and which dosing schedules to recommend must be individualized. It is the responsibility of the clinician to consider potential side-effects, drug interactions, allergic response, life-threatening reactions, dosing changes due to renal or hepatic dysfunction, etc., before administering any drug to any patient, including those listed above. Dr. Boeve, Mayo Foundation, and the publisher will not be responsible for any adverse reactions of any kind to any patient regarding the content of this information.

The Food and Drug Administration (FDA) has issued warnings about the increased frequency of hyperglycemia/diabetes, stroke, and mortality associated with some or all of the atypical neuroleptics; increased mortality associated with galantamine in patients with mild cognitive impairment, and other warnings (refer to the FDA website: www.fda.gov). The FDA has also issued warning about the increased frequency of cardiac dysrhythmia, other morbidity, and death, associated with psychostimulant use. Clinicians, patients, and their families must carefully weigh the risks and benefits before commencing any of these agents.