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Treatment of sleep disorders in dementia

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Introduction

Dementia is associated with sleep and circadian disturbances, worse than the expected gradual sleep quality with aging[1], which negatively affect patient quality of life and increase caregiver burden [2]. Disrupted sleep and circadian functions in dementia are attributed to neurodegeneration of brain regions and networks involved in these functions, such as the suprachiasmatic nucleus [3, 4]; however, there are additional factors that contribute to the burden of sleep disturbances in dementia. Alzheimer's Disease (AD) is associated with a delay in circadian phase, unlike the typical advance in circadian phase with aging [5]. This delay likely contributes to sundowning—agitation and confusion in the evening—as well as to difficulty sleeping at night. Due to wandering and subsequent risk of injury, nighttime insomnia increases morbidity and mortality directly, and therefore is a common reason for institutionalization [6]. During the daytime, excessive sleepiness may contribute to worse cognitive function, unintentional naps that impact driving safety, and decreased ability to engage in social functions and therapies. Given the substantial negative impact of sleep and circadian problems in dementia patients, there is keen interest in identifying effective treatments, with the hope of reducing caregiver burden, improving patient quality of life, postponing institutionalization, and potentially slowing cognitive decline.

Dementia subtypes and sleep disorders

Various etiologies of dementia are associated with different types of sleep and circadian disturbances. In AD, the most common cause of dementia, 44% of patients are affected with

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a sleep disorder[7, 8], and the prevalence and severity of sleep disorders increase with dementia severity. Sleep disturbance occurs very early in AD; even the preclinical stage of AD prior to cognitive symptoms is associated with worse sleep quality and shorter sleep duration [9, 10]. There is increasing evidence that there is a bi-directional relationship between AD pathology, especially amyloid-β plaque accumulation, and poor sleep[11]. Additional sleep disturbances in AD include daytime hypersomnia, delayed circadian phase, sundowning, and adverse effects of dementia medications such as acetylcholinesterase inhibitors [12]. Obstructive sleep apnea (OSA), a primary sleep disorder, is particularly common in AD[13, 14].

Dementia with Lewy bodies (DLB) and Parkinson's disease (PD) with dementia (PDD) are pathologically similar and can be grouped together as Lewy Body Disease (LBD). LBD has the highest prevalence of sleep and circadian disturbances of any dementia, affecting approximately 90% of patients [15]. Insomnia is the most common sleep disturbance in LBD, a combination of prolonged sleep latency, increased sleep fragmentation, nightmares, and early-morning awakenings [16]. Daytime hypersomnia, including “sleep attacks,” is also common (~50% prevalence) and contributes to worse quality of life and safety risks in LBD[17, 18]. Hypersomnia may be related to loss of orexinergic neurons[19] However, there are no studies correlating orexin (hypocretin) levels with hypersomnia severity in LBD. Hallucinations, particularly visual hallucinations in the evening or night, may contribute to sleep problems in LBD. In terms of primary sleep disorders, REM sleep behavior disorder (RBD), a parasomnia characterized by potentially violent or injurious dream enactment behavior, is common in LBD and is a supportive diagnostic criterion for DLB. In fact, the majority of patients with RBD in “idiopathic” form without dementia develop LBD eventually[20]. Another primary sleep disorder associated with PD is restless legs syndrome (RLS), with a prevalence of approximately 20%[21].

Vascular dementia (VD), the second leading cause of dementia, is commonly associated with OSA. In the acute post-stroke period, there is a high prevalence of central apneas, which typically resolve[22]. Otherwise, due to the wide range of vascular disease (localization in the brain, micro- versus macro-vascular disease, and co-occurrence with other neurodegenerative pathology), there are no other characteristic associations with specific sleep disorders or symptoms.

There is a similar prevalence of sleep disorders in frontotemporal dementia (FTD) as in AD, but they differ in their manifestation[23]. The activity rhythm in FTD is more fragmented, and there can be circadian advance or delay[24].

In addition to the sleep and circadian disturbances primarily associated with various dementias, there are additional factors that may worsen symptoms or complicate treatment. Co-morbidities that cause pain or discomfort, or psychiatric conditions such as depression[15], worsen nighttime insomnia. Medications for the underlying dementia as well as medications for co-morbid conditions (*e.g.* β2 agonist inhalers for pulmonary disease, anti-hypertensive medications) may contribute to sleep disturbance. Sleep hygiene, which includes the regularity and timing of sleep, napping, bedtime ritual, daytime activity, light and nocturnal noise (especially in nursing homes [25]), may be poor in dementia and

therefore exacerbate sleep-wake problems[8]. Due to the complex inter-relationships between dementia pathophysiology, dementia effect on sleep hygiene, co-morbid primary sleep disorders, medication effects, and other factors, a comprehensive approach is necessary for diagnosis and treatment of sleep disorders in dementia. (Table 1)

Assessment

Assessment of sleep and circadian disturbances in dementia begins with a complete history. Since demented people may not recall symptoms accurately, collateral history from caregivers is essential. The clinical history should assess for symptoms of primary sleep disorders, such as snoring, hypersomnia, witnessed apneas, parasomnias, restless legs, and leg movements during sleep. The timing and regularity of nighttime sleep and daytime naps (intentional and inadvertent) are important to ascertain. In addition to these clinical features typically queried during a sleep evaluation, individuals with dementia should be specifically asked about sundowning, hallucinations, sleep attacks, injurious parasomnias, and nighttime wandering. If the cause of dementia is known, the history should query for sleep-wake problems characteristic of the underlying disease. For example, in someone with Parkinson's Disease, a detailed temporal relationship between dopaminergic medication dosing and RLS symptoms should be obtained. In all cases, the overall burden of sleep disturbances on both patient and caregiver should be taken into account.

Contributory factors should be assessed, including 1) depression and anxiety; 2) co-morbidities causing pain or discomfort; 3) co-morbidities that cause awakenings (*e.g.* prostatic hypertrophy causing frequent nocturia); 4) medications including supplements and over-the-counter medications; 5) current and prior alcohol, tobacco, caffeine, and other substance use; 6) living and sleeping arrangements; 7) degree, frequency, and regularity of physical activity; 8) social and occupational activity; 9) timing and regularity of meals; 10) light and noise exposure during daytime and nighttime.

Scales typically used for sleep evaluation, such as the Epworth Sleepiness Scale (ESS) [26] or Pittsburgh Sleep Quality Index (PSQI) [27] have not been validated specifically for use in dementia, and, caregivers may complete questionnaires for patients. Therefore, typical normal/abnormal cutoffs may not be applicable. However, these and other scales are still useful for following individual trends over time. Additionally, dementia-specific scales may be helpful. Examples include the Sleep Disturbance Inventory (SDI), which was developed to assess caregiver burden due to sleep disturbance in AD [28], and the Behavior Pathology In Alzheimer's Disease Rating Scale (BEHAVE-AD). In LBD, the Parkinson's Disease Sleep Scale and the SCOPA-sleep scale may be helpful[29].

Objective data about circadian activity patterns and overnight sleep are helpful for diagnosing sleep disorders and assessing response to treatment. Sleep logs alone may not be accurate in individuals with dementia. Actigraphy, using non-invasive wearable motion sensors, is helpful for assessing suspected circadian disorders. Furthermore, validated sleep-scoring algorithms are available to analyze actigraphy data, to calculate objective measurements of nocturnal sleep such as total sleep time and sleep efficiency. The standard practice committee of the American Academy of Sleep Medicine (AASM) has

recommended actigraphy and sleep logs to be routinely used to assess for irregular sleep wake rhythms in dementia[30].

If there are symptoms of a primary sleep disorder such as OSA, periodic limb movement disorder, or RBD, polysomnography (PSG) is the gold standard for diagnosis. If possible, a caregiver should stay in the sleep lab to assist with PSG, since a strange environment and numerous sensors may cause confusion. Ambulatory studies for OSA can be done in the patient's usual sleeping environment, however patients with dementia may have difficulty using the home recording devices. Additionally, ambulatory studies are less sensitive for mild OSA compared to PSG[31].

Approach to treatment

The treatment approach to sleep problems in dementia is similar to that in the general population, but with additional attention paid to avoid exacerbating cognitive dysfunction, reducing injury risk, and reducing caregiver burden. First, any underlying primary sleep disorders should be assessed for and treated. Second, any co-morbid mood and anxiety disorders should be addressed. Third, pain, nocturia, or other comorbid conditions that interfere with sleep should be addressed to the best extent possible, and medications that affect sleep (including those for the underlying dementing disease) should be adjusted to optimize sleep-wake functioning. For example, acetylcholinesterase inhibitors (*e.g.* donepezil and rivastigmine) and MAO-B inhibitors (*e.g.* selegiline) may cause insomnia, and dosing should be moved earlier in the daytime. Additionally, dopaminergic medications for Parkinsonism should be adjusted to minimize bothersome nighttime motor symptoms that may awaken the patient, as well as minimize sedating effects during the daytime (especially dopamine agonists). Management of a patient's co-morbid conditions and medications requires close co-ordination with the patient, the caregiver, and the patient's other physicians and other healthcare professionals, and is usually the most time-consuming aspect of care of demented patients with sleep disturbances. Lastly, if sleep-wake problems persist, non-pharmacological treatments are preferred, due to the risk of sedation, cognitive symptoms, falls, injuries, and medication interactions with pharmacological treatments. In recalcitrant cases, pharmacological treatments can also be added cautiously. Ideally, objective measurements such as actigraphy and subjective measurements of patient and caregiver symptoms should be obtained serially to follow response to treatment.

Treatment of primary sleep disorders

The treatment of sleep disturbance in dementia should always begin with treatment of any primary sleep disorders. Sleep disorders increase with aging, and are very common in people with dementia. In the general population, OSA contributes to nighttime sleep fragmentation, insomnia, daytime hypersomnia, cognitive dysfunction, and decreased mood. Therefore, it is expected that in the demented population, OSA would have similar and potentially worse effects. OSA is very common in AD, present in 40% of AD patients overall and increasing to 70% in the institutionalized setting[13, 14]. In fact, having OSA increases risk of dementia. In the Study of Osteoporotic Fractures, OSA increased the risk of incident cognitive decline by an adjusted odds ratio of 1.85[32]. In the AD Neuroimaging Initiative

cohort, participants who reported having OSA were diagnosed with mild cognitive impairment and AD about 13 and 5 years earlier, respectively, than those who did not. [33]. In patients who already have dementia, the existing data support treating any OSA. In a small, randomized study of demented patients, treatment of OSA with positive airway pressure (PAP) helped slow cognitive decline[34]. Furthermore, in a longitudinal extension of the study, PAP was associated with improved subjective sleep scores such as ESS and PSQI[35]. In another nonrandomized study of 23 mild to moderate AD patients with severe OSA, there was a slower decline in cognition if patients used PAP; the effect as measured by Mini-Mental Status Exam score was a decline of 0.7 points annually for PAP versus 2.2 points annually without PAP [36]. OSA is also common in vascular dementia, however no randomized studies of PAP have been published about this population. Non-PAP treatments such as mandibular advancement devices have not been tested in randomized studies in the dementia population, but may be a reasonable alternative in patients who are unable to use PAP.

Restless legs syndrome and periodic limb movement disorder (PLMD) are common in LBD, especially PDD. Treatment approach is the same as idiopathic RLS and PLMD. Iron deficiency can worsen RLS and PLMD, and should be treated with supplementation. Medications typically used for RLS and PLMD such as dopamine agonists and gabapentin are effective in the demented population, however, since dopamine agonists are also prescribed for motor symptoms, treatment regimens should be coordinated between sleep medicine and dementia/movement disorders physicians.

REM sleep behavior disorder requires PSG confirmation, showing REM sleep without atonia[37]. Behavioral precautions including removing weapons from the bedroom, moving furniture far from the bed, and putting a rug on hard floors should be advised. In cases where the patient or bed-partner are at risk of injury, both clonazepam and melatonin have been shown to be effective for reducing oneiric behaviors [38]. Melatonin is preferred if there is concern for cognitive or sedating side effects of clonazepam. In all patients with PD, RBD should be assessed for because it is prognostically useful; RBD predicts a PDD phenotype and more rapid progression[39]. Unfortunately, treatment of RBD symptoms has not been shown to slow the progression of the underlying neurodegenerative process.

Hypersomnia may persist despite treatment of primary nocturnal sleep disorders, particularly in LBD. Some dementia patients meet formal criteria for narcolepsy or idiopathic hypersomnia. Treatment with stimulant medications, anti-cataplectic agents, or sodium oxybate may be appropriate if patients have *bona fide* narcolepsy, however, exceptional care should be taken to minimize side effects, particularly worsening of cognitive symptoms or any co-morbid cardiovascular disease.

Non-pharmacological treatments

Sleep hygiene education

Optimal sleep hygiene includes behaviors that promote consolidated sleep at night, including regular and adequate nocturnal sleep periods, minimizing naps, minimizing sleep-disrupting substances (alcohol, tobacco, caffeine, and other), obtaining regular vigorous physical

activity, avoiding excessive light close to bedtime, developing a bedtime routine to transition from wake to sleep, sleeping in a sleep-conducive (dark, cool, quiet, no television) environment, and using the bed only for sleep (*i.e.* stimulus control). Educating dementia patients and their caregivers about sleep hygiene has generally been used as a control group for other interventions, or has been used in combinations with other approaches in multi-modality treatment[40-42]. In one small study of dementia patients residing in group homes, sleep hygiene education resulted in a longer total sleep time at night as measured by actigraphy, 9.6 hours, as compared to controls, 7.8 hours[43]. Sleep efficiency, the percentage of time in bed that is spent asleep, also was improved, 84% in the sleep hygiene group versus 75% in controls[43]. However, another study in more severe, institutionalized dementia patients, did not find any positive effect of sleep hygiene education [44]. In general, although strong data for sleep hygiene education in dementia are lacking, since there are no anticipated adverse effects, good sleep hygiene serves as a foundation for insomnia treatment, including in the dementia population.

Physical and social activity

Increased daytime physical activity and social interaction have been shown to improve daytime alertness and nighttime sleep in the elderly population[45-48]. Potential mechanisms include increase of slow wave sleep following physical exertion, stronger circadian *zeitgebers* from regular physical/social activity, psychological factors, or other mechanisms. Many studies of physical and social activity as sleep interventions have used multi-modality treatment, therefore individual benefits of physical or social activity are difficult to ascertain. In an early study, a combination of sleep hygiene education, daily walking for 30 minutes, and bright light therapy for 1 hour at night decreased wake time at night by 36 minutes after 2 months of treatment[42]. A study of only exercise, 30 minutes of walking for 5 days per week, in moderately demented nursing home patients, showed no benefit on sleep [49]. McCurry *et al* compared physical activity (daily walking for 30 minutes for 2 months), bright light therapy, a combination of both, and control (sleep hygiene instruction) groups. They found that there was decreased wake time overnight on actigraphic measurement initially, but there were no significant benefits at 6 months [50]. A randomized controlled study in AD and PD showed a positive effect of more intense, structured physical activity. In this study, patients had exercise sessions for 1 hour, 3 times per week, for 6 months. Exercise routines were designed, individualized, and supervised by professionals, to target 60-80% of maximal heart rate. Participants who were able to maintain this level of regular physical activity demonstrated benefit in sleep as measured by the Mini Sleep Questionnaire, and in daily activities [51].

Social and occupational activities provide *zeitgebers* for circadian clock entrainment and discourage people from sleeping during the daytime. In a demented, nursing-home population, an intervention of only structured social activity reduced actigraphically-measured daytime sleep, and—in the subset of participants with poor nighttime sleep efficiency—increased nighttime total sleep time [48]. In a larger study that examined general nursing home and assisted-living center residents, a combination of structured social activity *and* physical activity improved nocturnal sleep as measured by PSG, however, neither intervention alone had a significant effect [47].

Overall, structured physical and social activities have neutral to positive effects on sleep, with a trend for more benefit with multi-modality treatment and with more vigorous physical activity. Again, in the interest of minimizing harm, this type of intervention should be encouraged as tolerated in demented patients with sleep and circadian disturbances, prior to pharmacological therapies. Unfortunately, there are no widespread, standardized programs for structured physical or social activity in dementia, although training programs for caregivers are under development[52]. Therefore, in clinical practice, patients should be advised to exercise vigorously regularly (3-5 times per week for 30-60 minutes), if possible with a professional trainer using a target heart rate. Additionally, all demented patients should be advised to have regular social interactions, although there are no formal or standard recommendations for frequency, quantity, or quality.

Bright light therapy

Bright light therapy (BLT) is an intervention used to treat circadian disorders. BLT involves exposure to light, which activates the retinohypothalamic tract to the suprachiasmatic nucleus, thereby entraining circadian phase. The effect of light on circadian phase depends acutely on the time the light is delivered: light close to bedtime delays phase, while light close to waketime advances phase. The AASM has published parameters for the use of BLT in circadian disorders[53]. Studies investigating the effect of BLT specifically in dementia patients show mixed results. A systematic Cochrane meta-analysis in 2014 examined the effectiveness of BLT on sleep disturbance in dementia [54], and included 10 studies assessing sleep [50, 55-63]. Seven of the studies delivered BLT using a light box (2500-10,000 lux) for 1-2 hours [50, 55-60], while other methods were used for the other studies [61-63]. BLT was administered in the morning[57-60, 63], evening[50], both [55, 56], or all day [61, 62]. Treatment duration ranged from 10 days to 10 weeks. Sleep was measured in all studies with total sleep time, except for one that assessed nighttime activity[60]. Pooled data revealed no effect of BLT on nocturnal total sleep time. However, there was a significant decrease in night-time awakenings, particularly in the studies using morning BLT. There were insufficient data to clearly recommend any of the BLT modalities, dose (lux or duration), timing, or treatment duration options tested. Two additional small, randomized studies have been published since that review, again with neutral to positive effect of BLT[64, 65]. Another meta-analysis, by van Maanen *et al* in 2015[66], included 5 studies excluded from the Cochrane review (for not being randomized controlled trials) [67-71], and excluded 5 studies included in the Cochrane review (because inclusion criteria required a sleep complaints) [55, 56, 59, 61, 63]. This meta-analysis reported a significant benefit of BLT for sleep disturbances in dementia, for sleep onset latency, total sleep time, time in bed, and sleep efficiency. To summarize, data regarding BLT for sleep disturbances in dementia are mixed but generally trend toward a positive effect, with the most potential benefit for morning BLT and for individuals with sleep disturbances. Since BLT does not have significant adverse effects, it is reasonable to try morning BLT (particularly in combination with melatonin as discussed below), in demented individuals who have a sleep disturbance or delayed circadian phase.

Complementary alternative medicine

Several complementary and alternative modalities have been tested for sleep disturbances in dementia. Two small, non-randomized studies reported an improvement of sleep in dementia after acupuncture or accupressure [72, 73]. A randomized trial of a 3-minute back massage prior to bedtime showed a 36-minute, but non-significant, improvement in total sleep time [74]. A small, randomized study of Tai Chi in vascular dementia demonstrated a benefit in sleep, as measured by PSQI [75]. A study of a child-like robot for elderly women living alone (not necessarily with dementia) showed significant improvement in several sleep variables, including total sleep time, compared to a more mechanical robot[76]. These and other alternative, non-pharmacological interventions are under active investigation for sleep disturbance in dementia, however, none have been demonstrated to be effective in rigorous, double-blind, randomized, controlled trials. In general, if a patient or caregiver wants to pursue a potential non-pharmacological intervention without anticipated adverse side effects or excessive cost, it is reasonable to perform a trial of the intervention, with serial objective measurements (such as actigraphy) or subjective scales over a short period, to assess response.

Pharmacological treatment

Melatonin

Melatonin is released from the pineal gland in the evening in dim light, and mediates the relationship between the circadian clock and sleep. Exogenous melatonin has circadian phase-shifting effects opposite to that of light, and also exerts a mild soporific effect. Melatonin levels are decreased in AD[77, 78]. Melatonin has been shown to improve cognition, emotional performance, and sleep-wake patterns in mild cognitive impairment[79], suggesting a possible beneficial role for melatonin in dementia. However, existing data on melatonin in dementia are equivocal. A Cochrane meta-analysis in 2014, including 3 randomized, controlled studies [58, 80, 81], found no benefit of melatonin in dementia patients *with sleep complaints*[82]. Dowling *et al* used melatonin 5 mg for 10 weeks, in a mixed-modality treatment with BLT, and found a benefit[58]. Serfaty *et al* used 6 mg slow release melatonin for two weeks[80], and Singer *et al* used 10 or 2.5 mg for 8 weeks[81]; neither study found any difference between melatonin and control groups. Another meta-analysis in 2015 by Xu *et al* included 7 randomized, controlled studies that examined melatonin in people with dementia, *not necessarily with sleep problems*[83]. This meta-analysis included four studies in addition to the three in the Cochrane review[61, 84-86], and found a benefit for melatonin of approximately 24 minutes on TST, small (~2%) improvements in sleep efficiency, and no cognitive benefits. The largest study included 189 nursing home residents, the majority (87%) of whom had dementia. In this study, melatonin 2.5 mg given 1 hour before bedtime increased sleep duration by 27 minutes. However, melatonin was associated with worse withdrawn behavior and depression; the behavioral effects were ameliorated by BLT [61]. Of the other three studies, one showed no effect of either 8.5 mg immediate release or 1.5 mg sustained release melatonin at 10PM, [85] one showed a small improvement with 3 mg melatonin at 10:30 PM in total sleep time [84], and one did not assess sleep outcomes[86]. Another more recent randomized controlled study using 2 mg slow release melatonin for 24 weeks in a multi-site study of mild-to-moderate

AD (n=80) [87], found that, compared to placebo, there was less decline in mini mental state examination (MMSE) and instrumental activities of daily living (IADLS) with melatonin. Sleep was assessed only with PSQI, and only the sleep efficiency component of this index improved; this difference was more pronounced for those starting with insomnia as defined by PSQI ≥6, (n=13)[87].

Melatonin receptor agonists such as ramelteon simulate the action of melatonin. One randomized controlled trial has been performed with ramelteon. There is no publication associated with this study, however the synopsis of the study from the manufacturer[88] and a summary of information provided to the Cochrane meta-analysis investigators[82] were reviewed. There was no benefit of ramelteon after 1 week on actigraphically-determined total sleep time in mild to moderate AD patients. No data are available regarding outcomes at the end of the planned 8-week treatment period. Ramelteon was also assessed in a small case study in four PDD patients, in which scores of ESS and PSQI improved in all patients after treatment with ramelteon for 8 weeks[89]. There are several reports of a beneficial effect of ramelteon on sundowning or delirium; these studies are beyond the scope of this review.

Altogether, the existing data on melatonin suggest a possible benefit in terms of nocturnal sleep of approximately half an hour, and reduced frequency of awakenings. There is no known benefit of ramelteon or extended-release melatonin. Melatonin is considered a nutritional supplement in the US and is not subject to the same standards as a prescription medication. Furthermore, different dosages and timing (which affects phase shifting action of melatonin) varied between studies. Therefore, it is difficult to suggest a specific dose or timing, particularly since many of the studies used dosing at bedtime, which is later than would be typically used to advance sleep phase. Additionally, there was possible negative effect on mood and behavioral indices in one study, except when combined with BLT. In general, melatonin is well-tolerated with minimal side effects at low doses. Therefore, in individuals who do not respond to maximal behavioral interventions, it is reasonable to try a low dose of melatonin (2-5 mg) at night, together with BLT, while closely monitoring for depressive symptoms, and objectively following sleep/circadian measurements.

Sedating anti-depressants

Sedating anti-depressants are prescribed frequently for their soporific qualities, but there are very limited data on anti-depressants for sleep in dementia. One study of trazodone 50 mg at bedtime in AD demonstrated an improvement of 42.5 minutes in total sleep time at night, and there were no significant adverse effects—including cognitive—that were reported[90]. Another study, of mirtazapine 15 mg, found no benefit on sleep after 2 weeks in AD patients, and there was increased daytime sleepiness [91]. Interestingly, a meta-analysis of cost-effectiveness of depression treatment in dementia found no cost benefit to either mirtazapine or sertraline compared to no treatment, however the number of caregiver hours required was reduced with mirtazapine, 6.7 versus 12.3 hours, which the investigators hypothesized was due to improved sleep in the mirtazapine group[92]. Anti-depressants with anti-cholinergic properties (such as tricyclic antidepressants) may worsen cognition in AD and LBD, and most anti-depressants also worsen RLS. Therefore, while modest data suggest

trazodone may improve nocturnal sleep in dementia, sedating anti-depressants should be used cautiously, with close monitoring of cognitive and RLS symptoms.

Benzodiazepine receptor agonists

Typical benzodiazepines, especially long acting ones, have been associated with increased risk of falls, anterograde amnesia, daytime sleepiness, confusion, negative effect on cognition, and risk of dependence or abuse[3, 93]. Long term usage of benzodiazepines has been suggested to be associated with an increased risk of AD[94-96], but this association is not conclusive [97]. Non-benzodiazepine benzodiazepine-receptor agonists (NBBRAs, e.g. zolpidem and zaleplon) are preferred, since they have a shorter half-life and are generally better-tolerated, with less risk of dependence or abuse. However, NBBRAs have not been tested specifically in the dementia population. Furthermore, they are associated with adverse side effects such as morning sedation and parasomnias in the general population, and falls in the older population[3, 98]. Therefore these medications should be used sparingly only in demented patients who have attentive caregivers and living/sleeping situations that maximize safety, and patients should be seen frequently to assess for potential side effects and to ensure objective improvement in sleep.

Other hypnotic medications

In a small (20 treatment vs 22 placebo) post-hoc analysis of a memantine trial in LBD, there was less nocturnal activity in the memantine group measured by questionnaire, but no differences in ESS. The decrease in nocturnal activity was interpreted as reduced RBD, however this finding has not been confirmed by PSG[99].

In a *non-randomized* study of newly-diagnosed AD patients, those with frequent awakenings per night (n=93) were offered treatment with risperidone 0.5-1 mg, zolpidem 5-10 mg, melatonin 2.55 mg, or no drug treatment, in addition to donepezil 5-10mg. After 5 years, the risperidone group did not have deterioration in ESS and PSQI, compared to the other groups, who had worsening in both measures [100].

There are no reports of trials of orexin recenptor antagonists (*e.g.* suvorexant) or other hypnotic classes in dementia.

Stimulants

While stimulants such as methylphenidate have been tested in dementia to address apathy, there are limited studies examining stimulants for hypersomnia in dementia. Daytime hypersomnia is particularly common in LBD, and two small studies examined modafinil for this indication. One showed slight improvements in physical fatigueability but not hypersomnia [101], and the other showed no benefit [102]. Therefore, while stimulants may be used for formally-diagnosed hypersomnia disorders in dementia patients, there is no evidence currently to recommend stimulants for general use in dementia.

Conclusion

Sleep and circadian disturbances are common in all types of dementia, and can manifest in symptoms around-the-clock. The clinical approach to sleep and circadian disorders in dementia begins with assessing for and treating primary sleep disorders, then managing co-morbid conditions and medications that may be negatively affecting sleep, then behavioral interventions, and then pharmacological treatments. Studies have shown neutral to positive effects of sleep hygiene education, physical and social activity, bright light therapy, and melatonin supplementation, without significant adverse side effects. There are scant data to support the use of hypnotic medications for sleep disturbances in dementia, with only one small study showing a benefit of low-dose trazodone. Due to risk of sedation, falls, and worse cognitive function from hypnotic medications, they should be used very cautiously, with frequent serial assessments for safety and objective measurements of drug efficacy. Well-designed studies using specific criteria for dementia etiology, formal assessment for primary sleep disorders, incorporation of circadian phenotype into treatment strategy, and treatment dosing and methods appropriate for the dementia population are sorely needed to identify truly effective interventions for sleep and circadian disturbances in dementia.

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Opinion statement

Sleep and circadian disorders occur frequently in all types of dementia. Due to the multifactorial nature of sleep problems in dementia, we propose a structured approach to the evaluation and treatment of these patients. Primary sleep disorders such as obstructive sleep apnea should be treated first. Comorbid conditions and medications that impact sleep should be optimally managed to minimize negative effects on sleep. Patients and caregivers should maintain good sleep hygiene, and social and physical activity should be encouraged during the daytime. Given the generally benign nature of bright light therapy and melatonin, these treatments should be tried first. Pharmacological treatments should be added cautiously, due to the risk of cognitive side effects, sedation, and falls in the demented and older population. Regardless of treatment modality, it is essential to follow patients with dementia and sleep disorders closely, with serial monitoring of individual response to treatment.

Table 1
Recommended clinical approach to sleep disorders in dementia

Current existing evidence and expert guidelines on the evaluation and treatment of sleep disorders in dementia are summarized. The approach should proceed in the listed order, starting with “Clinical Assessments,” and proceeding downward only if symptoms persist. “Benefits” listed for sleep treatments include only RCT's and meta-analyses.

Assessment or Treatment	Details	Benefits	Cons	Notes
Clinical Assessments				
History	Collateral source is critical Collect information about symptoms of primary sleep disorders, sleep habits/ hygiene, co-morbidities, medications, dementia-specific symptoms Assess for depression and anxiety		Time-intensive	Obtain information about caregiver burden
Sleep scales and questionnaires	General: Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, Insomnia severity index, etc Dementia-specific: Sleep Disturbance Inventory, SCOPA sleep scale, etc			Use serially to determine response to treatment
Actigraphy	Several days to weeks To assess circadian phase and amplitude To assess nocturnal sleep variables	Non-invasive, able to get data in patient's usual setting	Usually not reimbursed by insurers	Obtain concurrent sleep log Use serially to determine response to treatment
Polysomnogram	For suspected obstructive sleep apnea, periodic limb movement disorder, RBD (or other parasomnia)	Gold standard diagnosis	Inconvenient Demented patients may have confusion/agitation	Caregiver should stay with patient if possible Ambulatory (home) studies may have high failure rate in dementia
Treat primary sleep disorder				
Obstructive sleep apnea	Positive airway pressure	Slower cognitive decline Less snoring, improved sleep, improved daytime alertness	Patients may not be able to tolerate PAP Caregiver burden	Common in AD, vascular dementia No data on non-PAP treatments
Restless legs syndrome	Iron supplementation Dopamine agonists, gabapentin, other typical RLS medications	Improve symptoms	Sleep attacks and compulsive/addictive behavior with dopamine agonists Sedation with gabapentin	Common in PD Coordinate dopamine agonists with PD doctor
REM sleep behavior disorder	Clonazepam or melatonin Safety precautions	Reduced risk of injury	Sedation with clonazepam	In DLB and PDD
Hypersomnia	Stimulants, sodium oxybate, anti-cataplectic agents	Improve alertness	Cardiovascular risk, irritability, risk of abuse/ dependence Sedation with sodium oxybate	Common in DLB and PDD Only for true primary hypersomnia such as narcolepsy
Optimize co-morbidities and medications				

Assessment or Treatment	Details	Benefits	Cons	Notes
Treat mood and anxiety disorders	Anti-depressants, psychotherapy, anxiolytics	Improve psychiatric and sleep symptoms (usually insomnia)	May cause sedation and worse cognition Worse RLS Time-intensive	Coordinate with other physicians and healthcare professionals
Treat pain, and other co-morbidites causing disrupted sleep	Varies	Improve sleep	Pain and bladder medications may cause sedation and worse cognition Varies by co-morbidity Time-intensive	Coordinate with other physicians and healthcare professionals
Minimize or adjust medications causing sleep disruption or hypersomnia	Dementia and Parkinsomnism medications Pain medications, stimulants, β2 agonist inhalers, anti-hypertensives, bladder medications, anti-retrovirals, steroids, etc	Improve sleep	Varies by medication Time-intensive	Coordinate with other physicians and healthcare professionals
Behavioral sleep treatments				
Sleep hygiene education	See text Frequently used in MMT	Modest improvement in TST in one study (43)	Caregiver and patient burden	May be difficult to implement in institutionalized setting
Physical activity	3-5 times per week, 30-60 minutes, vigorous Can use in MMT	Neutral effect on actigraphy measures (42,49,50) Vigorous activity showed modest improvements in subject sleep scales in one study (51)	Caregiver and patient burden Discomfort or cardiovascular risk for patients with co-morbidities	Ideally with professional therapist or trainer
Social activity	Unknown Better in MMT with physical activity	One small study showed improvement in TST and reduced daytime sleep (48)	Caregiver and patient burden	No standard
Bright light therapy (BLT)	Morning, 2500-10000 lux, 1-2 hours Can use in MMT	Reduced night-time awakenings (meta-analysis; 54) Increased total sleep time if patients have pre-existing sleep complaint (meta-analysis; 66)	Caregiver and patient burden Eyestrain	Ideally assess circadian phase, and time therapy to shift phase appropriately
Complementary and alternative modalities	Varies, see text	No large RCT	Varies	If no adverse effects and low cost, reasonable to try with close monitoring
Pharmacological sleep treatments				
Melatonin	Studies support 2-5 mg immediate release, at bedtime. Recommended starting dose 1.5mg, increase by 1-2 mg every few days; additional benefit unlikely above 10mg. Can use in MMT particularly with BLT	~25 minutes total sleep time (meta-analysis; 83)	One study showed increased depressive symptoms. Sedating effect may be more pronounced in elderly or demented patients, therefore assess for risk of falls/injuries.	No data on dosing other times of day
Sedating anti-depressants	Study supports Trazodone 50mg, at bedtime. Recommend starting dose 25mg, increase by 25mg increments. Max 200mg. Taper gradually if >50mg.	42.5 minutes total sleep time in one study (90)	May cause sedation and increased risk of falls/ injuries. particularly in elderly/demented Worse cognition,. in dementia Worse RLS	

Assessment or Treatment	Details	Benefits	Cons	Notes
NBBRA	No data to support specific treatment Typical doses for elderly: zolpidem 2.5-5 mg, eszopiclone 0.5-2mg, zaleplon 5-10mg.	No large RCT	May cause sedation and worse cognition Falls/ injuries, especially in elderly Parasomnias	
Benzodiazepines	No data to support specific treatment	No large RCT	May cause sedation and worse cognition Falls/ injuries Risk of abuse/dependence	
Stimulants	No data to support specific treatment	No large RCT	Cardiovascular risk, irritability, risk of abuse/ dependence	

MMT = Multi-modality treatment
RCT = Randomized controlled trial
RLS = Restless legs syndrome
NBBRA = Non-benzodiazepine benzodiazepine receptor agonists
BLT = Bright light therapy