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Sleep in Parkinson's Disease Dementia

Matthew Chow

Abstract

Sleep disruption and daytime somnolence are common in Parkinson's disease dementia (PDD). In this condition, the clinical features of Parkinson's disease (PD) and dementia with Lewy bodies (DLB) converge. Both PD and DLB populations have different sleep disturbances that are amplified when combined. Hence, sleep disruption is often significant and multifactorial in PDD. It is proposed that sleep-wake neural networks are affected early in the neurodegenerative process. The resultant lack of sleep results in impaired clearance of toxic metabolites, hastening disease progress. As the motor and nonmotor symptoms of PDD worsen, sleep becomes more disturbed. Medications used to control these symptoms can be sedating or cause insomnia. Comorbid sleep disorders are also often present. All of these factors contribute to poor sleep in these patients. Management is centered on symptom control, quality of life, and treatment of comorbidities.

Keywords: Parkinson's disease dementia, Lewy body dementia, glymphatic system, REM sleep behavior disorder, circadian rhythm disturbance, insomnia, obstructive sleep apnea, restless legs syndrome, nocturia

1. Introduction

Sleep-wake disturbances play an important role in the clinical presentation of the disease in patients with PDD. Involvement of brainstem and diencephalic structures result in dysfunction of the reticular activating system and other structures related to sleep-wake homeostasis. The resultant sleep disruption may impair the clearance of these abnormal proteins through slow wave sleep-mediated glymphatic drainage. Thus, neurodegeneration and sleep disruption interact in a feedforward loop, increasing the progression of disease. PD is classically recognized for its motor symptoms of tremor, rigidity, bradykinesia, and postural instability. However, sleep disturbances, broadly classified as one of the nonmotor manifestations of the condition, are quite common and associated with significant morbidity. Nocturnal motor symptoms, nocturia, dopaminergic medications, comorbid medical, psychiatric, sleep disorders, and environmental factors can all contribute to poor sleep in these patients. On the other end of the clinical spectrum, disturbance of sleep-wake mechanisms is a core feature of DLB. There are fluctuations of attention and arousal manifesting as variability in the ability to organize thoughts throughout the day and frequent daytime lethargy and napping despite an adequate sleeping period at night. The presence of REM sleep behavior disorder (RBD), a sleep disorder characterized by the enactment of dream activity due to loss of the normal muscle paralysis associated with REM sleep, is highly prevalent in DLB and is often one of

the first signs of the disease. DLB patients are also notably sensitive to neuroleptic medications, which can present as confusion, inattention, and somnolence upon exposure to this class of medication. Unfortunately, this is often discovered on the road to diagnosis in an attempt to manage the behavioral manifestations of the disease. These clinical features are often present in PD as well; however, they are often identified retrospectively or later in the course of the disease. PDD, on the spectrum of PD and DLB, is characterized by the onset of cognitive decline in patients with an established diagnosis of PD. All of the aforementioned sleep disturbances seen in PD and DLB can coexist in PDD and are often historically difficult to disentangle. While present as a core feature of DLB and a common nonmotor manifestation of PD, sleep disturbances are often underappreciated in these diseases, especially in the prodromal phase. The presence of disturbed sleep and/or daytime sleepiness in a patient with cognitive impairment or subtle signs of Parkinsonism should alert the clinician to the possibility of a neurodegenerative process. Sleep disruption often presents years prior to the motor or cognitive stigmata of these conditions; however, it may be overlooked as nonspecific or regarded as typical of age-related changes in sleeping patterns. A sleep-focused history, review of systems, standardized questionnaires, neurological examination, and polysomnography can aid in identifying sleep–wake disturbances in these patients. Early recognition is important for expectant disease management, counseling, and research into neuroprotective agents with the aim of halting or altering the trajectory of illness in these diseases.

2. Neurodegeneration of sleep–wake systems

Primary neurodegeneration in PDD causes excessive daytime sleepiness and disruption of sleep–wake architecture. Sleepiness and daytime napping are common in the older general population and not specific for the presence of a neurodegenerative condition. Clinical tools used to assess daytime sleepiness include quantitative questionnaires of subjective sleepiness like the Epworth Sleepiness Scale (ESS) as well as nocturnal polysomnography in combination with daytime nap testing, such as the multiple sleep latency test (MSLT). Patients with alpha-synuclein disease present with increased sleepiness by both subjective and objective measures compared to age-matched controls [1]. Within this population, daytime sleepiness also tends to increase with the presence of dementia with patients with PDD exhibiting increased sleepiness compared to patients with PD alone [2]. This daytime somnolence is in large part due to sleep disruption at night with associated alterations in underlying sleep architecture seen with polysomnography. Studies in patients with PD have shown poorer sleep quality with a delay in sleep onset, reduced N3 sleep, REM sleep, total sleep time, and sleep efficiency. This is similar to studies in patients with DLB that have also shown increased wake after sleep onset and N2 sleep [3]. These patients are also more frequently afflicted with EMG augmentation during REM sleep and confusional arousals from NREM sleep. These polysomnographic findings suggest that disruption of sleep–wake neural networks is common to both clinical conditions with overlap in their neuropathological spread. Posterior dominant slowing of background rhythms in REM sleep and wakefulness, temporal slowing with wakefulness, and impairment in spindle generation appear to be electrographic biomarkers for the development of PDD [4, 5]. This mirrors neurohistopathological findings that show increased Lewy body deposition in brainstem and limbic structures, which colocalize with the wake-promoting reticular activating system (RAS) and thalamocortical circuitry involved with spindle generation, respectively. The Unified Staging System for Lewy Body Disorders suggests that the involvement of these structures occurs early on in the disease course with brainstem involvement

Figure 1.
 Relevant neuroanatomical regions implicated in the pathogenesis of PDD.

(IIa) characteristic of more parkinsonian-type features and limbic involvement (IIb) characteristic of a more dementing-type illness. It is at these stages of disease that sleep disturbances likely become apparent. PDD would be identified in the transition from mostly brainstem involvement (IIa) to both brainstem and limbic involvement (III). After both neuroanatomical regions become involved, there is subsequent spread to the neocortex (IV) (**Figure 1**) [6].

Of course, it is important to note that the clinical picture is not always this clear. PD patients can also have Alzheimer's and cerebrovascular disease. These patient populations also suffer from daytime sleepiness and sleep disturbances. Amyloid plaques, neurofibrillary tangles, and ischemic changes can be seen on pathological examination. Often, a detailed neurologic history can aid in distinguishing these entities. In summary, PDD patients have increased sleepiness compared to healthy elderly subjects and PD patients without dementia. This is in large part due to degradation of sleep architecture from Lewy body disease in the brainstem and limbic structures.

3. Impaired clearance and disease progression

Impaired clearance of abnormal proteins in the central nervous system has been hypothesized as a mechanism for disease progression in alpha-synuclein disease as well as other neurodegenerative conditions. Recent discovery of the glymphatic system, a perivascular pathway that promotes the clearance of waste products facilitated by aquaporin-4 (AQ4) astrocytic water channels, has shown to be associated with amyloid-beta clearance. The glymphatic system is most active during sleep, notably slow wave sleep, due to reduced cellular swelling, expansion of the extracellular space with flow driven by cardiac pulsations [7]. These findings have implications in the pathogenesis of Alzheimer's disease and the role of sleep in general. While amyloid-beta levels have been shown to oscillate in CSF analysis of human subjects with the sleep-wake cycle, no such data exist with regard to alpha-synuclein. In a mouse model of PD, reduced glymphatic flow via ligation of deep cervical lymph nodes, yielded worsening of motor deficits and perivascular aggregation of alpha-synuclein [8]. Given sleep disturbances often occur early in alpha-synuclein disease and associated with more cognitive dysfunction, a feed forward mechanism for disease progression has been proposed. Primary neurodegeneration of sleep-wake structures in the brainstem leads to increased sleep disruption, which then impairs glymphatic clearance of abnormal proteins

accumulated during wakefulness. This then causes worsening of the underlying neurodegenerative disease further disrupting sleep. Even if alpha-synuclein is not cleared by the glymphatic system, PD patients are not immune from developing Alzheimer's disease (AD) pathology, which likely contributes to a subset of the PDD phenotype as mentioned previously. Reduction of comorbid amyloid-beta pathology could reduce central nervous system disease burden. Aging itself may be a risk factor for impaired glymphatic drainage as mouse models have demonstrated reduced beta-amyloid clearance with advancing age [9]. The importance of screening for comorbid sleep disorders in patients suspected of alpha-synuclein disease cannot be understated, as many of these disorders have established and effective therapies. Treatment of sleep disorders represents one of the significant modifiable risk factors in disease progression in patients who go on to develop PDD. In summary, the glymphatic system is hypothesized to play a role in alpha-synuclein accumulation through feed forward mechanisms. Comorbid AD pathology, advancing age, and sleep disorders can be contributory.

4. REM sleep behavior disorder as a biomarker

REM sleep behavior disorder is often prodromal in PDD and may represent a unique subtype of PD patients. The early and often initially isolated presence of RBD provides a window into the prodromal stages of Lewy body disease. The perilocus coeruleus in the pontine tegmentum projects to medullary magnocellularis neurons via the lateral tegmental-reticular tract. These neurons then project to motor neurons in the anterior horn cells of the spinal cord to produce paralysis during REM sleep. Disruption of this pathway can lead to REM sleep without atonia (RSWA) and manifest clinically as RBD. Consistent with the hypothesis that Lewy body disease presents early in brainstem structures, the presence of RBD can predate the onset of parkinsonism or cognitive decline by years (**Figure 2**).

PD patients with RBD appear to have increased cognitive impairment than PD patients without RBD [10]. They also share a number of clinical features more characteristic of patients with DLB than classic tremor-predominant idiopathic Parkinson's disease patients. An akinetic-rigid motor phenotype, hallucinations, and autonomic dysfunction have been more frequently described in PD patients with RBD than in those without. They also have more dense and diffuse pathology

Figure 2.
Relative symptom onset with disease progression in Lewy body disease.

on autopsy [11]. These clinical findings are supportive of a specific pathological subtype among patients with PD. Prospective studies in patients with idiopathic RBD who have yet to develop symptoms of parkinsonism or dementia have yielded similar conclusions. A study in a cohort of presumably idiopathic RBD (iRBD) patients has uncovered a number of interesting findings. (1) The large majority of iRBD patients actually have prodromal alpha-synucleinopathy. (2) Quantitative motor evaluation was both predictive of phenoconversion to parkinsonism AND dementia. (3) The diagnoses of DLB and PDD may mostly be a clinical distinction in that phenoconversion to parkinsonism first versus dementia first was similarly predictive of DLB [12]. These findings suggest a predictable pattern of disease in patients with iRBD with a common endpoint, which can be assessed in the clinic. A patient with iRBD who develops motor features consistent with parkinsonism is at risk for PDD. Similarly, opposed to the notion that dementia precedes parkinsonian features in DLB, this did not seem to matter in patients with RBD with patients presenting with parkinsonism first having a similar risk for developing DLB. Of note, most of these studies focused on the prodromal or early stages of PD and dementia. Less is known about patients with longstanding PD who develop RBD later in the disease course. In summary, the mere presence of RBD may portend the development of PDD and DLB, which likely have the same pathological underpinnings with a more aggressive disease progress and poor prognosis.

5. Case study

History of present illness:

A 57-year-old left-handed retired salesman with a past medical history significant for restless legs syndrome (RLS), transient ischemic attack (TIA) with word-finding difficulties at the time, and concussion in his youth presents with a 10-year history of episodes of violent dream reenactment with sleep. Episodes occur monthly to a couple of times per week. They usually occur a couple of hours upon falling asleep. He will often kick off his covers, talk, yell, and curse. This is accompanied by dreams of trying to run away from an attacker or kick himself free. He may wake up in the midst of one of these episodes and realize they have occurred. It has also been witnessed by others. Alcohol and sweets prior to bedtime may precede an episode. Ropinirole and imipramine prescribed by a neurologist in the past seemed to be beneficial. Clonazepam was ineffective. He denies any associated symptoms, specifically, no difficulties with memory, complex tasks or judgment, visuospatial ability, language, or behavior. He also denies a loss of taste or smell, constipation, muscle stiffness, slowness of movement, tremor, or falls. He feels his mood is good and denies any hallucinations. He denies any loss or near loss of consciousness.

The patient presents with isolated violent dream enactment behavior suspicious for RBD. His age of onset is consistent with the usual initial presentation for Lewy body disease (>50 years old). Violent content, usually in the act of defense, is common. Time of onset in the night is usually in the latter half of the night due to more prolonged REM periods with successive sleep cycles; however, episodes can occur anytime the patient enters REM sleep. Waking in the midst of episodes and dream recall is common as REM sleep is a “lighter” stage of sleep with an EEG profile similar to wakefulness (low amplitude mixed frequency EEG). Some studies have reported an association with RBD and alcohol, however, only in the context of chronic and heavy consumption. Clonazepam is usually first line in the treatment of RBD; however, the patient felt this was subjectively ineffective. There is little data to support the use of dopamine agonists or tricyclic antidepressants in the treatment

of RBD, with some concern that this may exacerbate the condition; however, the patient found these medications subjectively beneficial.

Medications: Aspirin, atorvastatin, vitamin D, and a multivitamin.

Allergies: No known drug allergies.

Past medical history: RLS, TIA, concussion, hypertension, hyperlipidemia, Gilbert's syndrome, and vitamin D deficiency.

Past surgical history: Tonsillectomy.

Social history: No history of learning difficulties. Earned his bachelor's degree. Recently retired due to work-related stress (not due to disability or job performance). Lives with his wife. Independent with his activities of daily living. Good social support. Rare alcohol. No smoking or recreational drug use.

Family history: Mother diagnosed with DLB, stroke in her 60s, and colon cancer. Died at 80 years old. Sister with breast cancer. Alive.

Of note, the patient is not on antidepressant or anticholinergic medications, which can mimic or "unmask" RBD. The patient has a family history of DLB in his mother. Having a family member with DLB may increase one's risk of developing DLB; however, DLB is generally not considered a genetic disease with most mutations being sporadic. Genes implicated in DLB include APOE, GBA, SNCA, BIN1, and TMEM175 [13].

Exam: The patient is obese with stage 1 hypertension. All other vital signs were stable. General physical exam was normal. On neurological exam, he scored a 26/30 on the MOCA with points missed for copying the image of the cube (visuospatial), identifying the association between a train and bicycle (abstraction), and 3/5 on word recall (delayed recall). He also had difficulty with identification with the alcohol sniff test. Otherwise, his neurological exam was unremarkable.

The patient was within the lower end of the normal range on his MOCA with deficits in visuospatial, abstraction, and delayed recall. Cognitive deficits in Lewy body disease have attention, executive function, and visuospatial perception disproportionately involved. Nonspecific but possibly the most clinically relevant finding on exam was his impaired sense of smell with olfactory bulb involvement common in prodromal Lewy body disease and consistent with his largely isolated RBD presentation.

Neuropsychological testing: Evaluation revealed normal cognition with testing in the average to superior range in attention, processing speed, language abilities, memory, and executive functioning. His performance in visuospatial tasks was overall normal; however, this may possibly reflect area of very subtle weakness in comparison to other areas.

MRI of the brain: Mild generalized brain parenchymal volume loss without lobar predilection.

Diagnostic polysomnogram revealed the following (**Figure 3**):

Phasic EMG activity in the bilateral arms and leg leads throughout as well as increased chin tone in the latter half of this 30-second epoch is observed. The background EEG is of low amplitude and mixed frequency with phasic "saw wave" eye movements observed in the EOG. The sleep technologist noted a behavioral manifestation in the corresponding video recording (not pictured here). These polysomnographic findings are consistent with RSWA and confirmatory of a diagnosis of RBD in the appropriate clinical setting.

6. Sources of sleep disturbance

There are a number of clinical symptoms associated with PDD that contribute to sleep disruption. Nocturnal motor and cognitive symptoms, pharmacologic

Figure 3.
 A 30-second epoch from a polysomnogram showing RSWA.

(dopaminergic, acetylcholinesterase, antidepressant, and neuroleptic) therapy, circadian rhythm disturbances, mood disorder, nocturia, insomnia, obstructive sleep apnea (OSA), and RLS can all play a role.

6.1 Nocturnal motor symptoms

While the motor manifestations of parkinsonism classically abate with sleep, sleep is often disturbed by the presence of akinesia, rigidity, cramping, tremor, and dystonia. These motor manifestations of PD are caused by the loss of dopaminergic neurons in the substantia nigra. The degree to which these motor symptoms cause sleep disruption trends with the progression of the disease. The obvious challenge with assessing nocturnal motor symptoms is that treatment decisions are largely based on retrospective patient report and daytime motor assessment, which can be challenging in patients with PDD. There are a couple of tools that have been developed to address this need. The Parkinson's disease sleep scale (PDSS) is a validated, short, 15-item inventory covering some of the most common sleep-related complaints in patients with PD with items 9–13 particularly focused on motor-related symptoms. However, this too relies on accurate patient or caregiver report [14]. More recently, and perhaps more objectively, actigraphy has emerged as an effective means of assessing nocturnal motor symptoms [15]. Patients in the early phase of the disease tend to show more frequent turning, similar to controls, however, with reduced speed and amplitude. More advanced PD patients show less turning, overall, with more time spent upright. This can be used to not only track disease progression but also response to therapy. Polysomnography would represent the “gold standard” assessment for these motor symptoms; however, it is not used clinically for this purpose outside of drug trials. It is mostly helpful in the identification of comorbid sleep disorders, such as RBD, OSA, and periodic limb movement disorder (PLMD). It would be impractical in monitoring the response to dopaminergic therapy. Long-acting preparations of levodopa, pramipexole, ropinirole, and a transdermal rotigotine patch have been developed. These medications have shown to be effective in treating nocturnal motor symptoms and reducing PDSS scores. Such preparations reduce the need for nocturnal medication administration. They also increase the amount of time the patient spends in the therapeutic range,

without having to augment the dose, which can cause toxicity. In summary, motor symptoms of PDD can cause sleep disruption. Accurate assessment of these symptoms can be challenging in patients with cognitive impairment. Actigraphy offers an objective measure of motor symptoms that can be tracked over time and assessed in response to therapy. Long-acting dopaminergic preparations are helpful in alleviating motor symptoms causing sleep disruption.

6.2 Dopaminergic therapy

Proper timing and titration of dopaminergic therapy to address nocturnal motor symptoms specifically, as opposed to simply sleep disturbance in general, are critical. Bradykinesia, rigidity, and tremor can give way to dyskinesias in a hyperdopaminergic state. Dopamine also has direct wake-promoting properties and can cause insomnia. Most stimulant medications exert their wake-promoting effects through dopamine pathways. Rebound “sleep attacks” are also a well-known phenomenon, mostly related to dopamine agonists. While this may be less of a concern at night, it can be problematic for PDD patients who already exhibit fluctuations in attention and arousal. Dopamine-promoting medications have also been implicated in circadian rhythm disruption, causing increased melatonin production and an “uncoupling” of circadian phase and behavioral sleep onset (delayed relative to dim light melatonin onset [DLMO]) in PD patients on versus off therapy [16]. Lastly, PDD patients are also prone to complex visual hallucinations, which can be exacerbated by these drugs. In summary, while dopaminergic medications can treat motor symptoms causing sleep disruption, they can also disturb sleep through dyskinesias, insomnia, fluctuations in arousal, circadian uncoupling, and hallucinations. Caution is advised. Long-acting and levodopa-based medications are preferred. Short-acting dopamine agonists should be avoided.

6.3 Cognition

“Sundowning” or nocturnal delirium, hallucinations, and fluctuations in cognition, attention, and arousal can disturb sleep in patients with PDD. These symptoms can cause difficulty with sleep onset, long periods of wakefulness in the middle of the night, and disturb the homeostatic drive for sleep at night due to daytime somnolence (**Figure 4**).

Such symptoms can be seen across the spectrum of dementia. Nocturnal agitation can be one of the most disturbing and disabling symptoms for patients and their caregivers. This can lead to injury, particularly falls at night, in patients already prone to these issues. The mechanism for “sundowning” is unknown; however, it is felt to be multifactorial with circadian rhythm dysfunction and absence of environmental sensory cues hypothesized to play a driving role. Management can be challenging. Alternative causes should be excluded, such as toxic/metabolic encephalopathies, infection, and subdural hematoma. Nonpharmacologic interventions are considered first line despite the lack of randomized controlled trials in the PDD population due to their relative safety. Bright light therapy (on the order of 10,000 s of lux) in the morning for delayed sleep phase chronotype and in the evening for advanced sleep phase chronotype can be helpful. Daytime physical exercise can help entrain daytime wakefulness while consolidating sleep at night. It has also shown to improve multiple metrics in PD including: cognition [17], motor symptoms, and falls. Behavioral multicomponent interventions (cognitive behavioral therapy for insomnia) have shown to be effective in elderly adults with mixed results in patients with dementia. This can take the form of stimulus control, sleep restriction, relaxation exercises, paradoxical intention, psychotherapy, and

Figure 4.
Sleep–wake disturbance with circadian and homeostatic sleep drive dyssynchrony.

sleep hygiene. However, such interventions may be challenging in PDD patients due to the degree of understanding and participation required. This is most useful early in the disease course and with caregiver support. Melatonin has shown to be helpful with “sundowning” in patients with Alzheimer’s dementia [18]. This agent has a dual benefit in PDD as melatonin is effective in suppressing the behavioral manifestations of RBD as well. In summary, nocturnal delirium, hallucinations, and fluctuations in arousal seen in PDD can cause sleep disturbance. Secondary causes should be considered. Nonpharmacologic strategies in the form of bright light and physical exercise are preferred as they carry little risk and show some benefit. Melatonin may help with delirium and improve RBD symptoms.

6.4 Medical management of behavioral symptoms

Pharmacological interventions in PDD are largely centered on improving cognitive symptoms and psychosis with improvements in sleep being of secondary benefit. Donepezil, rivastigmine, and memantine have been studied in PDD and DLB and have been shown to be effective in mitigating cognitive symptoms and hallucinations. Cognitive benefits seen in PDD and DLB may even exceed the benefits seen in AD [19] as patients with Lewy body disease have more relative cholinergic deficiency. However, similar to dopaminergic therapy, finding the minimum effective dose is important as acetylcholinesterase inhibitors (AChEIs) can cause nightmares due to their REM sleep-enhancing and consolidating effects. If hallucinations and delusions are distressing and dopaminergic therapy has been optimized, an atypical antipsychotic can be considered to facilitate sleep in psychotic patients. These typically have less D2 receptor blockade than typical antipsychotics to which PDD and DLB patients are particularly sensitive owing to the deficiency in striatal D2 receptors in these patients [20]. The lowest effective dose of quetiapine, clozapine, or aripiprazole dosed at night due to their sedating effects, is preferred. Pimavanserin, a selective serotonin 2A receptor inverse agonist, is a newer dopamine-sparing antipsychotic used in the treatment of PD psychosis. Its effects appear more robust in patients with greater cognitive impairment with concomitant AChEI use [21]. Of note, neuroleptic sensitivity and increased morbidity and mortality with antipsychotics are of concern in this particularly vulnerable population. Antipsychotics should be used sparingly for distressing hallucinations and delusions impacting the patient’s quality of life. As previously mentioned, excessive

daytime sleepiness, daytime napping, and fluctuations in arousal are common in PDD. If behavioral interventions are insufficient, stimulants can be considered. These largely exert their effects through dopaminergic and adrenergic mechanisms. Modafinil, armodafinil, methylphenidate-based derivatives, and amphetamine salts can all help to promote wakefulness. Monitoring of cardiovascular parameters and symptoms of sympathetic hyperactivation is required. In summary, AChEIs, NMDAR antagonists, atypical antipsychotics, and stimulants are effective in managing cognitive fluctuations and psychotic features disturbing sleep in PDD with monitoring for adverse effects, which can contribute to morbidity and mortality.

6.5 Mood disorders

Depression and anxiety are common comorbidities in PDD and DLB that can impact sleep and neurocognitive outcomes. Despite evidence showing higher rates of depression in patients with Lewy body disease (~20%) compared to AD (~9%) [22], guidelines regarding treatment in this patient population are lacking. Depression can cause a delay in sleep onset, earlier REM sleep onset, poorer sleep efficiency, earlier waking, and increased time in bed. Medications in the selective serotonin reuptake inhibitor (SSRI) and serotonin norepinephrine reuptake inhibitor (SNRI) classes seem to be similarly effective. Tricyclic antidepressants (TCAs) are generally avoided owing to their anticholinergic properties. At least in the general population, treatment of depression appears to improve sleep quality, regardless of whether the medication used is activating or sedating. In PDD, caution must be given to worsening of RBD and RLS/PLMD with antidepressant medication initiation as these are known sleep-related side effects of these medications. In such cases, a reduction in dose or retiming of the medication is effective. If not, bupropion can be used as an alternative agent as it is the only antidepressant that has not been associated with these conditions. In summary, mood disorders are common in PDD and can disturb sleep. SSRIs and SNRIs are recommended if depression/anxiety is present. These can potentially worsen RBD and RLS/PLMD. Bupropion is a viable alternative.

6.6 Nocturia

Nocturia, or the need to urinate at night, significantly disrupts sleep in patients with Lewy body disease. Urinary urgency and frequency are well-known nonmotor symptoms in patients with PD and DLB with the highest prevalence in DLB [23]. Lewy body disease causes disinhibition of the micturition reflex causing an overactive bladder [24]. Obstructive uropathy in men and pelvic insufficiency in women are often contributory. While frequent trips to the bathroom may be tolerated during the day, these trips cause sleep fragmentation and can be dangerous at night. The combination of akinesia, postural instability, dementia, and autonomic instability in PDD patients is a recipe for falls. Additionally, patients may restrict fluid intake to mitigate symptoms that can cause dehydration and exacerbate orthostatic hypotension. Historically, neurologists have been limited in their interventions with nonpharmacologic therapies being the mainstay. Scheduled toileting (before bed), pelvic floor exercises, and adaptive techniques (bedside commode) have been used. Medications have generally been avoided due to the anticholinergic mechanism action of these drugs, which can worsen confusion. Mirabegron, a beta 3-adreno-receptor agonist, can be used in those seeking to avoid this medication class. If an anticholinergic medication is to be chosen, trospium and darifenacin have shown to have less blood-brain barrier penetrance. Botulinum toxin injection into the detrusor muscle and percutaneous stimulation of the tibial nerve (PTNS) represent

third-line therapies, which have been found to be effective in small studies of PD patients. In summary, nocturia in PDD can cause sleep disruption and precipitate falls. Behavioral modification, beta-adrenoreceptor agonists, quaternary amine antispasmodics, botulinum toxin, and PTNS can help treat symptoms.

6.7 Insomnia

Insomnia is common in PDD as well as the general population, affecting up to 30% of the industrialized world. It also increases with age, cognitive impairment, and medical and psychiatric illness. Given its prevalence in the general population, it is not unsurprising that insomnia and daytime sleepiness do not appear to be biomarkers for the development of neurodegenerative disease in RBD patients [25]. The quandary in PDD lies in identifying the contributions of insomnia to sleep disruption from secondary causes and underlying neurodegeneration. Insomnia is conventionally a state of hyperarousal characterized by difficulty with sleep onset, maintenance, and early waking. Excessive daytime sleepiness and sleep maintenance out of proportion to sleep onset difficulties should alert the clinician to secondary causes for the patient's insomnia suggestive of sleep deprivation due to sleep fragmentation. However, in PDD, especially as the disease progresses, daytime hypersomnolence and disruption of sleep–wake architecture usually occur. Comorbid sleep disorders like OSA, RLS, RBD, and circadian rhythm disturbances are common. It is for these reasons that primary insomnia should be considered a diagnosis of exclusion in PDD patients with disturbed sleep. Behavioral measures (see recommendations for “sundowning” above), such as bright light, physical exercise, and cognitive behavioral therapy for insomnia are recommended. Patients with objectively shorter sleeping periods (<6 hours) may be less responsive to behavioral therapy [26]. Pharmacotherapy should be reserved for patients whose insomnia is refractory to these measures and cause distress and impairment in daytime functioning. PDD patients are particularly vulnerable to the side effects of sedative/hypnotic medications as these can cause morning after sedation, cognitive and motor slowing, amnesia, and parasomnias. Clinical practice guidelines for the pharmacologic treatment of chronic insomnia for elderly and cognitively impaired patients do not exist. Choice of therapy should take into account a number of factors: (1) type of problem (sleep onset, maintenance, or both), (2) duration of therapy, (3) adverse effects, (4) medical/psychiatric comorbidities, (5) medication interactions, (6) secondary indication, (7) patient preference, and (8) cost. For isolated sleep onset difficulties, dual orexin receptor antagonists (suvorexant and lemborexant), a melatonin agonist (ramelteon), and a short-acting benzodiazepine receptor agonist (zaleplon) could be considered. Suvorexant, lemborexant, and ramelteon have been studied in patients with dementia [27]. Benzodiazepines should generally be avoided due to their amnestic effects. Some nonbenzodiazepine receptor agonists (BzRAs) have been associated with an increase in parasomnias. For sleep onset and maintenance difficulties, a dual orexin receptor antagonist (DORA) is recommended. For patients with comorbid depression, low-dose trazodone or mirtazapine can be effective. TCAs are generally avoided due to their increased anticholinergic effects. For patients with comorbid RBD, high-dose melatonin or low-dose clonazepam (with caution and if RBD refractory to melatonin) is used. For patients with comorbid, disabling, and refractory psychosis, quetiapine can be considered. In summary, insomnia is common in PDD as well as the general population. Secondary causes for insomnia should be investigated. Behavioral interventions are first line in the treatment of insomnia in PDD. If refractory, there are a number of medication options available based on insomnia subtype and safety profile.

6.8 Obstructive sleep apnea

High rates of OSA have been observed in polysomnographic studies in patients with PD and DLB, affecting up to one-third of these patients [28]. Bulbar symptoms related to parkinsonism are presumed to contribute to airway collapse. This is partially offset by weight loss, often observed as the disease progresses. Patients with loud snoring, witnessed apneas, excessive daytime sleepiness, hypertension, obesity, large neck circumference, older age, and male gender are at increased risk for OSA. Sleep disruption and hypoxia from this condition contribute to neurocognitive decline, affecting attention, concentration, and mood. Additionally, OSA is associated with increased cerebrovascular disease, which can lead to vascular dementia. Motor outcomes in PD patients with OSA are also poorer compared to PD patients without OSA [29]. OSA can also be associated with REM sleep fragmentation with arousal-related motor manifestations out of REM sleep simulating RBD, or so-called pseudo-RBD. Due to REM atonia, the upper airway becomes more relaxed and accessory muscles of respiration become paralyzed, worsening OSA during this stage of sleep. Due to the effects OSA has on these aforementioned PDD-related symptoms, it is important to screen all patients for this condition. There are a number of OSA screening questionnaires that have been developed; however, it is important to note that these have not been validated in the PDD population. Polysomnography and increasingly, home-based sleep apnea testing, are used to diagnose this condition. In-lab testing is preferred in PDD patients as it is monitored by a sleep technologist who can assist with the setup and maintain the quality of the recording. Patients with PDD also often have other sleep disorders, such as RBD and PLMD, which home testing is usually not powered to detect. Continuous positive airway pressure (CPAP) remains the gold standard therapy for OSA. While studies have showed mixed results, CPAP appears to improve cognitive, motor, mood, and sleep quality outcomes in PD [30]. It also improves excessive daytime sleepiness. The cardiometabolic benefits of CPAP remain controversial. As with any behavioral therapy, but especially in PDD patients, adherence and tolerance to CPAP therapy are challenges. The cognitive impairment, trips to the restroom due to nocturia, dryness, and lack of dexterity to apply and adjust the mask are frequently reported issues. Patient education, frequent follow-up, and heated humidification have shown to improve compliance. In mild–moderate cases of OSA, a mandibular advancement device (MAD), a dental appliance that protrudes the jaw and increases the anterior to posterior upper airway diameter at the level of the tongue base, can be used as an alternative therapy. Upper airway surgery can be considered in patients with moderate–severe OSA in which CPAP is not tolerated; however, the risks of surgery and likely more prolonged postoperative course outweigh the benefits in the PDD population. Neuromodulation with a hypoglossal nerve stimulator (HGNS) that promotes tongue protrusion and airway patency represents an interesting less invasive option with minimal postoperative discomfort. Lifestyle measures including weight loss (if obese), positional therapy (side sleeping or head of bed elevation), and myofunctional therapy (mouth and throat exercises) are supplemental and recommend for all patients. It is worth noting that PDD patients spend more time in the supine sleeping position in which OSA is shown to be worse. In summary, OSA contributes to the symptomatology of PDD through different mechanisms. CPAP can improve the impact of OSA on these symptoms; however, adherence and tolerance are issues in this population. MAD, HGNS, and lifestyle measures are alternative and complementary options.

6.9 Restless legs syndrome/periodic limb movement disorder

RLS and PDD pathogenesis, clinical presentation, and therapy significantly overlap. In PD, there is a loss of dopaminergic neurons in the substantia nigra resulting in reduced striatal dopamine. In RLS, there is dopaminergic dysregulation and reduced iron in the basal ganglia with increased striatal dopamine, suggesting reduced sensitivity as opposed to deficiency. Interestingly, as opposed to RLS that shows reduced brain iron transport, PD patients show brain iron accumulation. It is unclear whether iron has a toxic effect in PD or whether this is a by-product of neurodegeneration. RLS is characterized by an urge to move the legs, sometimes associated with an unpleasant sensation, worse with rest, better with movement, and predominant in the evening. Akinesia, tremor, and dystonia may be misinterpreted as restless legs symptoms leading to overdiagnosis. It is important to make sure patients meet all clinical criteria before making the diagnosis of RLS. Periodic limb movements of sleep (PLMS) are common in RLS and PD, which may or may not be of clinical significance. PLMS must cause significant sleep fragmentation with resultant daytime symptoms to make a diagnosis of PLMD. This phenomenology can overlap with the nocturnal motor manifestations of PD and are often difficult to distinguish. Ultimately, RLS is a clinical diagnosis based on patient or caregiver history, which can be challenging in patients with dementia. The symptoms of RLS and motor manifestations of PD are treated similarly, making the diagnostic distinction between the two entities less critical. Oftentimes, PD patients are already on dopaminergic therapy, which can be adjusted to address evening and nighttime RLS symptoms. While generally not first line in RLS-only patients due to high rates of augmentation, levodopa is the preferred choice in PDD due to its dual benefit and lower rates of augmentation [31] in this population. This difference may best be explained by the dopamine deficiency seen in PD. Long-acting oral dopamine agonists and transdermal preparations can also be used. Alpha-2-delta ligand medications, such as gabapentin encarbil and pregabalin, are also considered first line in RLS. These can help with neuropathic pain and sleep induction but do not have activity on the motor manifestations of PD. Serum ferritin is checked systematically and iron supplemented if <50 ng/ml. A trial of oral iron supplementation is reasonable; however, due to constipation, which is already an issue in PD, an iron infusion may be required. Lifestyle measures include light exercise, stretching, avoidance of alcohol and sleep deprivation, and various forms of counter stimulation (vibrating pad, compression stockings, etc.). If medically refractory, a low-potency opioid could be considered with precautions. In summary, RLS and PDD both involve dysfunction in basal ganglia dopaminergic pathways, have overlapping symptoms that can make them difficult to distinguish, and benefit from dopaminergic therapy. Iron, alpha-2-delta ligand medications, behavioral interventions, and opioids are additionally used in RLS.

7. Conclusions

PDD is a clinical subtype on the spectrum of Lewy body disease. It is characterized by multidimensional and multifactorial sleep disturbances, which occur early and contribute significantly to the overall disease burden. Daytime sleepiness and disturbed sleep at night are merely symptomatic endpoints. Predictable brainstem, limbic, and subsequent neocortical spread of Lewy body pathology is responsible for early sleep disruption, followed by motor and then cognitive symptoms. This prodromal sleep disruption is hypothesized to perpetuate disease progression through a feed forward mechanism involving impaired glymphatic

clearance. RBD is an example of sleep's role as a biomarker for the alpha-synucleinopathies. The convergence of PD and DLB symptoms in PDD causes further deterioration in sleep. Treatment of these symptoms is a double-edged sword. Medications can ameliorate but also exacerbate sleeping difficulties. Trial data on therapeutics in PDD are lacking with most recommendations being inferred from studies in PD and AD. Sleep disorders, such as circadian rhythm disturbances, insomnia, OSA, and RLS, are common. These often go unrecognized due to attribution to the underlying neurodegenerative process. Most of these conditions have established treatment protocols that can be adapted to the PDD population.

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Conflict of interest

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Author details

Matthew Chow

University of California, Davis Medical Center, Sacramento, California, USA

*Address all correspondence to: mtchow@ucdavis.edu

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