Sleep disturbance in Parkinson’s disease (PD) and dementia with Lewy bodies (DLB) is common and can have a debilitating effect on quality of life due to the effects of daytime somnolence on cognition, motor function, potential for injury and capacity to manage activities of daily living. Sources of excessive daytime sleepiness in PD and DLB often include sleep fragmentation, side effects of medications, and sleep disorders that disrupt night-time sleep continuity. The parasomnia of REM sleep behavior disorder has also been shown to be an early feature of PD and DLB and a risk factor for dementia in PD. Dysfunction of the dopamine nigrostriatal and mesolimbic systems is involved in Lewy body disease, but several other neurotransmitter systems have Lewy body pathology and neuronal loss that may be responsible for abnormal sleepiness and REM sleep behavior disorder in these conditions.

Excessive daytime sleepiness refers to a tendency to doze off or fall asleep in situations where one is expected to maintain wakefulness. Daytime sleepiness is a serious clinical issue in Parkinson’s disease (PD) and dementia with Lewy bodies (DLB). In PD, excessive somnolence is associated with cognitive impairment, dementia, interference with activities of daily living, and increased risk of driving accidents [1, 2]. In a study of 3,078 men, those with excessive daytime sleepiness were three times more likely to develop PD, a finding not related to insomnia, mood or cognitive function, indicating somnolence may precede PD [3]. Excessive daytime sleepiness is now part of the proposed criteria for dementia associated with PD [4], and disturbed arousal is a common feature of DLB and appears related, in part, to the core feature of fluctuations in DLB [5, 6].

The estimated frequency of abnormal sleepiness in PD ranges from 15 to 81% [7–9]. In the early stages of DLB later confirmed by autopsy, we found the frequency of abnormal sleepiness to be 61% and greater than an age- and dementia-matched AD cohort.
Polysomnography and Multiple Sleep Latency Tests

In PD, overnight sleep studies using polysomnography reveal increased sleep fragmentation and a reduction in total sleep time, slow wave sleep and lower sleep efficiency [10]. Although nocturia, dyskinesia, dystonia, parkinsonism severity, and wearing off phenomena may fragment night-time sleep and result in daytime sleepiness, these factors do not entirely account for reduced sleep efficiency or daytime sleepiness [11, 12]. We found a similar pattern in a cohort of 78 DLB patients in the early and middle stages of DLB, and 50% of the sample had sleep efficiency less than 70%. Although about half the sample met criteria for obstructive sleep apnea (OSA) or periodic limb movements of sleep (PLMS), 76% of the sample had five or more spontaneous arousals an hour, not accounted for by respiratory or motor issues. This suggests that a component of the sleep fragmentation in DLB may have a primary neurologic basis.

The ‘gold standard’ for the objective assessment of daytime sleepiness uses the Multiple Sleep Latency Test (MSLT). The MSLT is a daytime polysomnographic study that records initial sleep latency (ISL) with four or five sequential laboratory-based nap opportunities spaced every 2 h. The mean value for the initial sleep latencies across the naps is the mean ISL. Mean ISL values less than 10 min are considered abnormal, and values less than 5 min reflect severe daytime somnolence. In a sample of 24 PD patients, despite normal nighttime sleep efficiency, the mean ISL for daytime naps was abnormally low (mean 9.2 ± 6.4 min), and the mean ISL in 42% of the 125 nap opportunities the mean ISL was clearly pathologic (≤5 min) [11]. Similarly, an MSLT study of 54 PD patients found more than half fell asleep within 5 min [13]. These findings provide objective evidence of abnormal daytime sleepiness in PD.

We carried out polysomnography and daytime MSLT in 31 DLB and 16 AD patients matched for gender and mild to moderate dementia [14]. Results revealed both groups had a mean night-time sleep efficiency of 70%, but the DLB group was more likely to fall asleep on the MSLT, and those that did fall asleep, did so faster than the AD group. Specifically, mean ISL <10 min occurred in 81% of DLB vs. 44% of AD (p < 0.01), and mean ISL <6 min occurred in 61% of DLB versus 19% of AD (p < 0.01). These data are similar to the studies of PD and provide objective confirmation of abnormal daytime sleepiness in DLB.

Sleep Attacks and Medication Side Effects

In the last 10 years, the phenomena of sleep attacks in PD, defined as an event of falling asleep suddenly, unexpectedly and irresistibly while engaged in some activity (e.g. during a meal, telephone call, driving a car) have received a great deal of attention.

Compared to levodopa, the ergot agonists (e.g. bromocriptine, pergolide) and non-ergot D2-D3 dopamine agonists (e.g. pramipexole and ropinerole) show an increased risk of daytime sleepiness and episodes of unintended sleep [15–17]. With
the exception of a dose-related effect, levodopa is generally not sedating in PD or DLB [9, 18, 19]. In a sample of 6,620 PD respondents to a questionnaire, 42.9% reported the sudden onset of sleep that was predicted by exposure to a non-ergot dopamine agonist [20]. Factors contributing to sleepiness with dopamine agonists include older age, male gender, history of sleep problems, cognitive impairment, dysautonomia and an overall higher dopaminergic load [20, 21]. Unlike levodopa, the ergot and non-ergot dopamine agonists are more likely to aggravate cognitive impairment and may elicit or intensify hallucinations [22].

Polysomnography data reveal that sleep attacks are objectively characterized as intrusions of non-REM stage 1 and 2 sleep, and a subset are represented by microsleep episodes, which last 15–120 s [23]. Whether sleep attacks are truly abrupt and occur in the absence of a history of sleep disturbance is a point of contention, particularly since patients often have reduced awareness of daytime sleepiness [11, 24] and microsleep episodes are often not perceived by patients [23].

Profound cholinergic neuronal loss in the basal forebrain and severely depleted choline acetyltransferase levels occurs in DLB and in PD with dementia [25]. Further reduction of an already vulnerable system may trigger delirium or delirium-like features [26]. Patients with parkinsonism are often given drugs with anticholinergic properties (e.g. amantadine, antihistamines, antidepressants, medication for incontinence, siallorhea), and patients with DLB or PD with dementia exposed to anticholinergics are at greater risk for confusional episodes, greater functional impairment and the development or worsening of psychosis. Therefore, it is prudent to limit or eliminate the anticholinergic load in patients with DLB or PD with cognitive impairment, and to consider a cholinesterase inhibitor in an effort to augment existing cholinergic availability for the diffuse connectivity of the basal forebrain.

**Sleep Disorders**

When considering sleep disturbance in PD and DLB, it is important to consider an underlying sleep disorder as the potential culprit or as an exacerbating factor. Treatment of a known sleep disorder may improve nighttime sleep continuity and daytime functioning.

**Insomnia**

Insomnia refers to difficulty initiating or maintaining sleep and is a common complaint in normal elderly. A study of over 9,000 normal elders >65 years showed that 42% reported difficulty initiating and maintaining sleep, and follow-up 3 years later revealed an annual incidence rate of about 5% [27]. In a sample of 39 DLB and PD with dementia, insomnia was reported in 47% of the cases [28]. In a study of 231 patients with PD, insomnia from delayed sleep initiation was reported in 23–30% and from frequent awakenings in 23–43% [29], similar to the population rates.
8-year follow-up, the complaint of insomnia in PD did not increase over time [29]. Factors associated with insomnia include mood, disease duration, female gender, vivid dreaming, trouble turning in bed, and nocturia [29, 30]. The causes of insomnia may also be related to non-PD related factors; underlying sleep disorders involve arousals due to motor, respiratory or circadian disturbance.

**Restless Legs Syndrome**

The diagnosis of restless legs syndrome (RLS) requires four essential features: (1) the urge to move the legs, usually accompanied by uncomfortable sensations in the legs (2) onset or worsening of symptoms during periods of rest or inactivity, (3) partial or total relief by movement at least as long as the activity continues and (4) worsening of symptoms in the evening or at night [31]. In the general population of individuals over 65 years of age, RLS occurs with a prevalence of about 8–10% [32] and typically interferes with sleep by causing insomnia. The same frequency of RLS is found in PD [33], though some argue that this is an underestimate since both use the same first-line treatment which may mask its appearance in PD. This seems unlikely though, since the dopaminergic dose needed to optimally treat RLS is much lower than that typically administered for PD, and when RLS does occur in PD, the extrapyramidal signs tend to precede the RLS by several years [34]. Also, although dopamine replacement therapy may help both conditions, RLS is known to respond to opioids, gabapentin and iron replacement therapy, which is not the case for PD. In one study of 303 consecutively treated idiopathic PD subjects, low serum ferritin levels predicted the occurrence of RLS in 20.8% of the group [35]. Moreover, idiopathic RLS is not associated with substantia nigra neuronal loss or Lewy body pathology [36]. In contrast, the hypothalamic dopaminergic diencephalic area that extends to the spinal cord has been considered, especially given mouse model findings of increased locomotion with 6-hydroxydopamine lesions to that region, and improvement of that increased locomotion with ropinirole [37].

**Periodic Limb Movements of Sleep**

About 80% of patients with RLS also have PLMS, but those with PLMS do not necessarily have RLS. PLMS are repetitive, stereotypic flexion movements of the legs that occur semi-rhythmically (up to 5 s in duration) separated by an interval of usually 20–40 s. They may cause arousals that fragment sleep and result in daytime somnolence. The treatments that are beneficial to RLS are also generally efficacious and well tolerated in those with PLMS. In PD, fragmentation of sleep due to PLMS is not correlated with the severity of daytime sleepiness, suggesting that although it is present and should be addressed, it is not likely the sole or primary source of daytime somnolence in PD [13, 38].

**Obstructive Sleep Apnea**

Sleep-related breathing disturbance, such as OSA, may cause sleep fragmentation, oxygen desaturation and associated daytime somnolence. Males are disproportionately
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represented in those with OSA, a pattern also seen in PD and DLB. In a sample of elderly community-dwelling men, the degree of frailty was associated with the nocturnal respiratory disturbance index with estimated rates of sleep-disordered breathing at about 24% in those with few or no signs of frailty, and 35% in those considered frail [39]. In PD, OSA has been observed in 20–30% of PD patients [40], suggesting rates of sleep-disordered breathing in PD are similar to rates in the normal population.

The apnea/hypopnea index (AHI) refers to the number of times per hour the patient demonstrates breathing cessation or partial obstruction. Several studies of PD demonstrate a mean AHI <10, indicating overall mild sleep-disordered breathing [12, 41, 42], but there is substantial inter-subject variability in PD with some demonstrating moderate to severe apnea, but many show no apnea at all [10, 13]. In one study, 36% of the sample had an AHI >10 [43] and another sample had 21% with AHI >15 (moderate to severe OSA) [40]. Therefore, a subset of patients with PD may be at greater risk for OSA despite normal body mass index (a primary predictor of OSA in the general population), and potential explanations include reduced tone in upper airway muscles, irregular respiratory flow oscillations, use of sedating medications, or perhaps dysfunction of the autonomic regulatory mechanisms for respiration [10, 40].

In DLB, our experience parallels that of PD, and reveals 37% with an AHI >10, 15% with an AHI >15 and no difference compared to AD [14]. Similarly, OSA occurs in a subset of patients but does not account for the overall excessive daytime sleepiness observed in DLB [14]. Nonetheless, it is important to screen for and treat sleep apnea in PD and DLB, in an effort to improve daytime alertness.

Circadian Dysrhythmia

Disrupted sleep architecture with reduced time spent in slow wave sleep (deep sleep) or altered circadian rhythm (associated with nocturnal melatonin peak) is not consistently found in PD and DLB [42, 44, 45]. Patients with hallucinations and cognitive impairment are more likely to have circadian dysrhythmia compared to healthy controls, but this relationship is not strong enough to account for the daytime somnolence in DLB [46].

Mechanism of Arousal in Parkinson's Disease and Dementia with Lewy Bodies

Lewy body disease affects the brainstem and hypothalamic sleep-wake centers, and the pathology affects multiple neurotransmitter systems [47]. Saper et al. [48] have provided data and a theoretical framework for a neuroanatomic flip-flop switch that regulates the transition from sleep to wakefulness. It includes mutually inhibitory elements responsible for sleep initiation, and brainstem nuclei that promote arousal. One hypothesis for the daytime somnolence in PD and DLB may be associated with the disruption of the wakefulness centers, but perhaps also to damage to the mechanism that switches and maintains wakefulness, presumed to reside in the hypothalamic hypocretin neurons. Involvement of the latter may lead to difficulty keeping the
arousal switch ‘in place’, which may result in trouble maintaining wakefulness and/or frequent brief transitions of sleep into wakefulness, or microsleeps.

**REM Sleep Parasomnia in Parkinson’s Disease and Dementia with Lewy Bodies**

REM sleep behavior disorder (RBD) was first described by Schenck et al. [49] and is characterized by a loss of normal muscle atonia during REM sleep associated with coordinated limb movements (i.e. punching, kicking, pushing, arm and leg movements that look like running or jumping) that mirror dream content. The actions made during REM sleep can be quite vigorous and themes often include defending oneself or others [50], though not exclusively [51], and may be associated with injuries. There seems to be far greater male representation in RBD, though it is unclear whether this reflects a referral bias, hormonal effects or a genetic relationship to the underlying pathology. The treatments of choice are clonazepam and more recently, melatonin [52].

It is important to distinguish RBD from other parasomnias or sleep disorders through polysomnography for proper intervention and to ensure that other sleep conditions are not present that may mimic RBD or that may be exacerbated with the use of clonazepam. For example, severe OSA may include flailing of the limbs and hollering, and nocturnal wandering, confusional arousals and sleep walking (which typically arise from non-REM stages of sleep), may also be hard to distinguish from RBD without polysomnography. Patients are often unaware of their sleep behavior, and it is crucial to obtain information from a bed partner or somebody who has witnessed the patient’s sleep.

RBD occurs with disproportionately greater frequency in DLB, PD and multiple system atrophy, also referred to as the synucleinopathies [53, 54]. In PD, the frequency of RBD is estimated to range between 46 and 58% [53, 55]. In DLB, the frequency of co-occurring RBD has been reported to be about 75% in autopsy-confirmed DLB [56]. In contrast, RBD in AD is quite rare, and occurred in only 2% of a clinical sample of 371 patients with AD or amnestic MCI [53] and in 0% of an autopsy-confirmed AD sample of 81 cases [56].

RBD often antedates the onset of the other clinical features by years and even decades [57–59]. The estimated 5-year risk of developing PD or DLB in a cohort with idiopathic RBD is 17.7%, and the 12-year risk is 52.4% [60]. Including RBD in the new DLB criteria improves diagnostic accuracy and leads to a 6-fold increase in the odds that the patient has autopsy-confirmed DLB [56]. When RBD is present with dementia but not parkinsonism or visual hallucinations, the cognitive pattern is indistinguishable from DLB and differs from AD. The pattern is characterized by impaired attention and visuoperceptual skills but relatively preserved memory and naming [59]. Patients with RBD and PD dementia show a similar cognitive pattern [61].

Follow-up of a subgroup of an RBD with dementia cohort revealed the eventual development of parkinsonism and/or visual hallucinations. Similarly, in Schenck
and Mahowald’s original RBD cohort [62], after 7 years of follow-up, 65% showed an eventual development of parkinsonism or dementia. In a group of 8 prospectively studied patients with RBD and MCI followed longitudinally, results revealed 7 developed DLB clinical features and all 8 had autopsy confirmation of DLB [63].

RBD in PD has been associated with orthostatism and non-tremor predominant (akinetic-rigid) parkinsonism [64, 65]. Those with PD and RBD are more likely to have cognitive impairment and an earlier onset of dementia than PD patients without RBD [61, 66, 67].

Results to date indicate that RBD and cognitive impairment may be an early harbinger of DLB and may be predictive of PD with dementia. Nonetheless, not all cases of idiopathic RBD develop cognitive impairment and/or parkinsonism, and it is not known whether there are protective factors that may keep the condition isolated in the brainstem.

The presumed pathophysiologic mechanism of RBD, based on the cat model, involves damage to the descending pontine-medullary reticular formation (including the gigantocellular medullary nuclei) that leads to a loss of the normal REM sleep inhibition of the spinal alpha-motor neurons. Smaller lesions in this region produce REM sleep without atonia, while larger lesions result in more elaborate motor behavior [68]. Some lesions in humans have been associated with polysomnography-verified RBD [50, 69], and two separate case reports of patients with idiopathic RBD revealed isolated brainstem Lewy body pathology with no evidence of dementia, parkinsonism or psychiatric features [69, 70]. Thus, RBD provides a reliable window into brainstem pathology and when combined with cognitive difficulties, is a predictor of DLB or PDD. Idiopathic RBD is a unique biomarker because it is treatable, and when it represents early neurodegenerative disease, the RBD is often present many years before the onset of the parkinsonism or dementia. Thus, RBD provides the potential for early detection for clinical trials and for early therapeutic and preventative intervention for DLB and PDD, once such therapies become available.

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