Rapid eye movement sleep behavior disorder (RBD) has been known to sleep medicine physicians for decades (Schenck, 2002). The association of RBD with idiopathic Parkinson’s disease (PD) has been appreciated, but it is only recently that RBD was considered a prodrome of the neurodegenerative diseases known as α-synucleinopathies, such as Lewy body dementia (LBD) (Schenck et al, 2013), which includes both dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) (Kurtz, Kaufer, 2011). Recent studies show that patients with idiopathic RBD will evolve into a neurodegenerative disease 91% of the time if followed for 14 years (Iranzo et al, 2014). Furthermore, RBD occurs in 80% of DLB patients (Boeve et al, 2007) as well as 37% of idiopathic Parkinson’s disease patients (Alatriste-Booth et al, 2015). As such, the

Sleep Centers: On the Frontline for the Future of Lewy Body Dementia

Chuck was brought in by his wife and daughter after his most recent fall, rib fracture, and hospitalization. He used a walker, had very short steps, and took “forever” to get in from the waiting room. His family described how on a recent evening walk with his wife he saw the moon rise quickly and a bear in the moonlight, neither of which was seen by his wife. He was restless when they went home, and by the time she took him to the ER, he was clearly hallucinating. The physician administered haloperidol and the patient became stiff, more agitated, and required ICU observation after lorazepam was given. He fell in the hospital during a dream, something he had done for years at home before she put his mattress on the floor.

The daughter recalls that Chuck had undergone a sleep study several years ago and was told he did not have sleep apnea, but that he did “act out his dreams.” A medication prescribed for this made him tired during the day, so it was stopped.

After listening to Chuck’s story, the physician gives a diagnosis: dementia with Lewy bodies.
consensus guidelines consider RBD a supporting diagnostic criterion for DLB (McKeith et al., 2005).

The relationship of RBD to LBD puts sleep centers in the position to make (or miss) the early diagnosis of the second most common neurodegenerative dementia in humans. The average DLB patient will see more than 3 physicians before a clinical diagnosis of DLB will be made (Galvin et al., 2010). Comedian Robin Williams saw many physicians, but his diagnosis was made only at autopsy after he committed suicide because of his unrelenting symptoms. His widow describes his disease course as living with a “terrorist inside my husband’s brain” (Williams, 2016). The very nature of undiagnosed LBD, aside from delaying access to appropriate care, can lead to iatrogenic and nosocomial catastrophes, which may be prevented by an early recognition of the disease.

Lewy body dementia is not rare. DLB is second only to Alzheimer’s disease as a cause of neurodegenerative dementia, and PDD develops in about 25% of patients with idiopathic Parkinson’s disease but can be as prevalent as 80% in patients with late onset PD (De Marchi, 2014). Collectively, DLB and PDD make up about 15-20% of dementia cases (Kurtz, Kaufer, 2011). The core features of DLB can include a fluctuating course of attention and alertness, visual hallucinations, and spontaneous parkinsonian features with falling, stiffness, and, occasionally, a tremor. A diagnosis of PDD requires a clinical course of PD for at least 1 year prior to the onset of dementia and can be supported by features that are consistent with the core features of DLB. Both DLB and PDD have a hypersensitivity to the adverse effects of neuroleptic medications (McKeith, 2005) (i.e. haloperidol), which is a particular problem for diseases that present with visual hallucinations.

Recognizing RBD and LBD has value in preventing iatrogenic and nosocomial complications and as an entry to appropriate care. There are no treatments with FDA-approved indications for RBD in LBD at this time. Off-label treatments for RBD have significant limitations. Clonazepam is commonly used. Like other long-acting benzodiazepines, clonazepam causes sedation, memory impairment, and falling. In fact, this class of drugs was the first to be associated with hip fractures in older patients (Boston Collaborative Drug Surveillance Program, 1973). This is particularly concerning in patients who are prone to falling due to their disease, be it DLB, PDD, or PD (Rudzińska et al., 2013; Allan et al., 2009). Melatonin has had some success in doses ranging from 3-12 mg, but large doses have been linked to daytime behavioral disturbances, including delusions and hallucinations (Boeve et al., 2003). Moreover, in the United States melatonin is largely unregulated, with unanswered questions over the assurances of the composition (Medical Letter, 1995). A safe, effective, and approved drug is needed for the treatment of RBD in Lewy body dementia.

Pharmacologic modulation of the 5HT2a serotonergic receptor offers an opportunity. Excess activity of the 5HT2a receptor has been associated with sleep disturbances in patients with Lewy body pathology (Ballanger et al., 2010; Yasue et al., 2016).

Nelotanserin, an investigational medication, is a highly selective inverse agonist of 5HT2a and has been shown to consolidate sleep patterns with reduced arousals and stage shifts in primary insomnia (Rosenberg et al., 2008). Nelotanserin is being studied for its effects on RBD as well as visual hallucinations in patients with LBD, with the rationale that the content of disruptive dreams in RBD is often the same as the visual hallucinations experienced in DLB and PDD.

A multi-center trial of nelotanserin in RBD complicating dementia with Lewy bodies and Parkinson’s disease dementia is underway in the United States with research sites near most metropolitan areas. These sites are currently enrolling new patients.

In this study, patients undergo 28 days of double blind treatment (nelotanserin or placebo) and have video polysomnography to characterize their RBD. The study is followed by long term open label access to nelotanserin for all subjects who complete if they so wish. The primary outcome measure of the study is to assess change in the frequency of REM sleep behaviors from baseline to the end of the treatment period (28 days).

Sleep centers are Ground Zero for making an early diagnosis of a serious and debilitating condition. So please ask yourself: What can I do to help these patients?
Making Progress in REM Sleep Behavior Disorder in Lewy Body Dementia Requires that Physicians:

**DIAGNOSE:**
Improve sleep technician awareness of RBD, the importance of finding it during polysomnography, and its association with serious neurodegenerative diseases such as LBD

**COUNSEL:**
Let your patients and their primary care physicians know there is an ongoing clinical trial of an investigational drug for RBD in DLB and PDD because patients with these conditions might be interested

**REFER:**
If you have patients with dementia with Lewy bodies or Parkinson’s disease dementia who have a concurrent diagnosis of RBD and would like to refer them to the study, or if you have patients with these conditions and are interested in taking part in the study, please contact Lydia Hatfield at (919) 425-0709 or by email at Lydia.Hatfield@axovant.com

References


