Dear Colleague:

There is no simple “quick fix” when a patient with Parkinson’s disease (PD) presents with a complaint of excessive daytime sleepiness (EDS). Each patient should be evaluated individually, and it is not uncommon for EDS to have multiple causes. Clinicians should give full consideration to all categories in the differential diagnosis of EDS: sleep problems, medications, and pathophysiology. Sleep problems were discussed in the last Treatment Reporter, and in this issue we will review the contributions of medications and PD pathophysiology to EDS in patients with PD. Clinicians should also be aware of several risk factors for EDS that may facilitate early diagnosis.

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Differential Diagnosis (Part 2) and Risk Factors

Introduction

Since almost all patients with PD have disturbed sleep,1,2 EDS is often attributed to poor nocturnal sleep. The last Treatment Reporter reviewed the types of sleep problems, including insomnia, sleep fragmentation, and disruptions in circadian rhythms, that affect patients with PD. Nighttime PD motor symptoms are particularly troublesome to patients with PD. Depression, anxiety, dementia, hallucinations, and medications can all interfere with sleep. Sleep disorders, such as sleep apnea, restless legs syndrome, and REM behavior disorder, appear to be more common in PD than in healthy, elderly controls.

However, disrupted sleep is clearly not the only cause of EDS to consider. Some investigators have asserted that EDS is actually not correlated with poor

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nocturnal sleep.1,3,4 In fact, Rye et al reported that those patients with more disrupted nocturnal sleep actually manifested higher levels of daytime alertness. In this Treatment Reporter, we consider disease pathophysiology and medications in the differential diagnosis of EDS in patients with PD.

**Pathophysiologic Causes of EDS**

The pathophysiology of EDS is not understood and is likely multifactorial. As aptly described by Rye, “Until more data are forthcoming, the most prudent clinical and experimental approaches should proceed from the assumption that the parkinsonian condition represents an underlying diathesis to sleepiness and sudden onset rapid eye movements (SOREMs) expression that can be exaggerated by numerous coexistent factors, including use of dopamine agonists and levodopa, sedative-hypnotics, and other medications, primary sleep disorders, and co-morbid conditions, such as dementia and depression.”

Support for the idea that PD pathophysiology directly affects areas of the brain involved in regulation of sleep and arousal comes from observations that EDS is more common and more severe in patients with PD than in healthy, age-matched controls.6 Sleepiness in newly diagnosed, unmedicated, or young patients with PD also suggests that the somnolence is related to PD pathophysiology.4,7 In addition, several studies have consistently shown that EDS in PD is significantly related to both disease severity and duration of disease.1,3,4,9 Other risk factors for EDS in PD, such as male gender, age,4,5,8 and cognitive impairment10,11 independently predict somnolence. Experience with PD patients in our clinic supports the idea that these patients have an overdependency on external arousal mechanisms. We find that they are not sleepy as long as they are involved with their environment. While these patients seem to have a low threshold for falling asleep, they are easily awakened when stimulation returns.

To date, the only identified genetic risk factor for EDS in PD, aside from male gender, is C-O-methyl transferase (COMT) activity status. Hogl et al12 recently reported that patients with PD subjects who were homozygotic for low activation COMT (LL) demonstrated higher Epworth Sleepiness Scale (ESS) scores than heterozygotes (HL) despite similar medication doses. This relatively small study will need confirmation in larger trials.

The role of CSF orexin-hypocretin in PD-associated EDS is not clear. Very low levels of CSF hypocretin are associated with narcolepsy/cataplexy. This neuropeptide projects diffusely through the brain and has reciprocal connections with dopaminergic areas affected in PD. It is now thought that this neuropeptide is necessary to maintain normal wakefulness. A preliminary report did not find abnormally low hypocretin levels in two patients with PD. However, subsequent work has demonstrated that many patients with PD have low or even undetectable hypocretin levels. Furthermore, low CSF orexin-A correlated with more severe daytime sleepiness as measured by ESS scores, and more severe PD.14 This physiologic link awaits further investigation.

In the 1970s and 1980s, dopamine was afforded only a marginal role in sleep-wake control. Other monoamines, such as serotonin, norepinephrine, and histamine, as well as acetylcholine were believed to play more important roles. More recently, evidence has accumulated to support a role for dopamine in arousal state control.15 For instance, chemical lesions of nigrostriatal dopamine cells in rats with 6-hydroxydopamine or in monkeys with MPTP decrease wake time and increase sleep.15 In narcoleptic dogs, infusion of D2/D3 agonists into the ventral tegmental area, but not the substantia nigra, facilitated cataplectic attacks. These agonists may activate receptors, located presynaptically or on dopaminergic neuron cell bodies, to inhibit activity of dopaminergic cells, although the actual mechanism of action is unknown. These findings suggest the importance of the dopaminergic mesolimbocortical system in control of sleep and wakefulness. Dopamine-specific reuptake blockers also promote wakefulness in normal and sleep-disordered narcoleptic animals.16 In mice, deletion of the gene controlling the dopamine transporter (DAT), the most critical determinant of synaptic dopamine agonist (DA) levels, decreased non-REM sleep time, increased wakefulness, and attenuated the response of wake-promoting agents, such as modafinil and methamphetamine.17 Finally, the significant sleepiness and sleep disruptions seen in patients with Parkinson’s disease are seen as critical clinical evidence supporting the thesis that dopaminergic pathways are involved in modulating sleep and wakefulness. Dopaminergic agents generally have complex effects on the sleep/wake state, and depend on both the dose and DA receptor subtype. In general, low doses promote sleep—possibly by inhibitory D1 receptors—while higher doses increase locomotor activity, enhance wakefulness and suppress slow wave and REM sleep via D2-like postsynaptic receptors.18 This, however, has also varied among different mammalian species.

The neural substrates for Parkinson-related sleep/wake impairments are not yet delineated. Some suggestions include targets of ventral tegmental area dopamine neurons (including the prefrontal cortex, cholinergic magnocellular basal forebrain, and midline thalamic nuclei) and nuclei comprising the ascending reticular activating system (such as the dorsal raphe, locus coeruleus, and pedunculopontine nucleus).19
Medication-Induced EDS
A variety of medications used in PD can aggravate sedation. Many of these, such as hypnotics, narcotics, antipsychotics, tricyclic antidepressants, SSRIs, benzodiazepines, and antihistamines, are well known since they also have soporific effects on healthy people. However, the role of dopaminergic medications in daytime somnolence in patients with PD has been a more recent finding. Now there is little doubt that all dopaminergic medications, including levodopa, result in a greater propensity to fall asleep, although they do not necessarily result in fatigue or other sequelae that are sometimes associated with daytime somnolence. Dopaminergic medications appear to lower the threshold for falling asleep.

Dopamine Agonists
The association between levodopa and EDS in patients with PD has been known for many years. For instance, in 1979, Lesser et al. reported levodopa monotherapy caused somnolence that limited levodopa dosage in 14% of patients with PD. Pramipexole was the first DA to be widely associated with somnolence. In a 10-week safety and efficacy study of pramipexole for PD, somnolence was the most frequently noted adverse event, reported in about 30% of patients receiving 3 mg to 6 mg per day.

Subsequent investigation has demonstrated that this is a class effect, although DAs may have a more soporific effect than levodopa. In controlled, randomized, double-blind clinical trials, somnolence occurred as an adverse event in 32.4% of patients treated with pramipexole compared with 17.3% of those treated with levodopa (P < .01) and in 27.4% of patients treated with ropinirole versus 19.1% of levodopa-treated patients (ns) (Fig. 1).

Sleep Attacks
In 1999, a paper by Frucht et al described 9 patients with PD who fell asleep while driving and had motor vehicle accidents while taking either pramipexole or ropinirole. The described sleep attacks (SA) are defined as sudden, irresistible urges to sleep without any prior warning. This classification created considerable controversy. Subsequent studies have found that 19% to 22.6% of PD patients taking dopaminergic medications fall asleep while driving. Hobson et al. reported that half of all patients with PD who drove met the criteria for EDS. Studies of patients with PD have reported that up to 30% of those who take dopaminergic medications have SAs. In a review of the literature between July 1999 and May 2001, Homann et al. found descriptions of 124 of 1787 patients (6.9%) with “sleep events,” ranging from “sudden and irresistible sleep confirmed by reliable sources” to “not sudden but irresistible onset of daytime sleep.” More recently, Schlesinger and Raven reported that 34% of 70 patients with PD taking DAs experienced “irresistible daytime sleepiness.” Some investigators feel that a sleep attack simply represents the extreme end of a spectrum of daytime somnolence. For example, some people may fall asleep while watching TV (daytime somnolence). Those more severely affected may fall asleep while sitting at the dinner table (EDS), while those even more severely affected might fall asleep while stopped at a red light while driving (sleep attack).

While some people say they are unaware of an impending sleep attack, testing has demonstrated that most of these individuals have high levels of baseline EDS and demonstrate several minutes of soporific behavior prior to falling asleep. In a study of 201 patients with PD and 214 controls, patients with PD were seven times more likely than controls to experience a sleep attack. ESS scores in those patients with PD who had sleep attacks were much higher than those who did not experience SAs (11.0 versus 4.0, P < .0005). Higher dose of levodopa and longer duration of disease were found to be predictive factors for SAs. No clear documented evidence exists to show that patients who have sleep attacks have different sleep architecture or sleep physiology than patients with less severe EDS.
Conclusions

Sleep attacks have generated considerable interest in the media, because falling asleep while driving represents a major public health issue, whatever the cause. Since patients with PD who drive generally are younger than those who do not and are frequently employed or required to drive for other reasons, the decision to treat these patients with dopaminergic medications presents a clinical dilemma. When sleep attacks were first discussed, some of the European regulatory agencies actually prohibited patients taking DAs from driving. In the United States, no formal criteria have been established and each case should be evaluated individually. In our clinic, we educate people about the risks of EDS and sudden sleepiness when we start DA medications for a PD patient, but we do not recommend complete cessation of driving.

In conclusion, careful consideration should be given to the many causes of EDS in patients with Parkinson’s disease in order to make informed treatment decisions. It is probably the rule rather than the exception that EDS may have more than one etiology. It appears likely that EDS reflects intrinsic pathophysiology, probably related to dopaminergic mesolimbocortical pathways. EDS can be exacerbated by medications, including dopaminergic therapy used to manage PD motor symptoms. These medications predispose some patients with PD to episodes of sudden sleepiness, which probably represent an extreme manifestation of EDS. The next Treatment Reporter will present treatment options for PD patients with EDS.

References

CME Instructions

To receive documentation of your participation in this 6-part CME activity (for which each newsletter equals .50 hours of CME credit) for a total of 3.0 hours of CME credit, please complete the following steps:

1. Read each newsletter carefully.
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Please indicate your answers below:

1. EDS may be a concern for patients with PD who are taking:
   a. Levodopa
   b. Ropinirole
   c. Pramipexole
   d. All of the above

2. Under US law, patients who take dopaminergic medications are required to stop driving within 1 month of drug initiation.
   a. True
   b. False

3. The complex effects of dopaminergic medications on sleep and wakefulness appear to reflect:
   a. Dose
   b. Receptor type
   c. All of the above
   d. None of the above

4. All of the following are risk factors for EDS in patients with PD, except:
   a. Female gender
   b. Increased disease duration
   c. Older age
   d. Greater disease severity

Thank you for your participation.