Awake and Involved: Addressing Excessive Daytime Sleepiness in Patients with Parkinson’s Disease

Part 4 of 6: Treatment Strategies for Management of EDS

Dear Colleague:

In previous issues of the Treatment Reporter we have learned that excessive daytime sleepiness (EDS) in patients with Parkinson’s disease may have multiple etiologies. From this knowledge, the clinician can make informed and appropriate choices among different treatment strategies to minimize or eliminate EDS. While sleepiness may be intrinsic to Parkinson’s disease of long standing, it is clear that EDS can be exacerbated by other factors, such as medications and sleep disorders. By correcting these problems and carefully utilizing medications to enhance alertness, the clinician can significantly reduce the debilitating burden EDS has on the lives of both patients with PD and their caregivers.

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Treatment Strategies for Management of EDS

Introduction

Previous issues of this Treatment Reporter series have discussed the many sleep problems associated with Parkinson’s disease (PD) and key elements that should be included in the clinical assessment of the Parkinson’s patient with excessive daytime sleepiness (EDS). Other subsequent issues have highlighted sleep problems, medications, and the disease process itself as prime potential causes of EDS in patients with PD. This Treatment Reporter discusses selection of the most appropriate treatment option for each patient by tailoring the therapy to the cause (or causes) of EDS (Table 1).

Table 1. Treatment Strategies for EDS in Parkinson’s Disease

- Encourage good sleep hygiene
- Treat underlying sleep disorders or sleep-disturbing medical conditions
- Assess PD medication use
- Withdraw daytime sedatives
- Consider pharmacologic treatments (eg, stimulants, modafinil)

continued on page 2, column 1

Part 4 of a 6-Part Series

Watch Your Mail for the Next Issue!

Learning Objectives

This activity has been designed for neurologists who treat patients with Parkinson’s disease. After completing this 6-part activity, the physician should be able to:

- Describe the burden of illness that excessive daytime sleepiness imposes on patients with PD.
- Recognize the possible etiologies of excessive daytime sleepiness in patients with PD.
- Employ effective measures to assess sleepiness to inform clinical decision making.
- Examine pharmacotherapies aimed at reducing excessive daytime sleepiness in patients with PD.
- Incorporate new approaches to the management of excessive daytime sleepiness in PD patients to maximize quality of life and patient satisfaction.

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Improving Sleep Hygiene

The first step a clinician should take in treating a patient with PD for EDS is to provide counsel about nonpharmacologic strategies that may improve sleep cycle disturbances. A nonpharmacologic approach is especially suitable for this population, which is generally elderly, with multiple co-morbidities and concomitant medications. Helpful recommendations may include restoring appropriate sleep, wake, and meal times, and scheduling activities at times of predicted somnolence (eg, a midday walk in the mall). Exposure to early morning sunlight during wake time and limiting environmental interruptions—noise, light, and awakenings by the bed partner—during the night may readjust circadian rhythm disruptions. Patients should be advised to minimize late-day caffeine, nicotine, and alcohol consumption. Since gastric emptying is often delayed in patients with PD, they should avoid eating within 2 to 3 hours of anticipated bedtime. Frequent, small meals may reduce postprandial sleepiness.1 Some investigators have suggested that EDS may actually be caused by deterioration of sleep hygiene (eg, increasingly sedentary lifestyle, unlimited daytime napping).2

Correcting Underlying Sleep Disorders and Sleep-Disturbing Medical Conditions

Nocturnal PD symptoms

Nighttime motor symptoms are a primary cause of sleep interruption in patients with PD, so treating such nocturnal symptoms often allows the patient to sleep better at night and be less sleepy during the day. For patients taking levodopa or a dopamine agonist, the use of controlled-release levodopa preparations or a COMT inhibitor along with levodopa will sometimes delay the re-emergence of PD symptoms and improve sleep. Bedtime dosing in these patients results in fewer awakenings—at least during the initial part of the night—and may facilitate sleep throughout the night.3

REM sleep behavior disorder

Patients with REM sleep behavior disorder (RBD) are generally treated without regard to whether they also have PD. The recommended treatment is clonazepam 0.5 mg, with a possible dose range of 0.5 mg to 2 mg. Because of the long half-life of clonazepam, bedtime administration can result in daytime somnolence. Administration earlier in the day can help avoid this potential complication. If tolerance develops to clonazepam, the patient can be switched to lorazepam (0.5–1 mg) for a month and then returned to clonazepam. An alternative treatment that may be helpful is melatonin (3–9 mg).3

Sleep apnea

This particular variation of apnea can lead to nocturnal hypoxia, cardiac arrhythmias, sleep fragmentation, and EDS. Sleep apnea can be either central (airflow ceases due to absent activation of respiratory muscles) or obstructive (airflow reduced or absent despite respiratory muscle effort). A polysomnogram can differentiate the type of apnea. Obstructive sleep apnea is treated effectively with continuous positive airway pressure (CPAP) while central sleep apnea is more difficult to treat and may require nocturnal oxygen or assisted ventilation.4

Restless legs syndrome/periodic limb movement disorder

Dopaminergic drugs are the treatment of choice for restless legs syndrome (RLS) in patients with PD. While both levodopa and dopamine agonists can be effective, long-acting dopamine agonists, such as pergolide and ropinirole, are useful because of their long half-lives and reduced risk for augmentation and rebound.5,6 Low doses should be sufficient. Controlled-release levodopa at bedtime or the addition of a COMT inhibitor may improve RLS symptom control in patients on levodopa. Other agents that may be beneficial for RLS in patients with PD include gabapentin and opioid drugs (codeine or propoxyphene).5,7

Nocturia

Urinary symptoms are common in PD, leading to urinary urgency, increased urinary frequency, impaired ability to urinate, and nocturnal polyuria.8 Bladder dysfunction progresses with advancing disease.9 The clinician may wonder if a patient with PD who awakens frequently during the night complaining of the need to urinate is actually being awakened by nocturnal PD motor symptoms. Therefore, nocturia in a patient with PD may require a two-pronged approach. Such patients may benefit from both improved control of nocturnal PD motor symptoms, as discussed in the preceding section, and direct treatment of nocturia. Intranasal desmopressin has been shown to be a safe, effective medication for nocturnal polyuria in PD at doses of 5 mg to 40 mg per day at bedtime.10 Patients taking desmopressin are at risk for hyponatremia and must be monitored for serum sodium levels.10 These patients may also respond to the muscarinic receptor antagonist tolterodine tartrate.

Hallucinations

Drug-induced hallucinations in patients with PD may occur secondarily to antiparkinsonian, anxiolytic, sedative, or antidepressant medications, so reducing or discontinuing the troublesome medication may alleviate the problem.9 Patients taking antiparkinsonian medications should be treated by gradual withdrawal of dopaminergic medications, beginning with the least potent agents (eg, anticholinergics, amantadine, and selegiline). The next step could be reducing or discontinuing levodopa or dopamine agonists, as long as this does not allow the re-emergence of serious parkinsonian symptoms. In that case, a small bedtime dose of the atypical antipsychotic quetiapine may be used. The prescribing of other antitypical antipsychotics, such as olanzapine and risperidone, is less desirable because they may worsen PD,9 and may produce EDS if taken other than bedtime. If these strategies fail, a low dose of clozapine (12.5–50 mg per day) can be tried, but regular blood monitoring for agranulocytosis is required.

Depression

Optimal treatment of PD motor symptoms may relieve depression in some patients with PD. The dopamine agonist pramipexole has significant antidepressant activity in addition to its ability to control motor symptoms.9 If depression persists, treatment may include medication, psychotherapy, and electroconvulsive therapy. For the depressed, sleepy patient with PD, selective serotonin reuptake inhibitors (SSRIs) in general and fluoxetine in particular may be helpful because, unlike the tricyclic antidepressants (TCAs), they do not have anticholinergic adverse effects, and they exert an “activating” effect. Daily doses of 20 mg to 40 mg of fluoxetine or 50 mg to 150 mg of sertraline are generally effective. Clinicians should be aware that SSRIs may worsen parkinsonian symptoms, disrupt sleep, and interact adversely with selegiline.11 For patients with PD who sleep poorly, TCAs such as amitriptyline (10–50 mg per day), desipramine (25–50 mg per day), or nortriptyline (20–40 mg per day) may be preferred for their sedative properties.9

Insomnia

Fifteen years ago, it was reported that one third of PD patients were taking hypnotics, sedatives, or antidepressants to help them sleep,12 and the number is probably greater today. In addition to the general precautions that should be taken when prescribing sleep-promoting medications in elderly patients, suggesting a sedative medication to a patient with daytime somnolence can
be problematic. TCAs may reduce insomnia, but their anticholinergic side effects may be intolerable for elderly patients. TCAs may also aggravate periodic limb movement disorder or RLS. Amitriptyline is a useful sedative for patients who are not having problems with nightmares or vivid dreaming. For late-stage PD patients with weight loss, an added benefit of amitriptyline is that it also promotes weight gain. SSRIs may be prescribed to treat insomnia associated with depression, but may paradoxically disrupt sleep. A short-acting benzodiazepine (eg, triazolam) with a quick onset of action can be useful for patients who have difficulty initiating sleep. Benzodiazepines with intermediate duration of action and intermediate onset of effect (eg, temazepam, estazolam) are suited to those who have difficulty maintaining sleep or who experience early morning awakening, although EDS may be exacerbated.16 Short-term use of zaleplon or zolpidem at bedtime may be prescribed to treat insomnia associated with depression, but may paradoxically disrupt sleep. A short-acting benzodiazepine (eg, triazolam) with a quick onset of action can be useful for patients who have difficulty initiating sleep. Benzodiazepines with intermediate duration of action and intermediate onset of effect (eg, temazepam, estazolam) are suited to those who have difficulty maintaining sleep or who experience early morning awakening, although EDS may be exacerbated.16 Short-term use of zaleplon or zolpidem at bedtime may be useful, although zaleplon may be preferred because the drug has a shorter duration of action and less residual sedative effects.17 The use of the antipsychotic quetiapine for sedation in the absence of hallucinations or psychotic features is controversial.

Treating EDS Pharmacologically

Reduce daytime sedating medications/adjust PD medications
Medication-induced EDS will likely respond to the reduction, elimination, or rescheduling of sedating medications (eg, Parkinsonian drugs, benzodiazepines, hypnotics, TCAs, SSRIs, antipsychotics, narcotics, antihistamines) or medications that interfere with drug metabolism, such as cimetidine. Medications for PD should be adjusted to the lowest dose that satisfactorily controls motor symptoms. Dosing should be carefully monitored, since low doses of dopaminergics can improve sleep by controlling parkinsonian dysfunction while higher doses can disturb sleep, produce heightened arousal, and cause EDS.18 While some antiparkinsonian medications, such as amantadine, may contribute to sedation, selegiline also has an alerting effect due to its amphetamine metabolite. For this reason, selegiline may be an appropriate choice for patients with PD who are sleepy in the mornings. These people may also demonstrate individual variability in their sedative/alerting responses to some medications.19

Pharmacologic treatment of EDS

If EDS continues to be a problem despite efforts to improve sleep hygiene, treat sleep disorders, and adjust medications, the physician may consider the use of agents to enhance alertness. Many of those being evaluated for EDS in PD have been used with varying degrees of success for patients with narcolepsy. Figure 1 is an algorithm for pharmacologic treatment of EDS in patients with PD.

![Figure 1. Suggested steps for pharmacologic treatment of EDS in patients with PD.](image)

### Stimulants

**Caffeine.** Because caffeine can impair nocturnal sleep and precipitate cardiovascular events, over-the-counter preparations containing caffeine (eg, No-Doz®) are not recommended as a treatment for EDS, especially in older individuals. Realistically, patients may find it helpful to drink coffee or caffeinated soft drinks in moderation early in the day when they feel sleepy.

**Amphetamine-Like Stimulants.** Amphetamines were widely used to treat patients with postencephalic parkinsonism in the 1930s.20-22 These patients showed subjective improvement in mood and energy, with reversal of disordered sleep rhythms but little or no objective improvement in motor symptoms. Parkes et al,23 found that levodopa-amphetamine produced a 20% improvement in total disability, which they termed “slight” and of little value in routine treatment due to adverse effects. No randomized, controlled clinical trials have been published to date on the use of amphetamines for EDS therapy in patients with PD.

Amphetamines are now rarely used to treat PD because they appear to have minimal benefit for motor symptoms and have adverse effects and abuse potential. In my practice, dextroamphetamine has been prescribed to two patients out of approximately 8000 with PD. These people had failed other treatment strategies and were required to have good social support and close supervision during dextroamphetamine therapy. Possible adverse effects to look out for with dextroamphetamine include psychiatric complications of paranoia, such as hallucinations and delusions, restlessness, irritability, insomnia, rebound hypersomnia, and anorexia. Sustained-release formulations may prevent rebound hypersomnia during the wearing-off stage. Concomitant use of monoamine oxidase inhibitors should be avoided.1

Methylphenidate is sometimes used as a stimulant for sleepy patients with PD. However, there has been very little formal study to support its benefit. In 1973, Miller and Nieburg24 reported that methylphenidate 10 mg/day eliminated signs of levodopa-induced lethargy and somnolence in 21 patients with PD. One recent case study showed that methylphenidate 5 mg/day improved levels of motivation/apathy in a patient with PD.25 Caution should be used when prescribing methylphenidate because it can interfere with nocturnal sleep and may precipitate cardiovascular events. The short-acting form may produce a rebound in sleepiness as the medication wears off.

**Modafinil.** Modafinil is a novel wake-promoting agent that has been shown in controlled clinical trials to improve daytime wakefulness without affecting nighttime sleep.26-27 It is indicated to improve wakefulness in patients with EDS associated with narcolepsy.28 It is also effective for EDS associated with sleep deprivation,29 multiple sclerosis,30 sleep apnea,31 and myotonic dystrophy.32 Modafinil has wakefulness actions like CNS stimulants. However, several preclinical studies have suggested a mechanism of action unlike that of the amphetamine-like stimulants.33,34 This agent is not a direct or indirect dopamine agonist and is inactive in preclinical models designed to detect enhanced dopaminergic activity. It is also not a direct or indirect α1-adrenergic agonist, although an intact noradrenergic system may be necessary for its wake-promoting activity.34 Unlike amphetamine, modafinil does not significantly increase locomotor activity, stereotypy, anxiety, blood pressure, or heart rate in animal models.35

Two randomized, double-blind, placebo-controlled crossover studies have been published that examine the effect of modafinil on EDS in patients with PD. In a 6-week study, 15 patients (12 completers) were prescribed modafinil 100 mg/day or placebo for 1 week, and then modafinil 200 mg/day or placebo for 1 week. After a 2-week washout period, patients received the alternative treatment. Scores on the Epworth Sleepiness Scale (ESS) improved by a mean of 3.42 points compared with
shows no improvement after 30 days. As seen in the treatment algorithm (Fig. 1), modafinil is recommended before the use of methylphenidate. As an added benefit, modafinil may help patients who have disabling somnolence due to dopaminergic medications tolerate higher dosages for improved control of motor symptoms.  

Figure 2. Modafinil in PD: Results

Conclusions

Treating EDS in patients with PD is not a simple task. Thorough consideration must be given to lifestyle, risk factors, co-morbidities, medications, and the many causes of sleep disturbances. Even the choice and timing of dopaminergic antiparkinsonian medications must be carefully determined to optimize control of motor symptoms while maximizing the desired effects on sleep or wakefulness. Treatment is even more difficult because a great number of patients are elderly and the disease is progressive, with changing symptoms. Nonetheless, the clinician now has a broad array of therapeutic options available for EDS that ranges from sleep hygiene modifications, medication adjustments, treatments for sleep disorders and other causes of interrupted sleep, to the use of agents to enhance alertness, which should be tailored to fit each patient’s specific needs.

References


0.83 points during placebo treatment (P = .11).  

In a second study, 21 patients (1 noncompleter) received placebo or modafinil 200 mg/day during two 3-week sessions, separated by a 1-week washout. A carry-over effect between the first and second treatment periods was demonstrated, so data were analyzed for the first treatment period only. During that time, modafinil produced a mean increase of 3.4 points on the ESS compared with worsening by 1 point during placebo treatment (P = .039).  

Adverse events reported in these studies included elevated blood pressure, hot flashes, insomnia, constipation, dizziness, and diarrhea. Modafinil did not appear to negatively affect motor function.

In practice, modafinil therapy should begin with 100 mg every morning for 2 weeks. If necessary, the dosage can be increased to 200 mg/day. Improvement should be noted within 1 to 2 weeks of beginning therapy. Treatment can be terminated if the patient

<table>
<thead>
<tr>
<th>ESS Scale</th>
<th>Baseline</th>
<th>Week 3</th>
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<tbody>
<tr>
<td>Modafinil (N = 10)</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Placebo (N = 10)</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

All patients had ESS ≥10 before treatment. After treatment, ESS improved by 3.4 for modafinil compared with worsening by 1.00 for placebo (P = 0.039). Two patients had ESS <10 after treatment. From Adler CH, et al, with permission.
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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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Name __________________________________________________________________ Degrees/Credentials ________________

Mailing Address __________________________________________________________________________________________________

City _____________________________________________________________________ State ________ ZIP________________

Phone ________________________________________________ Office Fax ___________________________________________

E-mail _____________________________________________________________________________________________________

Please indicate your answers below:

1. RLS is best treated with:
   a. Pergolide  
   b. Entacapone  
   c. Elonazepam  
   d. Propoxyphene

2. Desmopressin (DDAVP) is an effective treatment for:
   a. PLMS  
   b. Sleep apnea  
   c. Hallucinations  
   d. Nocturia

3. In what order should the following treatment approaches be considered when evaluating a patient with PD for EDS:
   - Prescribe medication to enhance alertness
   - Adjust PD medications
   - Counsel patient about sleep hygiene
   - Treat sleep disorder
   a. Prescribe, adjust, counsel, treat  
   b. counsel, treat, prescribe, adjust  
   c. Counsel, adjust, treat, prescribe  
   d. Adjust, treat, counsel, prescribe

4. Which drug should you prescribe if you suspect that the EDS in a thin, late-stage patient with PD is due to insomnia?
   a. Triazolam  
   b. Zolpidem  
   c. Amitriptyline  
   d. Sertraline

Thank you for your participation.