

# New Guidelines Are Issued for Four Nonmotor PD Symptoms

BY KATE JOHNSON

**N**onmotor symptoms of Parkinson's disease remain underdiagnosed despite their widespread occurrence—which is the impetus behind new treatment guidelines from the American Academy of Neurology.

"Nonmotor symptoms are an integral part of this syndrome. These symptoms can be as troublesome as motor symptoms and impact activities of daily living, though they are often underrecognized by health care professionals," wrote Dr. Theresa A. Zesiewicz, lead author of the guidelines and professor of neurology at the University of South Florida, Tampa (Neurology 2010;74:924-31).

Treatment of depression, dementia, and psychosis in Parkinson's disease (PD) has been addressed in a previous guideline (Neurology 2006;66:996-1002), as has treatment of PD-related sialorrhea with botulinum toxin (Neurology 2008;70:1707-14).

However, there are many other nonmotor symptoms for which there is a paucity of research concerning treatment, wrote Dr. Zesiewicz and her colleagues wrote.

"The disease process of PD certainly contributes to many nonmotor symptoms, including autonomic dysfunction (orthostatic hypotension, gastrointestinal symptoms), depression, sexual dysfunction, and sleep dysfunction," said Dr. Zesiewicz in an interview. "However, medications used to treat PD can contribute to other nonmotor symptoms. For example, the use of some PD medications can contribute to excessive daytime sleepiness, while others can cause insomnia."

In general, treatment of most nonmotor PD symptoms should mirror the treatments given to non-PD patients, because "research is not currently available to support or refute their use specifically in PD patients," Dr. Zesiewicz said.

However, the new guidelines provide evidence-based recommendations for treating four conditions: erectile dysfunction, constipation, restless legs syndrome, and fatigue.

A wide range of nonmotor symptoms were reviewed for the guidelines, including autonomic dysfunction such as gastrointestinal disorders, orthostatic hypotension, sexual dysfunction, and urinary incontinence; sleep disorders, such as restless legs syndrome, periodic limb movements of sleep, excessive daytime somnolence, insomnia, and REM sleep behavior disorder; fatigue; and anxiety.

After conducting a literature search aimed at capturing articles pertaining to these symptoms published between 1966 and 2008, a panel review deemed 46 papers relevant for the development of evidence-based recommendations. They also concluded that there was insufficient evidence to make recommendations regarding the treatment of urinary incontinence, orthostatic hypotension, insomnia, REM sleep behavior disorder, and anxiety.

For the treatment of erectile dysfunction

(ED) in Parkinson's disease, the authors recommend that sildenafil citrate (50 mg) "is possibly efficacious."

Sexual dysfunction is common in both men and women with PD, they wrote. "Dysautonomia manifests as erectile dysfunction (ED) but also as reduced genital sensitivity and lubrication and difficulties reaching orgasm." Only one controlled clinical trial for the treatment of ED was available for review, however.

For constipation, they concluded that isotonic macrogol (polyethylene glycol) "possibly improves constipation in PD." Four studies evaluating the efficacy of pharmacologic agents for PD-related constipation were reviewed, and the recommendation is based

one class II study.

Regarding PD-related sleep dysfunction, the authors found sufficient evidence to make treatment recommendations for excessive daytime somnolence (EDS), and restless leg syndrome or periodic limb movements of sleep.

Based on the results of two class I studies, the authors recommend modafinil to improve patients' perceptions of wakefulness, though "it is ineffective in objectively improving EDS as measured by objective tests."

In addition, they said, levodopa/carbidopa "probably decreases the frequency of spontaneous nighttime leg movements," based on one class I study and should therefore be considered to treat periodic limb movements of sleep in PD.

And finally, "methylphenidate is possibly useful in treating fatigue in PD," they concluded, based on one class II study. However, there is potential for abuse, they warned. "Although there is no current evidence to suggest such a risk in PD, patients with PD do have a risk for dopamine dysregulation syndrome and impulse control disorders that share many clinical and functional imaging features with addiction," they cautioned.

"The same rules for treating PD patients with these medications would apply as when treating any patients, including careful monitoring of drug interactions and taking comorbid conditions into consideration," Dr. Zesiewicz said.

"Of course, it is important to recognize that the treatments recommended are not the only available treatments," commented Dr. Ronald B. Postuma, who is a PD researcher and assistant professor of neurology at the Montreal General Hospital. "The guidelines focus only on therapies that have good randomized controlled trial evidence. All experienced clinicians will recognize several useful treatments that are not in the recommendations because of incomplete evidence," he said in an interview.

Dr. Zesiewicz reported receiving funding for travel from and serving on speakers bureaus for Boehringer Ingelheim Inc. and Teva Pharmaceutical Industries Ltd.

She also reported that she had received research support from various pharmaceutical companies. ■

# PPN Stimulation Controls Parkinsonian Sleepiness

BY DAMIAN McNAMARA

**MIAMI BEACH** — Stimulation of the pedunculopontine nucleus could be a new target to treat excessive daytime sleepiness and other sleep disorders in people with Parkinson's disease, according to recent reports in the literature.

"Daytime sleepiness is a frequent and disabling problem in Parkinson's disease," Dr. Isabelle Arnulf said at the World Federation of Neurology World Congress on Parkinson's Disease and Related Disorders.

Although excessive daytime sleepiness can interfere with the activities of daily life for Parkinson's disease patients, a main concern is their increased risk for a driving accident.

Dr. Arnulf, a sleep disorders specialist at Hôpital Pitié-Salpêtrière in Paris, advised telling patients to be cautious when driving. "The most dangerous for driving are those who do not feel their own sleepiness."

In the first report of its kind, researchers at the University of Toronto demonstrated last year that deep brain stimulation of the pedunculopontine nucleus (PPN) alters human sleep patterns (Ann. Neurol. 2009;66:110-4).

They studied REM and non-REM phases for five parkinsonian patients undergoing unilateral deep brain stimulation of their PPN.

Nocturnal REM sleep time nearly doubled during stimulation, compared with periods when stimulation was turned off. The implication is that helping people with Parkinson's disease sleep better at night will decrease daytime sleepiness.

High frequency (80 Hz) PPN stimulation produces a sedative effect that "even occurs when the patient actively tries to maintain wakefulness," Dr. Arnulf said.

In her experience, patients trying to stay awake during this stimulation demonstrate periods of microsleep. She showed meeting attendees a video of a man undergoing stimulation who, despite trying to fight off sleep, went on to establish sleep stage I and then non-REM sleep stage II within 2 minutes. The patient fell asleep 10 out of 10 times, she said.

The results that were obtained in the pilot study suggest that the PPN "could be a new target for sleep disorders," she said.

Sleep attacks, or the sudden onset of sleep without prodroma, are primarily described in narcolepsy. Risk factors include an Epworth Sleepiness Scale score greater than 10 (range, 0-24), use of dopamine agonists, or high levodopa equivalent doses, Dr. Arnulf said.

Patients can be screened for excessive daytime sleepiness using objective measures such as the Multiple Sleep Latency Test and the Maintenance of Wakefulness Test.

Among the possible causes of excessive daytime sleepiness in people with Parkinson's disease are the side effects of dopaminergic agents, insufficient sleep at nighttime, and lesions in arousal systems.

To treat excessive daytime sleepiness, one could decrease or switch dopamine agonists, or con-

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sider replacement of a dopamine agonist with levodopa. Combining dopamine agonist therapy with a stimulant drug is another option, Dr. Arnulf said.

Reports in the literature support sleepiness as a medication side effect. For example, in one study, researchers observed a "huge increase" in sedation effects—a decrease in sleep latency—about 3-5 hours after 12 healthy volunteers took a dopamine agonist (Br. J. Clin. Pharmacol. 2009;67:333-40).

In another study, researchers found that 22% of 929 patients with Parkinson's disease who were prescribed a dopamine agonist reported an episode of "uncontrollable somnolence" (Arch. Neurol. 2005;62:1242-8)

The risk for uncontrollable somnolence was nearly tripled in participants taking a dopamine agonist compared with other medication types.

Dr. Arnulf said that a common question is whether sustained-release dopamine agonists are less sedative. Dopamine-related sleepiness usually occurs at the peak of the dopamine agonist effect, she said, but a blunted peak does not prevent sleepiness from occurring.

Dr. Arnulf had no relevant financial disclosures. ■