Guidelines Address Nonmotor PD Symptoms

**BY KATE JOHNSON**

Nonmotor 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.

“The disease process of PD certainly contributes to many nonmotor symptoms, including autonomic dysfunction (orthostatic hypotension, gastrointestinal symptoms), depression, [and] sexual [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, she said. However, the new guidelines provide evidence-based recommendations for the treatment of 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, REM sleep behavior disorder, fatigue, and anxiety.

The treatment of erectile dysfunction in PD, the authors recommend that sildenafil cite (50 mg) “is possibly efficacious.” 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 isosmotic 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 on one class II study. 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, they recommend modafinil to improve patients’ perceptions of wakefulness, though it cannot objectively improve EDS as measured by objective tests, they added.

In addition, they said, levo-dopa/carbipoda “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 warn. “Although there is no current evidence to suggest such a risk in PD, patients with PD do have a risk for dopamine dysregulation syndromes 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, 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 from and serving on speakers bureaus for Boehringer Ingelheim and Teva Pharmaceutical Industries Ltd. She also reported receiving research support from various pharmaceutical companies.

Magnetic Stimulation Device Effective Against Migraine Pain

**BY MICHELE G. SULLIVAN**

Active stimulation of the cortex with a single-pulse, transcranial magnetic hand held device gave patients with migraine and aura increased freedom from migraine pain.

The device was especially effective in patients who took migraine prevention drugs, according to Dr. Richard Lipton of the Albert Einstein College of Medicine, New York, and his associates, who reported that at 1 hour after treatment, 97% of those in the active group were pain free, compared with 65% of those in the sham group.

For patients who commonly have migraines, stimulation of an impending migraine, treatment with [the device] may abort progression of the attack and abate disabling pain and other symptoms,” wrote the authors (Lancet Neurol. 2010;doi:10.1016/S1474-4422(10)70054-5).

The portable machine delivers a brief magnetic pulse into the cortex of the brain, causing a counterclockwise flow of current. The intervention is thought to inhibit cortical spreading depression and prevent migraine from developing.

In a double-blind, sham-controlled trial, 201 patients with migraine and aura were randomized to either the actual device (102) or sham (99). They were instructed to apply the device be fore the onset of aura, and always with the device. Patients were instructed to apply the device being pain free after 2 hours treatment.

Significantly more of the actively-treated than sham-treated patients were pain free 2 hours after treatment (39% vs. 22%, respectively). The difference in being pain free remained significant at 24 hours (29% active group vs. 16% sham group), and at 48 hours (24% vs. 13%).

Other migraine symptoms at 2 hours—nausea, photophobia, and phonophobia—were significantly less common in the active group, but only in patients whose pain level was moderate or severe at baseline. Among those with an ongoing baseline headache line, there were no differences in those symptoms at 2 hours after treatment.

The investigators said use of migraine prevention drugs was significantly associated with a better 2-hour pain outcome. For those in the active group, the absolute risk reduction of pain at 2 hours was 32% for those who took the drugs and 8% for those who did not take them.

The device was well tolerated. One serious adverse event, a case of optic neuritis in one trial. It happened before a treatment, however, and so was deemed unrelated to the device. One of the device’s biggest benefits is that it is not invasive. “Treatment can be delivered to a circumscribed region of the brain, [in contrast with drugs that are delivered systemically],” they wrote. In an accompanying editorial, Dr. Hans-Christoph Diener said the findings were encouraging (Lancet Neurol. 2010;doi:10.1016/S1474-4422(10)70063-6). “The use of TMS could be a major step forward in [treating] migraine with aura, particularly in patients in whom presently available drug treatment is ineffective, poorly tolerated, or contraindicated.”

However, Dr. Diener, of the University of Dusseldorf, Germany, noted that caveats remain. TMS can theoretically trigger seizures, and should not be used in patients with concomitant epilepsy until the device has been investigated in such a population.

In addition, he noted that triptans are very effective and inexpensive medications. “Therefore, the manufacturer of the TMS device must show cost-effectiveness compared with standard drug treatment with triptans,” he said.