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 wrote.

"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.

A range of nonmotor symptoms of Parkinson's were reviewed for the new AAN treatment guidelines, including sexual dysfunction, sleep disorders, fatigue, and anxiety.

After 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 in PD, the authors recommend that sildenafil citrate (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 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 is ineffective in objectively improving EDS as measured by objective tests," they added.

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 warn. "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, 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 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 handheld 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 2 hours 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 aura as a signal 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 thus 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 below the occipital bone and deliver two pulses of energy as soon as possible after the onset of aura, and always within 1 hour. The patients were allowed to take migraine prevention drugs, but not analgesics, triptans, ergots, or other drugs that could confound pain assessment. They could take rescue drugs 2 hours after a treatment.

VITALS

Major Finding: A handheld transcranial magnetic stimulator eliminated migraine pain after 2 hours in 97% of patients with migraine and aura, compared with 65% of sham-treated patients; it was more effective in patients using migraine prevention drugs.

Data Source: A sham-controlled randomized trial of 201 patients.

Disclosures: Neuralieve Inc., maker of the device, funded the study. The lead author is a paid consultant and stockholder in the company. All of the other authors also have financial ties to the company.

Most of the patients were women (130); their mean age was 39 years. They had a mean of four migraine attacks a month. Of the total, 37 did not treat a migraine; the 164 who did were included in a modified intent-to-treat analysis.

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 (27% 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 no or mild pain at baseline, 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, occurred during the 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 Duisburg-Essen, 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. ■