Pimavanserin Shows Promise in PD Psychosis

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — The investigational agent pimavanserin appears to lessen psychosis in patients with Parkinson's disease without worsening motor function, according to a multicenter randomized phase II trial.

Pimavanserin is a potent, active 5-hydroxytryptamine 2A (5-HT_{2A}) serotonin receptor antagonist, said Dr. Stephen Revell of Acadia Pharmaceuticals Inc., which sponsored the study. However, it lacks the dopamine receptor (D_2) and histamine receptor (H_1) binding linked to the adverse effects of other antipsychotics.

Patients in the study had PD and psychosis and were given either pimavanserin (n = 29) or placebo (n = 31) on an outpatient basis for 28 days, starting at 20 mg daily on day 1, with dose escalations to 40 mg and 60 mg on day 8 and 15, respectively, depending on individual clinical response.

Pimavanserin patients demonstrated a 40% improvement in the Scale for the Assessment of Positive Symptoms (SAPS) combination score for hallucination and delusion, compared with an 11% improvement for placebo patients ($P = .05$), Dr. Revell reported in a poster at the 12th International Congress of Parkinson's Disease and Movement Disorders.

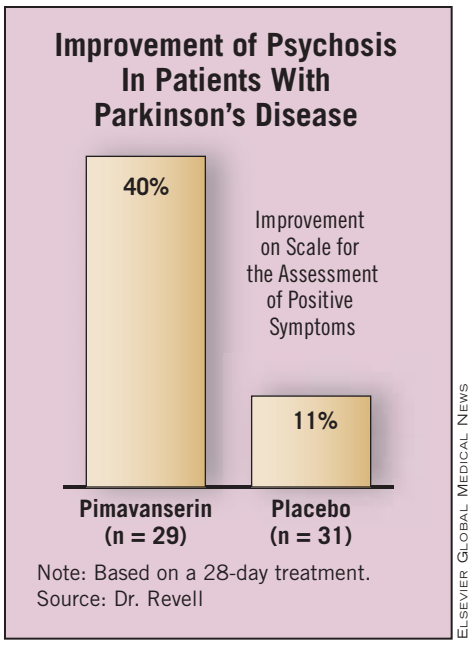
Statistically significant improvements also were seen for patients treated with pimavanserin on the mentation, behavior, and mood part of the Unified Parkinson's Disease Rating Scale (UPDRS) ($P = .05$).

There was no clinically significant difference between patients treated with placebo vs. pimavanserin in the absolute mean change from baseline to day 28 in UPDRS motor scores (–3.05 vs. –1.24, $P = .303$) or activities of daily living scores (–2.51 vs. –0.70, $P = .112$).

No differences in the groups were seen on the Schwab and England Activities of Daily Living Scale part of the UPDRS, the Clinical Global Impression Scale severity of illness subscale, or the Epworth Sleepiness Scale daytime sleepiness subscale. The most common adverse events were somnolence, edema, and increased blood urea.

In a second poster, pimavanserin was well tolerated and did not worsen Parkinsonism symptoms in 39 patients (mean age 72) with PD and psychosis at doses up to 60 mg/day for up to 42 months (mean 14 months). Somnolence, fatigue, or dizziness were uncommon, said Dr. Roger Mills, also of Acadia, who led the industry-sponsored, open-label extension safety study.

A case of rhabdomyolysis was the only serious adverse event. ■



Nortriptyline Beat SSRI for Depression in Parkinson's

BY SHERRY BOSCHERT
San Francisco Bureau

PHOENIX — Nortriptyline was more effective than paroxetine or placebo in treating depression in patients with Parkinson's disease, an 8-week pilot study of 52 patients found.

The study is the largest placebo-controlled trial of depression treatment in PD and the first in this population to compare a tricyclic antidepressant with a selective serotonin reuptake inhibitor (SSRI), in this case, controlled-release paroxetine (paroxetine CR), Dr. Matthew A. Menza said at a meeting of the New Clinical Drug Evaluation Unit.

Only 7% of patients with PD and depression are on a tricyclic antidepressant, noted Dr. Menza, professor of psychiatry and neurology at the University of Medicine and Dentistry of New Jersey, Newark.

The National Institute of Neurological Disorders and Stroke funded the study. Dr. Menza has financial ties to Eli Lilly & Co., which makes a brand of nortriptyline, and to GlaxoSmithKline, which makes paroxetine CR and provided the drug and matching placebo for the study.

The study randomized patients to 8 weeks of blinded treatment with nortriptyline, paroxetine CR, or placebo. About one-third of patients in each group discontinued treatment. Of those who completed the study, the average dose by the end of 8 weeks was 63 mg/day nortriptyline, 32 mg/day paroxetine CR, or two pills of placebo.

The nortriptyline group showed better results on the two primary end points—Hamilton Depression Rating Scale (HAM-D) scores and the proportion that showed a response to therapy, reported Dr. Menza and his associates.

Scores on the HAM-D changed by 11 points in the nortriptyline group, 7 in the paroxetine CR group, and 3 in the placebo group. The differences between the nortriptyline and paroxetine groups were significant at weeks 2 and 4, with a trend toward significance at week 8. Scores in the nortriptyline group were significantly different from the placebo group at all visits.

Total side effects did not differ between groups, but nortriptyline was tied to more anticholinergic effects.

DR. MENZA

The proportion of patients who responded to therapy was 53% in the nortriptyline group, 11% in the paroxetine group, and 24% on placebo. The nortriptyline response rate was significantly higher, compared with the paroxetine group, but not compared with placebo.

The total number of side effects did not differ significantly between groups, but the nortriptyline group had more anticholinergic effects, including constipation and dry mouth. No worsening in cognition or movement was seen.

Among the patients who showed an improvement in depression scores, 20 continued therapy in a 4-month blinded extension period after the 8 weeks ended. Two measures suggested that quality of life improved in these patients, whose depression improved, compared with baseline, he said.

The study excluded patients with dementia, psychosis, or motor fluctuations. Patients averaged 62 years in age and had had PD for 6 years on average. The cohort included 25 women and 27 men.

In two previous trials of 12 and 37 patients with PD, an SSRI showed no advantage over placebo, he said. ■

AE Risk Is High

Brain Stimulation *from page 1*

At least one serious adverse event was experienced by 40% of DBS patients, compared with only 11% of BMT patients.

The Deep Brain Stimulation vs. Best Medical Therapy trial included patients aged 22 years or older (mean age 63 years) with Hoehn and Yahr stage 2 or greater idiopathic Parkinson's disease responsive to L-dopa, but with persistent motor complications. BMT patients received optimized medical therapy, and DBS patients were further randomized to bilateral stimulation of the subthalamic nucleus (STN) or globus pallidus interna (GPi).

The BMT arm was discontinued early as there was sufficient power to compare the primary outcome with the first 255 patients. Most BMT patients proceeded to surgical treatment, Dr. Weaver, of Hines (Ill.) Veterans Affairs Hospital, said in an interview. Results of the DBS target (STN vs. GPi) portion are expected in 2009.

Results from the prospective, randomized COMPARE (Comparison of Best Medical Therapy and Deep Brain Stimulation of Subthalamic Nucleus and Globus Pallidus for the Treatment of Parkinson's Disease) trial will not end the controversy over which surgical target is best, but will provide the first level 1 evidence that may allow physicians to tailor DBS to the patient's symptoms, said Dr. Michael S. Okun, co–principal investigator.

"We should stop thinking of these comparisons as yes-or-no phenomena, but start to think of where one target might be better than another and match our patients up so they can achieve optimal benefit."

Six-month data on 45 of 52 patients (mean age 61 years) showed no significant difference between 22 STN and 23 GPi patients in seven of the eight subscales of the visual analog mood scale (VAMS), the primary outcome of the study. There was a significant difference between groups on the VAMS anger subscale; the mean change in anger scores was significantly larger with STN than with GPi (5.4 vs. –0.2).

Both groups reported significant improvements in VAMS scores on the tension and tiredness subscales, but the difference between groups was not significant.

Significant worsening of verbal fluency was seen in the STN group, but not in the GPi group (–5.6 vs. 0.4). This was true whether the stimulator was on or off. The pattern of deterioration in the STN group preliminarily suggested a surgical or lesional effect rather than a stimulation-induced effect, said Dr. Okun, codirector of the Movement Disorders Center, University of Florida, Gainesville, and national medical director for the National Parkinson's Foundation.

Both groups reported being significantly less happy, less energetic, and more confused when stimulation was delivered ventrally or one contact below the optimal stimulation site.

No significant difference was found in motor improvement between the STN and GPi groups (mean 29.9% vs. 26.6%), while medication reduction trended in favor of STN; however, the study was not powered for these outcomes.

There were 95 surgical adverse events with STN vs. 67 with GPi. There was one death from pneumonia in the STN group, said Dr. Okun, who has received speaking and consulting fees from the National Parkinson's Foundation and Medtronic Inc.

Full results of the COMPARE trial, funded by the National Institute of Neurological Disorders and Stroke and the University of Florida, are expected in the fall.

Additional level 1 evidence on DBS is expected later this year from the double-blind, prospective Deep Brain Stimulation for Parkinson's Disease trial comparing unilateral STN with GPi in 121 patients. Preliminary analysis of motor scores data at 6 months revealed no significant difference between the two target sites (STN and GPi), Dr. Jerrold Vitek of the Cleveland Clinic Foundation, said in an interview. Data verification is ongoing, and formal analyses will address issues including neuropsychological and psychiatric functioning, quality-of-life parameters, and other secondary variables.

Patients were randomized based on motor symptom symmetry to see if this can be used to decide whether patients require bilateral surgery or just unilateral stimulation, decreasing the risk and cost, he said. ■