Study Cites Preventable Reasons for DBS Failure

Many of the errors were either avoidable or correctable by more experienced physicians.

BY DAMIAN McNAMARA
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MIAMI BEACH — Operator errors are responsible for more than half of the failures of deep brain stimulation to lessen essential tremor or Parkinson's symptoms, according to the findings of one study presented at the American Academy of Neurology annual meeting.

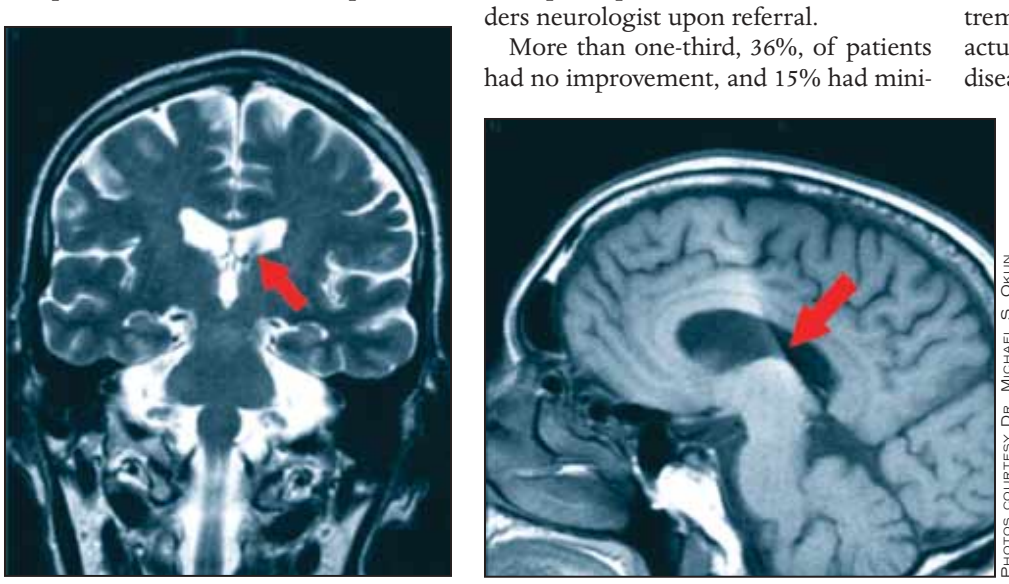
Many of these patients benefit when deep brain stimulation (DBS) is repeated at movement disorder centers by more experienced physicians.

The Food and Drug Administration approved a DBS system (Activa, manufactured by Medtronic Inc.) to treat patients with essential tremor or Parkinson's disease in August 1997. The agency expanded the system's indication to include patients with dystonia in April 2003.

DBS improves quality of life for many patients, but others do not respond. Incorrect diagnosis, surgical lead misplacement, and device-related errors are among the preventable problems identified by Michael S. Okun, M.D., and his associates.

"There has been a surge in centers providing DBS after its FDA approval and an increasing number of patients presenting to experienced DBS centers with complaints," said Dr. Okun, co-director of the Movement Disorders Center at the University of Florida in Gainesville. "About 12 patients per year are seen by centers of excellence for these referred problems."

A lack of consensus on patient screening, provider training, and the best multidisciplinary approach contribute to the failure rate, Dr. Okun said. In addition, there is no consensus on management of complications, some of which spur referral of the patient to an experienced DBS center for management.



Photos courtesy Dr. Michael S. Okun

Operator errors caused more than half of all cases of deep brain stimulation failure. Shown are examples of DBS lead misplacement: in the ventricle (left), atop the thalamus (right).

Records of 41 consecutive patients treated at the University of Florida movement disorders center or the movement disorders center at the Beth Israel Medical Center in New York City were reviewed. The average age was 63 years. Thirty patients (73%) saw a movement disorders specialist prior to DBS implantation. Five patients (12%) had significant cognitive dysfunction before implantation. The patients underwent the following types of DBS implantation: 21, bilateral subthalamic nucleus; 8, unilateral subthalamic nucleus; 8, unilateral ventral intermediate nucleus; 1, unilateral globus pallidus interna; 1, bilateral ventral intermediate nucleus; and 1, bilateral globus pallidus interna.

All participants saw a movement disorders neurologist upon referral.

More than one-third, 36%, of patients had no improvement, and 15% had minimal improvement. However, "51% had significant improvement or were rescued with good outcomes," Dr. Okun said.

"The reasons for DBS failures were not only surgical," Dr. Okun said.

The researchers identified a timeline of preventable problems associated with DBS surgery. "It is quite interesting because many things were quite correctable," Dr. Okun said. "There is an expertise factor we can improve on."

Preventable problems included:

- Incorrect diagnosis (10 instances).
- Inadequate medication trial/dementia (10).
- Misplaced leads (19).
- Inadequate device programming (15).
- Medication adjustments (30).

Preoperative diagnoses included 31 with Parkinson's disease, 9 with essential tremor, and 1 patient with dystonia. The actual diagnoses were 26 with Parkinson's disease, 5 with essential tremor, 1 with dystonia, 3 with Parkinson's disease with dementia, 2 with multiple system atrophy, 1 with Parkinson's disease/essential tremor, 1 with corticobasal ganglionic degeneration, 1 with progressive nuclear palsy, and 1 with myoclonus.

Patients improved after 7 of the 19 misplaced leads were replaced, and partially improved after 3 others were replaced.

Programming problems included inadequate programming (15 patients), no or poor access to programming (7 patients), and difficult access to follow-up because of relocation (2 patients, 2 physicians). Reprogramming was successful for 15 patients and partially successful for 6.

A majority, 73%, of participants required medication changes. Dr. Okun said, "This brings home the point that even after surgery patients often need medication adjustments."

Selection bias was a possible shortcoming of the study.

He said there are many improvements that can be made to prevent DBS failures and to improve outcomes.

Dr. Okun teaches programming the Activa DBS system for Medtronic. ■

Ropinirole Gets FDA Nod for Moderate to Severe Adult RLS

BY DAMIAN McNAMARA
Miami Bureau

MIAMI BEACH — The antiparkinsonism drug ropinirole is now indicated for the treatment of adults with moderate to severe restless legs syndrome.

The Food and Drug Administration approved the new indication based on three randomized, double-blind, controlled trials that showed significant improvements in patient and physician symptom ratings, compared with placebo.

One of these studies showed that ropinirole (Requip, from GlaxoSmithKline Inc.) was well tolerated and effective at improving symptoms in as little as 1 week. Richard Bogan, M.D., presented results of this phase III study at the annual meeting of the American Academy of Neurology.

Restless legs syndrome is a sensorimotor neurologic disorder affecting 5%-10% of the U.S. population. The condition causes considerable sleep disturbance and impairs quality of life for some patients. Although the pathogenesis is unknown, dopamine agonists such as ropinirole may be effective as first-line treatment for moderate to severe cases, according to Dr. Bogan of the University of South Carolina.

To test safety and efficacy, Dr. Bogan and his colleagues randomized 187 patients to ropinirole and 193 others to placebo in a 12-week, double-blind, multicenter trial. All participants had mild to moderate impairment; entry requirements included an International Restless Legs Syndrome (IRLS) study group criteria score of 15 or more, at least 15 nights of symptoms in the last month, and 4 nights of symptoms in the last 7 nights.

"Patients do have changes in quality of life, and ropinirole can improve their lives," said Dr. Bogan, president and medical director of SleepMed Inc.

The primary measure of efficacy was change in IRLS score between baseline and the last clinical observation before the end of the 12-week trial. Secondary outcomes included the change in IRLS score from baseline to week 1 and the proportion of patients in each group with a score of "much improved" or "very much improved" at weeks 1 and 12 on the Clinical Global Impression-Improvement scale. In addition, researchers assessed sleep quantity and quality with the Medical Outcomes Study sleep scale.

All participants were adults, with a mean age of 52 years (range 18-79 years). Women accounted for 58% of the ropinirole group and 63% of the placebo group. A total of 164 ropinirole recipients and 167 placebo recipients completed the study.

The treatment group received once-daily ropinirole 0.25 mg at baseline, 1-3 hours before bedtime. Dosages were titrated up to 4.0 mg/day to optimize efficacy without side effects. Dr. Bogan has received research grants from GlaxoSmithKline, the sponsor of this study.

There were "highly statistically significant" improvements in patient subjective assessments on the IRLS scale, Dr. Bogan said. Ropinirole reduced IRLS scores a mean of 3.7 points, compared with 2.0 points for placebo, at the patient's last clinical observation, which occurred either at 12 weeks or, in some cases, earlier.

Changes on the global impression scale "were highly statistically significant as well, although clearly, there is a placebo effect." The proportion of patients with a Clinical Global Impression score of "much" or "very much improved" was significantly higher for ropinirole than placebo at week 12 (2.1 adjusted odds ratio).

"I am frustrated by my inability to tease out the placebo effect, by the scales we use, and the variability of their symptoms," Dr. Bogan said in response to a question from the audience.

Ropinirole was associated with symptom relief as early as the first week of treatment. IRLS scores dropped by 4.1 points in the drug group versus 2.7 points in the placebo group at the end of the first week.

In addition, a significantly higher proportion of ropinirole participants had Clinical Global Impression improvements at week 1 (2.4 adjusted odds ratio).

The treatment also provided qualitative improvements in sleep. Measures of sleep adequacy and quantity showed patients on active therapy experienced "dramatic improvements, especially in quantity of sleep," Dr. Bogan said.

Ropinirole was generally well tolerated, he reported. The most common adverse events associated with ropinirole treatment were nausea, headache, and somnolence.

Nausea, for example, occurred in 42% of the treatment group, versus 8% of the placebo group. Withdrawals because of adverse events were similar; five patients in the ropinirole group and eight in the placebo group withdrew from the study. ■