

Brain Stimulation Bests Medical Therapy for PD

BY JEFF EVANS

Parkinson's disease patients report better quality of life after 1 year of deep brain stimulation than with best medical therapy, according to the largest randomized trial of the two treatment options for patients with advanced disease.

In the PD SURG trial, deep brain stimulation (DBS) resulted in greater improvement in motor function scores and complications of therapy, as well as lower use of dopaminergic drugs, than did best medical therapy. However, both arms of the open-label study experienced a similar amount of cognitive decline, with significantly poorer function in verbal fluency and vocabulary in DBS patients.

The trial largely corroborates the results observed in two previous trials of DBS vs. best medical therapy that recorded follow-up out to 6 months (*N. Engl. J. Med.* 2006;355:896-908; *JAMA* 2009;301:63-73).

"Surgery is likely to remain an important treatment option for patients with PD, especially if the way in which deep brain stimulation exerts its therapeutic benefits is better understood, if its use can be optimized by better electrode placement and settings, and if patients who would have the greatest benefit can be better identified," Dr. Keith Wheatley of the University of Birmingham (England) and his colleagues concluded (*Lancet Neurol.* 2010 April 29 [doi:10.1016/S1474-4422(10)70093-4]).

During 2000-2006, Dr. Wheatley and his associates randomized 366 patients evenly to either treatment group at 13 neurosurgical centers in the United Kingdom. The patients had a mean age of 59 years and were mostly men (about 70%) with a mean disease duration of 11.4 years. In each group, 45 patients were taking apomorphine at study entry; 145 total were taking it before the study.

Of 178 patients who underwent surgery, DBS targeted the subthalamic nucleus in 174 and the globus pallidus

VITALS

Major Finding: Measurement of quality of life with the PDQ-39 after 1 year improved significantly more in DBS patients than in medical therapy patients (-5.0 vs. -0.3).

Data Source: A randomized, open-label trial of 366 patients with Parkinson's disease.

Disclosures: Trial was funded by the U.K. Medical Research Council, Parkinson's U.K., and the U.K. Department of Health. Dr. Wheatley and most coauthors had no relevant disclosures. One coauthor received grants and fees from Medtronic for another similar study. Dr. Rodriguez-Oroz reported relationships with Medtronic and several companies that manufacture dopaminergic agents.

pars interna in 4. All but two of the surgeries were bilateral. A total of 12 patients in the best medical therapy arm underwent DBS surgery between baseline and 1 year but were analyzed in the medical therapy arm anyway.

Measurement of quality of life with the Parkinson's Disease Questionnaire (PDQ-39) after 1 year—the primary outcome—improved significantly more in DBS patients than in medical therapy patients (-5.0 vs. -0.3).

During "on" periods, the mean United Parkinson's Disease Rating Scale (UPDRS) total score after 1 year improved by a mean of 6.6 points in the surgery group and worsened by 1.6 points in the medical therapy group, which was a significant difference. In "off" time, UPDRS scores improved significantly more in DBS patients (-27.4) than in medical therapy patients (-0.9 points).

Cognitive status measured with the Dementia Rating Scale-II (DRS-II) declined by 0.4 points in each group after 1 year. Neuropsychological testing in a subset of patients revealed that verbal fluency and vocabulary had declined after 1 year significantly more in patients who had undergone surgery than in patients who took medication alone.

Treatment with DBS also resulted in a significantly lower mean levodopa equivalent dose after 1 year than did medical therapy alone (894 vs. 1,347 mg/day).

"The cost of surgery will be partly offset by the reduction in the amount of drug therapy required by patients who have had surgery. In particular, if apomorphine or continuous intestinal infusions of levodopa, with high recurrent costs, are the alternative drug treatment options, the cost-effectiveness equation might favor surgery ... thus, it is important to identify patients who are or are not likely to benefit from surgery when the risks and costs are taken into account," they wrote.

Overall, 36 surgery patients experienced 43 serious adverse events, including 16 infections. In the surgery group, 25 Parkinson's disease-related and drug-related serious adverse events occurred in 20 patients, compared with 14 events in 13 medical therapy patients. The two remaining serious adverse events in the group included one unsuccessful postoperative suicide and one death from hemorrhage during surgery.

The trial has a number of strengths that improved on previous trials, including a larger number of patients, a longer follow-up, and treatment with continuous infusions of apomorphine. Dr. Maria C. Rodriguez-Oroz wrote in an editorial (*Lancet Neurol.* 2010 April 29 [doi:10.1016/S1474-4422(10)70108-3]).

Dr. Rodriguez-Oroz of the Clinica Universidad de Navarra, Pamplona, Spain, added that some limitations of the trial raise questions about the results. For example, neither patients nor evaluators were masked to treatment. Evaluations of dyskinesia and "off" period time could have been done with a more reliable tool than the complications of therapy subsection of the UPDRS. Investigators made their own judgment about whether a patient was in the "on" state (without assessment of inter-rater reliability). The DRS-II might be inadequate to assess cognitive ability in Parkinson's. And the investigators did not record nonserious adverse events. ■

Brain Exercises Don't Improve General Cognitive Function

VITALS

Major Finding: Improvements seen in brain training tasks translated poorly to performance on benchmarking tests that used similar cognitive functions (effect sizes, 0.01-0.22).

Data Source: A 6-week trial of "brain training" exercises in 11,430 participants.

Disclosures: The authors reported having no financial conflicts of interest.

BY LEANNE SULLIVAN

Brain training" does not improve general cognitive function, according to a 6-week trial of more than 11,000 participants.

The study results "provide no evidence for any generalized improvements in cognitive function following brain training in a large sample of healthy adults," Adrian M. Owen and his colleagues reported.

The participants were divided into three groups: the experimental group 1 (4,678 subjects), which did six tasks emphasizing reasoning, planning, and problem solving; experimental group 2 (4,014 subjects), which practiced six tasks focusing on short-term memory, attention, visuospatial processing, and mathematics; and a control group (2,738 subjects), which answered various research questions using the Internet.

The tasks given to group 2 were con-

sidered to be most like those of commercially available "brain training" programs, said Mr. Owen of the Medical Research Council Cognition and Brain Sciences Unit, Cambridge, England, and his colleagues.

The participants were assessed before and after the intervention using benchmarking tests that measured reasoning, verbal short-term memory, spatial working memory, and paired-associates learning. Participants completed an average of 24 training sessions over the 6-week period (range, 1-188). The tasks were performed for a minimum of 10 minutes a day, three times a week.

All three groups improved on the tasks they had been assigned to practice during the trial (effect sizes: group 1, 0.73-1.63; group 2, 0.72-0.97; controls, 0.33). However, postintervention improvements on the benchmarking tests were much smaller (effect sizes: 0.01-0.22 for all groups). The control group improved slightly more than the experimental groups on two measures.

The groups were similar in age (average, 39-40 years) and gender (each group had 4-5 times as many female participants). No relationship was seen be-

tween number of training sessions performed or age of participants and postintervention benchmarking test scores.

Although participants improved at their assigned tasks, "training-related improvements may not even generalize to other tasks that use similar cognitive

functions," the researchers said (*Nature* 2010 Apr. 20 [doi:10.1038/nature09042]).

"Six weeks of regular computerized brain training confers no greater benefit than simply answering general knowledge questions using the Internet," they concluded. ■

Credible Study on Complex Question

The notion of exercising the mind to reduce its deterioration is popular in the world of Alzheimer's disease: Do more crossword puzzles and you will slow the progression of dementia. But is it true? Epidemiological studies have shown mixed results, possibly reflecting presymptomatic-stage disease, confounding medical issues, and medications influencing outcomes.

Most people "exercise" their brain during their daily activities whether they conceptualize it this way or not.

Cognitive tasks rely on the integration of multiple brain regions that are geographically distant and serve different functions. Because a

related, nonidentical task might use this network, it is conceivable that related tasks may be performed with greater facility and dexterity.

The background of the question is complex, but given the effort required to achieve even a "simple" practice effect, studies such as this one that fail to show any major translational skill differences after a mere 6 weeks of "brain exercises" are certainly credible.

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MY TAKE