A Second Honeymoon for Parkinson’s Disease?
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Parkinson’s disease is a chronic, progressively disabling neurodegenerative disorder that occurs late in life, causing motor, autonomic, emotional, and cognitive symptoms. The cost of Parkinson’s disease is substantial, including reduced quality of life, lost productivity, and increased health care expenditures. The number of persons with Parkinson’s disease worldwide is, conservatively, expected to nearly double by 2030, owing to overall aging of the population. Effective treatments for Parkinson’s disease are an imperative. Medical therapy for Parkinson’s disease is most effective in treating the motor symptoms of resting tremor, bradykinesia, and rigidity. Levodopa remains the most effective current treatment for motor symptoms; benefits are sustained through a honeymoon period that typically lasts for several years. In advanced Parkinson’s disease, motor fluctuations develop. Periods of immobility make up a greater proportion of each day. Periods of good mobility may be limited by the presence of dyskinesias.

Neurostimulation of the subthalamic nucleus is recommended for the management of motor fluctuations and dyskinesias in patients with advanced Parkinson’s disease and severe motor complications. Yet, for many of these patients, amelioration of motor complications may be too late — the onset of symptoms, such as cognitive impairment, that are unresponsive to treatment offsets the benefit of improved motor function. Reasoning that earlier intervention with neurostimulation might provide an improved motor benefit before disability from other symptoms has occurred, Schuepbach and colleagues evaluated neurostimulation combined with best available medical therapy in patients with Parkinson’s disease and early motor complications. As the investigators report in this issue of the Journal, neurostimulation with medical therapy was superior to medical therapy alone. Improvement was shown with the use of a patient-reported, quality-of-life questionnaire specific to Parkinson’s disease. In addition, patient diaries showed improved function during times of poor mobility as well as longer periods of good mobility. These patient-determined outcomes arguably provide the most important assessment of the clinical value of neurostimulation. Traditionally used, expert-derived measures of motor function also showed the benefit of neurostimulation.

This is one of the most rigorously conducted trials of neurostimulation. Medical treatment was provided systematically, in accordance with established evidence, and judged by an independent panel. Although true blinding is difficult in neurostimulation studies, reviewers who were unaware of the study assignments rated standardized videotaped assessments of motor function. The study protocol, which is available with the full text of the article at NEJM.org, will provide a useful resource for future trials.

There are caveats to the clinical application of this procedure. The patients included in this study do not represent most patients with Parkinson’s disease. All the patients were 60 years of age or younger at the time of surgery, were in good general health, did not have dementia, and had a good response to a levodopa challenge. Very few patients with Parkinson’s disease meet these criteria: only 11% of cases of Parkinson’s disease are diagnosed before the patient is 60 years of age, and on average, 30% of patients have dementia. Whether these results would be obtained in older patients with Parkinson’s disease or in less-experienced medical centers is not known.
In addition, suicide was increased in the neurostimulation group, even though mean scores in the assessment of depression improved in that group. Suicide has previously been associated with stimulation of the subthalamic nucleus but less so with other surgical targets used in the treatment of Parkinson's disease. Recognizing the importance of individual patient monitoring, the investigators instituted systematic monitoring for suicidality in this study.

Little is known about the long-term efficacy of neurostimulation. Motor improvement is sustained for as long as 10 years in a small number of selected patients. This would argue in favor of using neurostimulation in carefully chosen, young patients with a recent onset of motor fluctuations. Since the risk of suicide appears to persist for years after surgery, careful and sustained monitoring should be a requirement. Neurostimulation is also costly, although the postoperative reduction of medication for Parkinson's disease may offset the cost of surgery over time. The surgical benefit appears to depend on the experience of a large, multidisciplinary team of experts. Most important, neurostimulation has a beneficial effect only on selected motor symptoms. The underlying progression of Parkinson's disease and inevitable disability due to other disease features are not ameliorated.

Alternative treatments include neurostimulation of other targets, such as the globus pallidus, and improved methods for delivery of levodopa. In advanced Parkinson's disease, the benefit of pallidal stimulation may be similar to or less than the benefit of stimulation of the subthalamic nucleus. Sustained delivery of dopaminergic therapies has psychiatric and motor side effects that diminish efficacy. These approaches have not been compared with neurostimulation of the subthalamic nucleus in a population with early motor complications.

Ideally, treatment of Parkinson's disease should improve not only motor, but all, features of the disease. Neurostimulation of the subthalamic nucleus does not ameliorate all symptoms of Parkinson's disease, but for carefully chosen, highly functioning patients, it may provide many additional years of good functioning.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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